

## Delayed dual-pulse oral formulation

### Technical field

The present disclosure relates to a pulsatile release tablet formulation that enables a  
5 delayed pulse release of two or more active agents.

### Background

Parkinson's disease is a progressive neurological condition with disabling symptoms of  
tremor, rigidity and bradykinesia or akinesia. The symptoms are related to a depletion  
10 of dopamine in the corpus striatum of the brain. Dopamine cannot be administered  
orally or systemically due to its inability to cross the blood brain barrier. Levodopa is an  
exogenous dopamine precursor which is converted to dopamine after moving across  
the blood brain barrier. Levodopa is administered orally in the treatment of Parkinson's  
disease alongside a DOPA decarboxylase inhibitor, such as Carbidopa, which prevents  
15 peripheral metabolism of Levodopa thus enhancing central nervous system  
bioavailability, reducing the overall dose of Levodopa required and minimising  
Levodopa related side effects. Patients treated with Levodopa often develop motor  
fluctuations such as peak dose dyskinesia or end of dose akinesia. Producing a steady  
plasma level of Levodopa can attenuate these symptoms.

20 Mobility problems and recurring tremor early in the morning before the first intake of  
levodopa are early events in the development of motor complications associated with  
sustained oral levodopa treatment of Parkinson's Disease, PD. Recent surveys have  
indicated that early morning akinesia (or morning OFF episodes) are present in around  
25 60% of PD patients across all disease stages and that a similar number of patients are  
affected by nocturnal immobility with difficulties turning in bed. In most patients  
experiencing early morning akinesia, this is associated with non-motor symptoms such  
as anxiety, depression, pain, and urinary urge.

30 To manage early morning akinesia and episodes of nocturnal hypomobility, many  
patients use L-DOPA on an intermittent or as-needed basis. However, the slow or  
unpredictable onset of effect, as well as the short half-life, limits the clinical benefit.  
Alternative delivery of dopaminergic therapy by a non-oral route, such as subcutaneous  
apomorphine injection is used by patients with PD in the OFF state to revert to the ON  
35 state to control symptoms. However, an early morning subcutaneous self-pen injection

in disabled advanced PD patients could be troublesome. Inhalable and sublingual formulations of levodopa and sublingual formulations of apomorphine are also available as on-demand, rescue medicines, but these are all associated with a delay (time-to-ON) between administration and clinical relevant effect. This delay is troublesome for patients.

Levodopa is routinely administered in combination with a DOPA decarboxylase inhibitor such as carbidopa that prevents the conversion of levodopa to dopamine in the peripheral circulation before it can reach the brain and take effect, thereby allowing more levodopa to cross the blood-brain barrier into the central nervous system (CNS). Carbidopa enables a much lower dose of levodopa (80% less) and helps reduce the side effects of nausea and vomiting. By blocking the decarboxylase route of metabolism, circulating levodopa is primarily metabolized by catechol-O-methyltransferase (COMT) to 3-O-methyldopa (3-OMD). COMT inhibitors in combination with levodopa/DOPA decarboxylase inhibitor preparations are associated with an increase of CNS bioavailability of levodopa.

Carbidopa/levodopa tablets are available in immediate-release (IR) and extended-release (ER) forms as well as dissolvable tablets that are placed under the tongue. A small, portable infusion pump delivers carbidopa and levodopa directly into the small intestine. It has been suggested that pretreatment with carbidopa prior to levodopa in some instances increases levodopa plasma AUC compared to simultaneous administration (see e.g. Leppert et al. 1988).

Taken together, nocturnal immobility and morning akinesia are significant contributors to impaired sleep quality and reduced quality of life for patients. There are currently no effective, reliable, and easy to use treatment options available to satisfactorily address these problems.

### Summary

The present inventors have developed a delayed release dual pulse combined Carbidopa/Levodopa tablet formulation for improved management of nocturnal hypomobility and morning akinesia in individuals with Parkinson's disease. A combined or single-tablet formulation as provided herewith is shown to provide a clear and defined burst release. The formulation can be taken at bedtime to release a first

delayed pulse of Carbidopa about 4 to 6 hours after oral administration followed by release of a second delayed pulse of Levodopa which is delayed about 0.5 to 1 hr longer than the first delayed pulse. With this innovative formulation therapeutically relevant plasma levels and central levels of Levodopa can be delivered prior to waking and offering potential relief from nocturnal hypomobility and morning akinesia.

The present disclosure provides a tablet formulation, such as a press-coated tablet, for oral administration of two or more active agents, the tablet comprising:

- i) A core, such as a triple-layer core, comprising or consisting of
  - a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); such as wherein said first active agent is a DOPA decarboxylase inhibitor and/or a COMT inhibitor;  
alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug;  
and
  - b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug;  
such as wherein said second active agent is levodopa or a pharmaceutically acceptable derivative thereof,
  - c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer comprising or consisting of a wax and one or more binders and/or fillers,  
and
- ii) A delayed release layer surrounding the core, said delayed release layer comprising or consisting of a wax and one or more binders and/or fillers;  
wherein the release of the two or more active agents is delayed for 2 to 10 hours, and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours after oral administration to a subject. In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours after placing in an aqueous solution; such as placing in 500 ml aqueous solution comprising 0.1 N HCl at 37°C +/-  
5 0.5°C at 50 rpm.

In some embodiments the delayed release layer and the barrier layer comprises a wax and one or more low-substituted hydroxypropyl cellulose (L-HPC), and optionally further comprising a hydroxypropyl cellulose (HPC).  
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In some embodiments the first active agent is a DOPA decarboxylase inhibitor and the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof. In some embodiments the DOPA decarboxylase inhibitor is carbidopa, or a pharmaceutically acceptable derivative thereof.  
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Also disclosed are methods of making said tablet formulation and said tablet for use in the treatment of morning akinesia and for the treatment of nocturnal symptoms in a patient with Parkinson's disease.

## 20 **Description of Drawings**

Figure 1. Illustration of prototypes 1 to 5: Pulsatile release tablet formulations comprising carbidopa (CD) as a first active agent and levodopa (LD) as a second active agent. The tablet formulations comprise a core comprising the first and second active agent surrounded by an outer delayed release layer (see Example 1).  
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Figure 2: Representative anterior scintigraphic images with overlaid standard stomach outline for subject dosed with Treatment A at four time points post-dose. a) 90 mins post dose, tablet located in stomach, b) 270 mins post dose, tablet located in small intestine, c) 300 mins post dose, onset of radiolabel release in small intestine, d) 330  
30 mins post dose, released activity in small intestine (see Example 2).

Figure 3: Representative anterior scintigraphic images with overlaid standard stomach outline for subject dosed with Treatment B at four time points post-dose. a) 0 mins post dose, tablet located in stomach, b) 60 mins post dose, tablet located in stomach, c) 390



mins post dose, onset of radiolabel release in stomach, d) 480 mins post dose, released activity in small intestine (see Example 2).

### Definitions

5 The terms "dopamine," "DA" and "4-(2-aminoethyl)benzene-1,2-diol," refer to a catecholamine neurotransmitter and hormone. Dopamine is a precursor of adrenaline (epinephrine) and noradrenaline (norepinephrine) and activates the five types of dopamine receptors - D1, D2, D3, D4, and D5 - and their variants.

10 "L-DOPA", "3,4-dihydroxyphenylalanine" or "levodopa" is a precursor to the neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline). L-DOPA is able to cross the blood-brain barrier, and is used for treatment of Parkinson's disease and dopamine-responsive dystonia.

The term "pharmaceutically acceptable derivative" in present context includes pharmaceutically acceptable salts, which indicate a salt which is not harmful to the patient. Such salts include pharmaceutically acceptable basic or acid addition salts as well as pharmaceutically acceptable metal salts, ammonium salts and alkylated ammonium salts. A pharmaceutically acceptable derivative further includes esters, solvates and prodrugs, or other precursors of a compound which may be biologically metabolized into the active compound, and crystal and cocrystal forms of a compound.

15 A prodrug is a pharmacologically inactive compound that, after intake, is converted into a pharmacologically active drug.

The terms "Parkinson's disease," "Parkinson's" and "PD" refer to a neurological syndrome characterized by a dopamine deficiency, resulting from degenerative, vascular, or inflammatory changes in the basal ganglia of the substantia nigra. This term also refers to a syndrome which resembles Parkinson's disease, but which may or may not be caused by Parkinson's disease, such as Parkinsonian-like side effects caused by certain antipsychotic drugs and parkinsonism.

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The term "therapeutically effective amount" of a compound as used herein refers to an amount sufficient to cure, alleviate, prevent, reduce the risk of, or partially arrest the clinical manifestations of a given disease or disorder and its complications.

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The terms "treatment" and "treating" as used herein refer to the management and care of a patient for the purpose of combating a condition, disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the

patient is suffering, such as administration of the active compound for the purpose of:  
alleviating or relieving symptoms or complications; delaying the progression of the  
condition, disease or disorder; curing or eliminating the condition, disease or disorder;  
and/or preventing the condition, disease or disorder, wherein "preventing" or

5 "prevention" is to be understood to refer to the management and care of a patient for  
the purpose of hindering the development of the condition, disease or disorder, and  
includes the administration of the active compounds to prevent or reduce the risk of the  
onset of symptoms or complications. The patient to be treated is preferably a mammal,  
in particular a human being.

10 The terms "approximately" and "about" as referred herein are synonymous. In some  
embodiments, "approximately" and "about" refer to the recited amount, value, or  
duration  $\pm 5\%$ ,  $\pm 4.5\%$ ,  $\pm 4\%$ ,  $\pm 3.5\%$ ,  $\pm 3\%$ ,  $\pm 2.5\%$ ,  $\pm 2\%$ ,  $\pm 1.75\%$ ,  $\pm 1.5\%$ ,  $\pm 1.25\%$ ,  $\pm 1\%$ ,  
 $\pm 0.9\%$ ,  $\pm 0.8\%$ ,  $\pm 0.7\%$ ,  $\pm 0.6\%$ ,  $\pm 0.5\%$ ,  $\pm 0.4\%$ ,  $\pm 0.3\%$ ,  $\pm 0.2\%$ ,  $\pm 0.1\%$ . In some  
embodiments, "approximately" and "about" refer to the listed amount, value, or duration  
15  $\pm 2.5\%$ ,  $\pm 2\%$ ,  $\pm 1.75\%$ ,  $\pm 1.5\%$ ,  $\pm 1.25\%$ ,  $\pm 1\%$ ,  $\pm 0.9\%$ ,  $\pm 0.8\%$ ,  $\pm 0.7\%$ ,  $\pm 0.6\%$ ,  $\pm 0.5\%$ . In  
some embodiments, "approximately" and "about" refer to the listed amount, value, or  
duration  $\pm 1\%$ . In some embodiments, "approximately" and "about" refer to the listed  
amount, value, or duration  $\pm 0.5\%$ . In some embodiments, "approximately" and "about"  
refer to the listed amount, value, or duration  $\pm 0.1\%$ . In the context of an amount or  
20 dosage of an API the terms "approximately" and "about" as referred herein refer to the  
recited amount or dosage  $\pm 10\%$ ,  $\pm 9\%$ ,  $\pm 8\%$ ,  $\pm 7\%$ ,  $\pm 6\%$ ,  $\pm 5\%$ ,  $\pm 4\%$ ,  $\pm 3\%$ ,  $\pm 2\%$ ,  
 $\pm 1.5\%$ ,  $\pm 1\%$ ,  $\pm 0.5\%$ .

A tablet formulation refers to solid dosage forms designed for oral administration, and  
typically comprises one or more active agent(s) and other excipients that are required  
25 to enable the pharmacokinetic and mechanical properties of the final dosage form.  
These excipients are primarily diluents or fillers, compressing agents, binders,  
disintegrants and lubricants.

Reference to 'tablet formulation' herein refers to a solid oral dosage form which is a  
tablet formulation comprising a core, such as a triple-layer core, and an outer delayed  
30 release layer surrounding said core.

Reference to 'triple-layer core' as used herein refers to a tablet core comprising two  
cores or core layers ('dosage units'), each core or core layer comprising an amount of  
an API, and having a barrier layer between said two cores or core layers.

Reference to 'two or more active agents' herein refers to a first active agent and a second active agent as follows:

Reference to a 'first active agent' refers to an agent that prevents peripheral metabolism of levodopa (L-DOPA); alternatively an agent selected from dopamine, a  
5 dopamine agonist, a dopamine precursor and a dopamine prodrug;

Reference to a 'second active agent' refers to an agent selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug.

A 'binder' (tablet binder) or binding agent is an excipient used in oral solid dosage forms that helps bind excipients together and ensuring mechanical strength and proper  
10 release (also known as an adhesive). Binders are added in a formulation to form granules either in dry or liquid form during wet granulation or in dry form during dry granulation or directly compressed tablets. Tablet binders and disintegrants have the opposite use in an oral solid formulation; binders delay tablet disintegration while disintegrants increases tablet disintegration.

15 A 'filler' (tablet filler) is an excipient used in oral solid dosage forms (also known as a diluent). The main function of the filler is to increase the weight or volume of the tablet to increase tablet size, facilitate compression and reduce the cost of the solid material. The filler may also be added to improve the performance of the material. Generally, organic, inorganic, metal or non-metal powders that do not contain water, are neutral,  
20 and do not play a negative role with the material components can be used as fillers. Commonly used fillers include starches, sugars, celluloses and inorganic salts. The filler can be water-soluble or water-insoluble.

'Waxes' are a diverse class of organic compounds that are lipophilic, malleable solids near ambient temperatures. They include higher alkanes and lipids, typically  
25 with melting points above about 40 °C (104 °F), melting to give low viscosity liquids. Waxes are insoluble in water but soluble in nonpolar organic solvents. Natural waxes of different types are produced by plants and animals and occur in petroleum. Natural waxes may contain unsaturated bonds and include various functional groups such as fatty acids, primary and secondary alcohols, ketones, aldehydes and fatty  
30 acid esters. Synthetic waxes often consist of homologous series of long-chain aliphatic hydrocarbons (alkanes or paraffins) that lack functional groups. The term "wax" as used herein also comprises Water soluble waxes or Carbowax, which are polyethylene glycols (PEG) of varying degrees of polymerization and molecular weights, or polyethylene glycol fatty acid esters, such as polyethylene glycol  
35 monostearate. PEGs differ in their physical and chemical properties depending on their

molecular weight: PEGs are liquids when molecular weights are <1000 and the molecule turns to waxy solids with increasing molecular weights.

#### Detailed description

- 5 Pulsatile drug delivery is defined as the rapid and transient release of an active agent within a short time period immediately after a predetermined off-released period, i.e., lag time. Pulsatile drug delivery systems (PDDS) deliver the active agent at the right time, at the right site of action and in the right amount, and the active agent is released rapidly and completely as a pulse (or burst) after a lag time. Lag time is defined as the
- 10 time between when a dosage form is placed into an aqueous environment and the time at which the active agent begins to release from the dosage form. These products follow the sigmoid release profile characterized by a time period. Potential disadvantages include low drug loading capacity and multiple manufacturing steps.
- 15 It is an aspect of the present disclosure to provide a tablet formulation for oral administration that provides for a delayed, followed by a pulsed release of two or more active agents, preferably two active agents, i.e. the first and second active agent according to the present disclosure. The first active agent is an agent that prevents peripheral metabolism of levodopa (L-DOPA); alternatively an agent selected from
- 20 dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug. The second active agent is an agent selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug. The release of the two or more active agents is delayed for about 2 to 10 hours after oral administration, whereafter the two or more active agents are pulse released to target the desired time and place of
- 25 release. The two or more active agents may be pulse released essentially at the same time after the delay of 2 to 10 hours. In some embodiments the two agents are pulse released at differing times after the delay such that the first active agent is released before the second active agent is released. Preferably, the release of the second active agent is delayed for about 10 to 120 minutes more than the release of the first active
- 30 agent, which releases after about 2 to 10 hours delay. This provides for a delayed first pulse release of first active agent, followed within 10 to 120 minutes by a delayed second pulse release of a second active agent. In this way the release of the first and second active agent can be spaced in time and place.

In some embodiments there is provided a tablet formulation for oral administration that provides for a 2 to 10 hours delayed, followed by a pulsed release of a first active agent that prevents peripheral metabolism of levodopa; for example a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof; and a  
5 second active agent which is levodopa, or a pharmaceutically acceptable derivative thereof. In some embodiments the pulse release of the second active agent is delayed for 10 to 120 minutes after the pulse release of the first active agent.

In some embodiments there is provided a tablet formulation for oral administration that  
10 provides for a 2 to 10 hours delayed, followed by a first pulsed release of a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof, followed by a second pulse release of levodopa, or a pharmaceutically acceptable derivative thereof; wherein the DOPA decarboxylase inhibitor is pulse released before levodopa to mimic DOPA decarboxylase inhibitor pre-treatment.

15 Sufficient absorption and sufficient nocturnal coverage is not possible with the current marketed levodopa products, and the present invention thus provides a unique opportunity for managing nocturnal symptoms and morning akinesia in patients with e.g. Parkinson's disease.

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#### *Tablet formulation*

It is an aspect to provide a tablet formulation for oral administration of two or more active agents, the tablet comprising:

- 25 i) A core, such as a triple-layer core, comprising or consisting of
  - a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug,
  - 30 b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
  - 35 c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer comprising or consisting of a

wax and one or more binders and/or fillers, such as comprising one or more binders selected from L-HPC, HPC and other binders,

and

- ii) A delayed release layer surrounding the core, or triple-layer core, said delayed release layer comprising or consisting of a wax and one or more binders and/or fillers, such as comprising one or more binders selected from L-HPC, HPC, and other binders,

wherein the release of the two or more active agents is delayed for 2 to 10 hours and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

In a preferred embodiment there is provided a tablet formulation for oral administration of two active agents. In a preferred embodiment there is provided a tablet formulation for oral administration of exactly two active agents, or not more than two active agents. In a preferred embodiment the barrier layer does not comprise an active agent.

In a preferred embodiment the first core, or first core layer, comprises an amount of a single or sole first active agent (i.e. does not contain further active agents). In a preferred embodiment the second core, or second core layer, comprises an amount of a single or sole second active agent (i.e. does not contain further active agents).

Reference to 'wherein the release of the two or more active agents is delayed' and 'wherein the delayed release layer delays the release of the two or more active agents', may be used interchangeably herein.

Reference to 'the two or more active agents are pulse released' means that the 'the two or more active agents are pulse released from the core', specifically from the first and second core, or first and second core layer, respectively.

It is an aspect to provide a tablet formulation for oral administration of two or more active agents, the tablet comprising:

- i) A core, such as a triple-layer core, according to the present disclosure, and  
ii) A delayed release layer surrounding the core, according to the present disclosure,

wherein the delayed release layer delays the release of the two or more active agents for 2 to 10 hours and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents is released within 5 to 80 minutes.

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In some embodiments said tablet comprises:

- i) A triple-layer core, comprising or consisting of
  - a. A first core layer comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA);  
alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug,
  - b. A second core layer comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
  - c. A barrier layer interposed between the first and the second core layer, said barrier layer comprising or consisting of a wax and one or more binders and/or fillers, such as comprising one or more binders selected from L-HPC, HPC, and other binders,
- and
- ii) A delayed release layer surrounding the triple-layer core, said delayed release layer comprising or consisting of a wax and one or more binders and/or fillers, such as comprising one or more binders selected from L-HPC, HPC, and other binders.

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In some embodiments a tablet formulation for oral administration of two or more active agents is provided, the tablet comprising:

- i) A core, such as a triple-layer core, comprising or consisting of
  - a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA), and
  - b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active

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- agent is levodopa, or a pharmaceutically acceptable derivative thereof,  
and
- 5 c. A barrier layer interposed between the first and the second core, or first  
and second core layer, said barrier layer comprising or consisting of a  
wax and one or more binders and/or fillers, such as comprising one or  
more binders selected from L-HPC, HPC, and other binders,
- and
- 10 ii) A delayed release layer surrounding the core, or the triple-layer core, said  
delayed release layer comprising or consisting of a wax and one or more  
binders and/or fillers, such as comprising one or more binders selected from L-  
HPC, HPC, and other binders,
- wherein the release of the two or more active agents is delayed for 2 to 10 hours  
and thereafter the two or more active agents are pulse released, such that at least  
70% by weight of the amount of the two or more active agents is released from the  
15 first and second core, or core layer, within 5 to 80 minutes.

In some embodiments a tablet formulation for oral administration of two or more active  
agents is provided, the tablet comprising:

- 20 i) A core, such as a triple-layer core, comprising or consisting of
- a. A first core, or first core layer, comprising an amount of a first active  
agent and one or more excipients, wherein said first active agent is  
selected from dopamine, a dopamine agonist, a dopamine precursor  
and a dopamine prodrug, and
- 25 b. A second core, or second core layer comprising an amount of a second  
active agent and one or more excipients, wherein said second active  
agent is selected from dopamine, a dopamine agonist, a dopamine  
precursor and a dopamine prodrug, and
- 30 c. A barrier layer interposed between the first and the second core layer, or  
first and second core layer, said barrier layer comprising or consisting of  
a wax and one or more binders and/or fillers, such as comprising one or  
more binders selected from L-HPC, HPC, and other binders,
- and
- ii) A delayed release layer surrounding the core, or the triple-layer core, said  
delayed release layer comprising or consisting of a wax and one or more



binders and/or fillers, such as comprising one or more binders selected from L-HPC, HPC, and other binders,  
wherein the release of the two or more active agents is delayed for 2 to 10 hours  
and thereafter the two or more active agents are pulse released, such that at least  
5 70% by weight of the amount of the two or more active agents is released within 5  
to 80 minutes.

In some embodiments the one or more excipients are one or more pharmaceutically  
acceptable excipients. In some embodiments the one or more excipients are one or  
10 more immediate release excipients.

In some embodiments the tablet formulation is a pulsatile release tablet formulation.

In some embodiments the tablet formulation is a pulsatile release dosage form for oral  
administration.

In some embodiments the first and second core, or first and second core layers, are  
15 dosage units.

In some embodiments a tablet formulation for oral administration of two or more active  
agents is provided, the tablet comprising:

- 20 i) A core, such as a triple-layer core, comprising or consisting of
  - a. A first core, or first core layer, comprising an amount of a first active  
agent which is a DOPA decarboxylase inhibitor and/or a COMT inhibitor;  
and one or more excipients, and
  - b. A second core, or second core layer, comprising an amount of a second  
active agent which is levodopa, or a pharmaceutically acceptable  
25 derivative thereof, and one or more excipients, and
  - c. A barrier layer interposed between the first and the second core, or first  
and second core layer, said barrier layer comprising or consisting of a  
wax and one or more binders and/or fillers, such as comprising one or  
more binders selected from L-HPC, HPC, and other binders,  
30 and
- ii) A delayed release layer surrounding the core, or the triple-layer core, said  
delayed release layer comprising or consisting of a wax and one or more  
binders and/or fillers, such as comprising one or more binders selected from L-  
HPC, HPC, and other binders,

wherein the release of the two or more active agents is delayed for 2 to 10 hours and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of two or more active agents is released within 5 to 80 minutes.

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Reference to 'first core' and first core layer' may be used interchangeably herein. Reference to 'second core' and second core layer' may be used interchangeably herein. The terms 'core' and 'triple-layer core' may be used interchangeably herein.

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In some embodiments the first core, or first core layer, comprises an amount of a first active agent which is a DOPA decarboxylase inhibitor; such as carbidopa or a pharmaceutically acceptable derivative thereof; and one or more excipients, and the second core, or second core layer, comprises an amount of a second active agent which is levodopa, or a pharmaceutically acceptable derivative thereof, and one or

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more excipients.

In some embodiments the tablet formulation is a press-coated tablet, or tablet formulation.

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In some embodiments the tablet formulation is processed through direct compression and/or compression coating.

In some embodiments the tablet formulation of the present disclosure is a Tablet in Tablet dosage form (triple-layer core with outer coating).

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It follows that during the 2 to 10 hours delay of release; no, or essentially no, active agent is released from the core. In some embodiment the delayed release layer delays the release of the two or more active agents for 2 to 10 hours and thereafter the two or more active agents are pulse released from the core. It is understood that it is the delayed release layer that delays the release of the two or more active agents from the core.

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It follows that the pulse release of the two or more active agents starts after the 2 to 10 hours delay of the release of said two or more active agents.

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In some embodiment the delayed release layer is a delayed release barrier layer.

In some embodiment the delayed release layer is an erodible delayed release layer.

In some embodiment the delayed release layer is an erodible delayed release barrier layer. In some embodiments the delayed release layer is an erosion matrix.

5 In some embodiment the delayed release layer surrounding the core is an outer coating layer on the core. In some embodiment the delayed release layer surrounding the core forms a border or edging round the core.

10 In some embodiment the delayed release layer surrounding the core is a layer that covers the core, such as covers all sides of the core, such as covers the top, the bottom and the sides of the core. In some embodiment the delayed release layer fully surrounds the core. In some embodiment the delayed release layer surrounds all edges (or sides) of the core.

15 In preferred embodiments the core is entirely surrounded by the delayed release layer such that the core is not immediately exposed, such as exposed to the dissolution media, or to the gastroenteric environment following oral administration of the tablet formulation to a subject.

20 In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours after (or following) oral administration of the tablet to a subject. In some embodiments the subject is a human subject. In some embodiments the subject is a patient. In some embodiments the subject has Parkinson's Disease.

25 In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours after placing the tablet in an aqueous solution.

30 In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours after placing the tablet in an aqueous solution comprising about 0.1 N HCl at 37°C +/- 0.5°C, optionally in about 500 ml solution at about 50 rpm.

In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours after placing the tablet in an aqueous solution at pH 1.2 HCl at 37°C +/- 0.5°C, optionally in about 500 ml solution at about 50 rpm.

In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours after placing the tablet in an aqueous solution as measured by the USP 2 paddle method at about 50 rpm in about 500 ml of an aqueous solution at 37°C +/- 0.5°C at pH 1.2 HCl and/or comprising about 0.1 N HCl.

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In some embodiments the release of the two or more active agents is delayed for about 2 hours, such as for about 2.5 hours, such as for about 3 hours, such as for about 3.5 hours, such as for about 4 hours, such as for about 4.5 hours, such as for about 5 hours, such as for about 5.5 hours, such as for about 6 hours, such as for about 6.5 hours, such as for about 7 hours, such as for about 7.5 hours, such as for about 8 hours, such as for about 8.5 hours, such as for about 9 hours, such as for about 9.5 hours, such as for about 10 hours.

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In some embodiments the release of the two or more active agents is delayed for 2 to 2.5 hours, such as for 2.5 to 3 hours, such as for 3 to 3.5 hours, such as for 3.5 to 4 hours, such as for 4 to 4.5 hours, such as for 4.5 to 5 hours, such as for 5 to 5.5 hours, such as for 5.5 to 6 hours, such as for 6 to 6.5 hours, such as for 6.5 to 7 hours, such as for 7 to 7.5 hours, such as for 7.5 to 8 hours, such as for 8 to 8.5 hours, such as for 8.5 to 9 hours, such as for 9 to 9.5 hours, such as for 9.5 to 10 hours

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In some embodiments the release of the two or more active agents is delayed for 3 to 10 hours, such as for 3 to 9 hours, such as for 3 to 8 hours, such as for 3 to 7 hours. In some embodiments the release of the two or more active agents is delayed for 2 to 9 hours, such as for 2 to 8 hours, such as for 2 to 7 hours.

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In some embodiments the release of the two or more active agents is delayed for at least about 3 hours, such as at least about 3.5 hours, such as at least about 4 hours.

In some embodiments the release of the two or more active agents is delayed for 3 to 5 hours, such as for 3.5 to 4.5 hours, such as for 4 hours.

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In some embodiments the release of the two or more active agents is delayed for at least about 5 hours, such as at least about 5.5 hours, such as at least about 6 hours.

In some embodiments the release of the two or more active agents is delayed for 5 to 7 hours, such as for 5.5 to 6.5 hours, such as for about 6 hours.

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In some embodiments the delayed release layer comprises or consists of a wax and one or more binders and/or fillers in a ratio that provides for a release that is delayed for 2 to 10 hours, such as 3 to 8 hours, such as 4 to 6 hours. In some embodiments the  
5 delayed release layer comprises or consists of a wax and one or more binders and/or fillers in a ratio that provides for erosion of said delayed release layer to delay release for 2 to 10 hours, such as 3 to 8 hours, such as 4 to 6 hours.

In some embodiments the delayed release layer comprises or consists of a wax and one or more binders and/or fillers in a ratio that provides for a release that is pH  
10 insensitive and insensitive to stirring rate in dissolution experiments. The ratio of wax to binders and/or fillers is provided herein elsewhere ( $>30\%$  to  $<70\%$  w/w wax).

In some embodiments the thickness (the proportion of the final tablet weight) of the delayed release layer provides for a release that is delayed for 2 to 10 hours, such as 3 to 8 hours, such as 4 to 6 hours. The thickness of the delayed release layer is provided  
15 herein elsewhere (50 to 75% w/w of the final tablet weight).

In some embodiments the release of the two or more active agents is delayed for essentially the same period of time for both of said two or more active agents.

20 In some embodiments the two or more active agents are pulse released essentially at the same time.

In some embodiments the release of the first active agent is delayed for a shorter period of time, and the release of the second active agent is delayed for a longer period  
25 of time.

In some embodiments the second active agent is pulse released after the first active agent is pulse released, such as pulse released 10 to 120 minutes after the first active agent is pulse released.  
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In some embodiments the first active agent is pulse released before the second active agent is pulse released, such as pulse released 10 to 120 minutes before the second active agent is pulse released.

In some embodiments the barrier layer delays the start of the pulse release of the second active agent.

5 In some embodiments pulse release of the second active agent starts after the pulse release of the first active agent starts. It is understood that pulse release of the first active agent starts after the 2 to 10 hours delay of release.

10 In some embodiments pulse release of the second active agent starts 10 to 120 minutes after the pulse release of the first active agent starts.

In some embodiments pulse release of the second active agent starts 15 to 90 minutes, such as 15 to 60 minutes, such as 15 to 45 minutes; such as 30 to 60 minutes after the pulse release of the first active agent starts.

15 In some embodiments pulse release of the second active agent starts 10 to 15 minutes, such as 15 to 20 minutes, such as 20 to 25 minutes, such as 25 to 30 minutes, such as 30 to 35 minutes, such as 35 to 40 minutes, such as 40 to 45 minutes, such as 45 to 50 minutes, such as 50 to 55 minutes, such as 55 to 60 minutes, such as 60 to 70 minutes, such as 70 to 80 minutes, such as 80 to 90  
20 minutes, such as 90 to 100 minutes, such as 100 to 110 minutes, such as 110 to 120 minutes after the pulse release of the first active agent starts.

In some embodiments the pulse release of the second active agent is delayed for 10 to 120 minutes after the start of the pulse release of the first active agent.

25 In some embodiments the release of the two or more active agents is delayed for 2 to 10 hours, and the release of the second active agent is delayed 10 to 120 minutes longer than the release of the first active agent.

30 In some embodiments the release of the second active agent is delayed 15 to 90 minutes longer, such as 15 to 60 minutes longer, such as 15 to 45 minutes longer; such as 30 to 60 minutes longer than the release of the first active agent.

35 In some embodiments the release of the second active agent is delayed 10 to 15 minutes longer, such as 15 to 20 minutes longer, such as 20 to 25 minutes longer,

such as 25 to 30 minutes longer, such as 30 to 35 minutes longer, such as 35 to 40 minutes longer, such as 40 to 45 minutes longer, such as 45 to 50 minutes longer, such as 50 to 55 minutes longer, such as 55 to 60 minutes longer, such as 60 to 70 minutes longer, such as 70 to 80 minutes longer, such as 80 to 90 minutes longer, such as 90 to 100 minutes longer, such as 100 to 110 minutes longer, such as 110 to 120 minutes longer than the release of the first active agent.

In some embodiments the barrier layer comprises or consists of a wax and one or more binders and/or fillers in a ratio that enables control of the release of the two or more active agents. The ratio of wax to binders and/or fillers is provided herein elsewhere (>30% to <70% w/w wax).

In some embodiments the thickness (the proportion of the combined weight of the core, or of the final tablet weight) of the barrier layer enables control of the release of the two or more active agents. The thickness of the barrier layer is provided herein elsewhere (25 to 50% w/w of the combined weight of the core).

According to the present disclosure a pulse release is defined as wherein at least 70% by weight of the amount of an active agent is released within 5 to 80 minutes.

The delay of release and the subsequent pulse release occurs after oral administration of the tablet formulation to a subject, and/or after placing the tablet in a aqueous environment, according to the present disclosure.

In some embodiments at least 70% by weight of the amount of the two or more active agents in the first and the second core, or core layer, is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.

In some embodiments at least 80% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.

In some embodiments at least 90% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.

In some embodiments at least 95% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.

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In some embodiments 70-75%, such as 75-80%, such as 80-85%, such as 85-90%, such as 90-95% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.

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In some embodiments at least 70%, at least 80%, at least 90%, or at least 95% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.

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In some embodiments at least 70%, at least 80%, at least 90%, or at least 95% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes, after oral administration to a subject.

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In some embodiments the release of the two or more active agents is measured by the USP 2 paddle method at about 50 rpm in about 500 ml of an aqueous solution at 37°C +/- 0.5°C; at pH 1.2 HCl or in an aqueous solution comprising about 0.1 N HCl.

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In some embodiments at least 70%, at least 80%, at least 90%, or at least 95% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes, as measured by the USP 2 paddle method at about 50 rpm in about 500 ml of an aqueous solution comprising about 0.1 N HCl at 37°C +/- 0.5°C.

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In some embodiments at least 70%, at least 80%, at least 90%, or at least 95% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes as measured by the USP 2 paddle

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method at about 50 rpm in about 500 ml of an aqueous solution at pH 1.2 HCl at 37°C +/- 0.5°C.

*Excipients and ratios – Delayed release layer and Barrier layer*

5 The delayed release layer and the barrier layer of the present disclosure comprises a wax and one or more binders and/or fillers. In a preferred embodiment, the delayed release layer and the barrier layer does not comprise an active agent.

10 A wax according to the present disclosure comprises a lipophilic wax, or lipophilic wax-like solid, and a water-soluble wax, or water-soluble wax-like solid.

In some embodiments the wax is a lipophilic wax. A lipophilic wax may also be known as a lipid-based excipient. A lipophilic wax is a fatty material that consists of a long hydrocarbon chain, with or without a functional group. Common functional groups  
15 found in waxes include alcohol, ketone, aldehyde, and ester. Petroleum-derived waxes are mixtures of long-chain hydrocarbons, but are not esters. In preferred embodiments the wax comprises fatty acids and/or alcohols, such as long-chain fatty acids and/or alcohols (C16-C36). In some embodiments the wax is a wax ester (an ester of a fatty acid and a fatty alcohol).

20 In some embodiments the wax consists of a single wax. In some embodiments the wax is a combination of two or more waxes, such as two waxes, such as three waxes, such as three or more waxes. In some embodiments the wax comprises two or more waxes.

25 In preferred embodiments the delayed release layer and/or the barrier layer comprises more than 30% w/w of a wax (>30% w/w), such as at least 31% w/w of a wax, such as at least 32% w/w of a wax, such as at least 33% w/w of a wax, such as at least 34% w/w of a wax, such as at least 35% w/w of a wax, such as at least 36% w/w of a wax, such as at least 37% w/w of a wax, such as at least 38% w/w of a wax, such as at least  
30 39% w/w of a wax, such as at least 40% w/w of a wax, such as at least 42% w/w of a wax.

In preferred embodiments the delayed release layer and/or the barrier layer comprises less than 70% w/w of a wax (<70% w/w), such as 65% w/w or less of a wax, such as  
35 60% w/w or less of a wax.

In preferred embodiments the delayed release layer and/or the barrier layer comprises >30% to <70% w/w wax. In some embodiments the delayed release layer and/or the barrier layer comprises more than 30% w/w of a wax and less than 70% w/w of a wax.

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In some embodiments the delayed release layer and/or the barrier layer comprises >30% to 32% w/w of a wax, such as 32% to 35% w/w of a wax, such as 35% to 40% w/w of a wax, such as 40% to 42% w/w of a wax, such as 42% to 45% w/w of a wax, such as 45% to 50% w/w of a wax, such as 50% to 60% of a wax, such as 60 to 65% of a wax, such as 65 to 68% of a wax such as 68 to <70% of a wax.

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In some embodiments the delayed release layer and/or the barrier layer comprises >30% to <70% w/w of a wax, such as 32 to 68% w/w of a wax, such as 35 to 65% w/w of a wax, such as 35 to 60% w/w of a wax, such as 40 to 60% w/w of a wax, such as 42 to 50% w/w of a wax, such as about 42% w/w of a wax, such as about 50% w/w of a wax.

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In some embodiments the wax is selected from a glyceryl ester, a petroleum based wax (paraffin wax), a saturated solid triglyceride such as a hydrogenated oil, a long chain saturated carboxylic acid, saturated long chain monoglyceride, a long chain alcohol, a plant wax, an animal wax, montan wax, a PEG with a molecular weight of at least 1000, and any combination of waxes.

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax selected from a glyceryl ester, a petroleum based wax (paraffin wax) such as microcrystalline wax, a saturated solid triglyceride such as a hydrogenated oil such as hydrogenated castor oil and hydrogenated cottonseed oil, a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid (stearic acid, palmitic acid such as palmitic acid 98%, and stearic/palmitic acid), saturated long chain monoglyceride such as glycerol monostearate, a long chain alcohol such as stearyl alcohol, a plant wax such as carnauba wax, candelilla wax, jojoba oil and ouricury wax, an animal wax such as beeswax, spermaceti and lanolin, montan wax, a PEG with a molecular weight of at least 1000, and any combination of waxes.

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is a glyceryl ester. In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof.

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Glyceryl behenate is an ester of behenic acid and glycerol (glyceride). Glyceryl behenate is a mixture of mono-, di- and tri-esters of behenic acid (C22) and glycerol, the diester fraction being predominant.

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In some embodiments the wax is a glyceryl ester. In a particular embodiment the delayed release layer and/or the barrier layer comprises a wax which is a glyceryl behenate; such as a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof; such as a glyceryl behenate comprising a mixture of glyceryl behenate, glyceryl dibehenate and glyceryl tribehenate. In some embodiments said wax consists of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof. In some embodiments said wax consist of 100% w/w of a glyceryl ester such as a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof.

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In some embodiments said wax is a glyceryl ester such as a glyceryl behenate in combination with one or more other waxes or wax-like solids.

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In some embodiments said wax comprises 25 to 75% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof. In some embodiments said wax comprises 25 to 75% w/w of said glyceryl ester and 25 to 75% w/w of one or more other waxes or wax-like solids. In some embodiments said wax comprises about 50% w/w of said glyceryl ester and about 50% w/w of one or more other waxes or wax-like solids.

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is a petroleum based wax, such as microcrystalline wax. In some embodiments the wax consists of a petroleum based wax such as microcrystalline wax.

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In some embodiments the wax is a combination of a glyceryl ester and a petroleum wax. In some embodiments the wax is a combination of a glyceryl ester and a petroleum wax in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

5 In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and microcrystalline wax; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

10 In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is v. In some embodiments the wax consists of a hydrogenated oil.

In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is a hydrogenated oil, such as selected from hydrogenated castor oil and  
15 hydrogenated cottonseed oil. In some embodiments said wax is Kolliwax ®.

In some embodiments the wax is a combination of a glyceryl ester and a hydrogenated oil. In some embodiments the wax is a combination of a glyceryl ester and a hydrogenated oil in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

20 In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and hydrogenated castor oil or hydrogenated cottonseed oil; preferably hydrogenated castor oil; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50  
25 ratio.

In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is a plant wax, such as a plant wax selected from carnauba wax, candelilla wax, jojoba oil and ouricury wax. In some embodiments the wax consists of a plant  
30 wax, such as carnauba wax or candelilla wax.

In some embodiments the wax is a combination of a glyceryl ester and a plant wax. In some embodiments the wax is a combination of a glyceryl ester and a plant wax in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

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In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and carnauba wax or candelilla wax; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is an animal wax, such as an animal wax selected from bees wax, spermaceti and lanolin. In some embodiments the wax consists of an animal wax, such as bees wax.

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In some embodiments the wax is a combination of a glyceryl ester and an animal wax. In some embodiments the wax is a combination of a glyceryl ester and an animal wax in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

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In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and bees wax; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio; in other embodiments in a 95:5 to 50:50 ratio (95-50% w/w glyceryl ester, 50-5% w/w bees wax).

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is montan wax, such as Montan SX Wax. In some embodiments the wax is a combination of a glyceryl ester and montan wax. In some embodiments the wax is a combination of a glyceryl ester and montan wax in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

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In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and montan wax; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio; in other embodiments in a 95:5 to 50:50 ratio (95-50% w/w glyceryl ester, 50-5% w/w montan wax).

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is a long chain saturated carboxylic acid. A long chain saturated carboxylic

acid is a fatty acids with 14 or more carbon atoms (>C12), with no double bonds. In some embodiments the wax consists of a long chain saturated carboxylic acid.

5 In some embodiments said wax comprises a long chain saturated carboxylic acid selected from stearic acid (C18:0), palmitic acid (C16:0), and stearic/palmitic acid (C16/C18). In some embodiments said wax comprises palmitic acid, such as palmitic acid 98%. In some embodiments said wax comprises Kolliwax S.

10 In some embodiments the wax is a combination of a glyceryl ester and a long chain saturated carboxylic acid. In some embodiments the wax is a combination of a glyceryl ester and a long chain saturated carboxylic acid in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

15 In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and a long chain saturated carboxylic acid selected from stearic acid, palmitic acid and stearic/palmitic acid; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

20 In some embodiments the delayed release layer and/or the barrier layer comprises a wax which is a saturated long chain (>C12) monoglyceride. In some embodiments said saturated long chain monoglyceride is glycerol monostearate. In some embodiments said wax comprises Kolliwax GMS II. In some embodiments the wax consists of a saturated long chain monoglyceride.

25 In some embodiments the wax is a combination of a glyceryl ester and a saturated long chain monoglyceride. In some embodiments the wax is a combination of a glyceryl ester and a saturated long chain monoglyceride in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

30 In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and a saturated long chain monoglyceride which is glycerol monostearate; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio; in other  
35 embodiments in a 95:5 to 50:50 ratio.

In some embodiments the delayed release layer comprises a wax which is a long chain alcohol. In some embodiments said long chain alcohol is stearyl alcohol. In some  
embodiments said wax comprises Kolliwax SA. In some embodiments the wax consists  
5 of a long chain alcohol. In some embodiments the barrier layer does not comprise a  
wax comprising or consisting of a long chain alcohol, such as stearyl alcohol.

In some embodiments the wax is a combination of a glyceryl ester and a long chain  
alcohol. In some embodiments the wax is a combination of a glyceryl ester and a long  
10 chain alcohol in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

In some embodiments the wax is a combination of a glyceryl ester selected from  
glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof,  
and a long chain alcohol which is stearyl alcohol; in some embodiments in a 25:75 to a  
15 75:25 ratio, such as about a 50:50 ratio.

In some embodiments the delayed release layer and/or the barrier layer comprises a  
water soluble wax. Water soluble wax, Carbowax and polyethylene glycol (PEG) are  
terms used to describe the same material. Pharmaceutical-grade PEG is used as  
20 an excipient in many pharmaceutical products. PEGs are prepared by  
polymerization of ethylene oxide molecules to make joining units of ethylene glycol by  
an ether linkage, and are commercially available over a wide range of molecular  
weights (Mw). PEGs differ in their physical and chemical properties depending on their  
molecular weight: PEGs are liquids when molecular weights are <1000 and the  
25 molecule turns to waxy solids with increasing molecular weights. Pharmaceutical-grade  
PEG usually has a molecular weight of 20,000 or less. The molecular weight of a PEG  
is an average or mean molecular weight.

In some embodiments said wax is a PEG. In some embodiments said wax consists of a  
30 PEG (100% w/w). In some embodiments said wax comprises a PEG. In some  
embodiments said wax comprises or consist of a PEG with a molecular weight of at  
least 1000 (PEG1000), such as a PEG with a molecular weight of at least 1,450  
(PEG1450), such as a PEG with a molecular weight of at least 1,500 (PEG1500), such  
as a PEG with a molecular weight of at least 3,000 (PEG3000).

35

In some embodiments said PEG has molecular weight of 1000 to 20,000, such as 1,450 to 20,000, such as 3,000 to 20,000. In some embodiments said PEG has a molecular weight of 1000 to 100,000, such as 1,450 to 75,000, such as 3,000 to 50,000. In some embodiments said PEG has a molecular weight of 1,000 to 20,000, such as 1,450 to 20,000, such as 3,000 to 20,000.

In some embodiments said PEG has a molecular weight of 1000 to 1,450, such as 1,450 to 3,000, such as 3,000 to 5,000, such as 5,000 to 7,500, such as 7,500 to 10,000, such as 10,000 to 15,000, such as 15,000 to 20,000, such as 20,000 to 25,000, such as 25,000 to 50,000, such as 50,000 to 75,000, such as 75,000 to 100,000.

In some embodiments said PEG has a molecular weight of about 3,000 (PEG3000). In some embodiments said PEG has a molecular weight of about 20,000 (PEG20,000).

In some embodiments said wax is a combination of a glyceryl ester and a water soluble wax such as a PEG with a molecular weight of at least 1000. In some embodiments the wax is a combination of a glyceryl ester and said PEG in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

In some embodiments the wax is a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and a PEG of the present disclosure; in some embodiments a PEG with a molecular weight of at least 1000, at least 1,450, at least 3,000, such as a PEG with a molecular weight of 1,450 to 20,000 or 3,000 to 20,000; in some embodiments in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

In some embodiments there is provided a tablet formulation for oral administration of two or more active agents, such as two active agents, the tablet comprising:

- i) A core, such as a triple-layer core, comprising or consisting of
  - a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug,



- b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
- 5 c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer comprising or consisting of more than 30% w/w and less than 70% w/w of a wax, and one or more binders,
- 10 wherein said wax is selected from a glyceryl ester such as selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; a petroleum based wax such as microcrystalline wax, a saturated solid triglyceride such as a hydrogenated oil such as hydrogenated castor oil and hydrogenated cottonseed oil, a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid, a
- 15 saturated long chain monoglyceride such as glycerol monostearate, a plant wax such as carnauba wax, candelilla wax, jojoba oil and ouricury wax, an animal wax such as beeswax, spermaceti and lanolin, a PEG having a molecular weight of at least 1000, and any combination of said waxes,
- 20 and
- ii) A delayed release layer surrounding the core, said delayed release layer comprising or consisting of more than 30% w/w and less than 70% w/w of a wax, and one or more binders and/or fillers,
- 25 wherein said wax is selected from a glyceryl ester such as selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; a petroleum based wax such as microcrystalline wax, a saturated solid triglyceride such as a hydrogenated oil such as hydrogenated castor oil and hydrogenated cottonseed oil, a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid, a
- 30 saturated long chain monoglyceride such as glycerol monostearate, a long chain alcohol such as stearyl alcohol, a plant wax such as carnauba wax, candelilla wax, jojoba oil and ouricury wax, an animal wax such as beeswax, spermaceti and lanolin, montan wax, a PEG having a molecular weight of at least 1000, and any combination of said
- 35 waxes,

wherein the release of the two or more active agents is delayed for 2 to 10 hours and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

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#### Binders and fillers

The delayed release layer and the barrier layer according to the present disclosure comprises or consist of a wax and one or more binders and/or fillers.

10 In some embodiments the delayed release layer and the barrier layer comprises or consist of a wax and one or more binders. In a preferred embodiment the barrier layer comprises or consist of a wax and one or more binders. In some embodiments the delayed release layer and the barrier layer comprises a wax and two or more binders, such as two binders, such as three binders, such as three or more binders.

15 In some embodiments the delayed release layer and the barrier layer comprises or consist of a wax, one or more binders and one or more fillers. In some embodiments the delayed release layer and the barrier layer comprises a wax, a binder and a filler.

20 In some embodiments the delayed release layer and the barrier layer comprises or consist of a wax and one or more binders selected from L-HPC, HPC, isomalt, microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC), cellulose, methylcellulose, polymethacrylates, sodium carboxymethyl cellulose (sodium CMC), polyvinyl pyrrolidone (PVP), starch, pregelatinized starch, sodium alginate and gelatin.

25 In some embodiments the delayed release layer comprises or consist of a wax and one or more binders selected from L-HPC, HPC, isomalt, MCC, starch and pregelatinized starch.

In some embodiments the delayed release layer comprises a wax and two L-HPC and a HPC. In some embodiments the delayed release layer comprises a wax and  
30 pregelatinized starch. In some embodiments the delayed release layer comprises a wax and starch. In some embodiments the delayed release layer comprises a wax and isomalt. In some embodiments the delayed release layer comprises a wax and isomalt and MCC.

In some embodiments the barrier layer comprises or consist of a wax and one or more binders selected from L-HPC, HPC, isomalt, MCC, and pregelatinized starch.

In some embodiments the barrier layer comprises a wax and two L-HPC and a HPC.

In some embodiments the barrier layer comprises a wax and pregelatinized starch.

5 In some embodiments the barrier layer comprises a wax and isomalt.

In some embodiments the barrier layer comprises a wax and isomalt and MCC.

In preferred embodiments the binder is a dry binder. A dry binder can be added to a powder is a dry powder which is mixed with the other ingredients before compaction.

10 Notable dry binders are microcrystalline cellulose and (MCC) and polyvinyl pyrrolidone (PVP).

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more fillers.

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In some embodiments the delayed release layer comprises a wax, one or more binders and one or more fillers.

In some embodiments the delayed release layer and the barrier layer comprises a wax and one or more water-soluble fillers and/or water-insoluble fillers.

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In some embodiments the delayed release layer and the barrier layer comprises a wax and one or more fillers selected from mannitol, sorbitol, xylitol, lactose, sucrose, cellulose, glucose, calcium carbonate, calcium phosphate and calcium hydrogen phosphate dihydrate.

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In preferred embodiments the barrier layer comprises or consists of a wax and one or more binders, and no fillers. In some embodiments the barrier layer consists of a wax and one or more binders. In some embodiments the barrier layer does not comprise any fillers, such as does not comprise a filler selected from mannitol, sorbitol and lactose.

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In some embodiments the delayed release layer comprises a wax and one or more water-soluble fillers, such as a water-soluble filler selected from mannitol, sorbitol and lactose. In some embodiments the delayed release layer comprises a wax and one or

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more water-soluble fillers selected from mannitol, sorbitol and lactose. In some embodiments the delayed release layer comprises a wax, one or more binders, and one or more water-soluble fillers selected from mannitol, sorbitol and lactose.

5 In some embodiments the wax and the one or more binders and/or fillers are provided in a weight ratio of wax to binder and/or filler of 35:65 to 65:35 w/w, such as 40:60 to 60:40 w/w, such as 45:55 to 55:45 w/w, such as about 50:50 w/w, such as about 42:58 w/w. In some embodiments the wax and the one or more binders and/or fillers are provided in a weight ratio of wax to binder and/or fillers of about 40:60 to 55:45 w/w.

10 In some embodiments the wax and the one or more binders and/or fillers are provided in a weight ratio of wax to binder and/or fillers of about 40:60 w/w, such as about 41:59, such as about 42:58, such as about 43:57, such as about 44:56, such as about 45:55, such as about 46:54, such as about 47:53, such as about 48:52, such as about 49:51, 15 such as about 50:50, such as of about 51:49, about 52:48, about 53:47, about 54:46, about 55:45 w/w.

In some embodiments the delayed release layer comprises or consist of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% 20 w/w of one or more binders and/or fillers. In some embodiments the delayed release layer consist of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of one or more binders and/or fillers, wherein the wax and the one or more binders/fillers together make up 100% w/w of the delayed release layer.

25 In some embodiments the barrier layer comprises or consist of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of one or more binders. In some embodiments the barrier layer consist of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of 30 one or more binders, wherein the wax and the one or more binders together make up 100% w/w of the barrier layer.

In some embodiments there is provided a tablet formulation for oral administration of two or more active agents, such as two active agents, the tablet comprising:

35 i) A core, such as a triple-layer core, comprising or consisting of

- 5           a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug,
- b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
- 10           c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer consisting of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of one or more binders, and
- 15           ii) A delayed release layer surrounding the core, said delayed release layer consisting of more than 30% w/w and less than 70% w/w of a wax, and comprises more than 30% w/w and less than 70% w/w of one or more binders and/or fillers,
- 20           wherein the release of the two or more active agents is delayed for 2 to 10 hours and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

25           In some embodiments there is provided a tablet formulation for oral administration of two or more active agents, such as two active agents, the tablet comprising:

- i) A core, such as a triple-layer core, comprising or consisting of
- a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug,
- 30           b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
- 35           precursor and a dopamine prodrug, and

- c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer consisting of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of one or more binders,
- 5 wherein said wax is selected from a glyceryl ester such as a glyceryl behenate, a petroleum based wax such as microcrystalline wax, a saturated solid triglyceride such as a hydrogenated oil such as hydrogenated castor oil and hydrogenated cottonseed oil, a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid, a
- 10 saturated long chain monoglyceride such as glycerol monostearate, a plant wax such as carnauba wax, candelilla wax, jojoba oil and ouricury wax, an animal wax such as beeswax, spermaceti and lanolin, a PEG having a molecular weight of at least 1000, and any combination of said waxes,
- 15 wherein said binder is selected from L-HPC, HPC, isomalt, MCC, HPMC, cellulose, Methylcellulose, Polymethacrylates, sodium CMC, PVP, starch, pregelatinized starch, sodium alginate and gelatin; such as selected from L-HPC, HPC, isomalt, MCC, and pregelatinized starch, and
- 20 ii) A delayed release layer surrounding the core, said delayed release layer consisting of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of one or more binders and/or fillers,
- 25 wherein said wax is selected from a glyceryl ester such as a glyceryl behenate, a petroleum based wax such as microcrystalline wax, a saturated solid triglyceride such as a hydrogenated oil such as hydrogenated castor oil and hydrogenated cottonseed oil, a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid, a saturated long chain monoglyceride such as glycerol monostearate, a long chain alcohol such as stearyl alcohol, a plant wax such as
- 30 carnauba wax, candelilla wax, jojoba oil and ouricury wax, an animal wax such as beeswax, spermaceti and lanolin, montan wax, a PEG having a molecular weight of at least 1000, and any combination of said waxes,
- 35 wherein said binder is selected from L-HPC, HPC, isomalt, MCC, HPMC, cellulose, Methylcellulose, Polymethacrylates, sodium CMC,

PVP, starch, pregelatinized starch, sodium alginate and gelatin; such as selected from L-HPC, HPC, isomalt, MCC, starch and pregelatinized starch,  
wherein said filler is selected from mannitol, sorbitol, xylitol, lactose,  
5 sucrose, cellulose, glucose, calcium carbonate, calcium phosphate and calcium hydrogen phosphate dihydrate, such as wherein said filler is a water-soluble filler, such as wherein said filler is selected from mannitol, sorbitol and lactose,  
wherein the release of the two or more active agents is delayed for 2 to 10 hours  
10 and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

Low-substituted hydroxypropyl cellulose (L-HPC)

15 In some embodiments the delayed release layer and the barrier layer comprises a wax and one or more binders, wherein said one or more binder is L-HPC.

In some embodiments the delayed release layer of the present disclosure surrounding the core comprises a wax and one or more L-HPC. In some embodiments the delayed  
20 release layer comprises a wax and two L-HPC.

In some embodiments the barrier layer interposed between the first and the second core, or first and second core layers, comprises a wax and one or more L-HPC. In some embodiments the barrier layer comprises a wax and two L-HPC.

25 In some embodiments the wax and the one or more, such as two, L-HPC in the delayed release layer and/or in the barrier layer are provided in a weight ratio of wax to L-HPC of 30:70 to 70:30 w/w, such as of 35:65 to 65:35 w/w, such as of 40:60 to 60:40 w/w, such as of 45:55 to 55:45 w/w;  
30 such as a weight ratio of wax to L-HPC of about 35:65 to 55:45 w/w; such as of about 40:60 to 50:50 w/w; such as of about 60:40 to 50:50 w/w;  
such as a weight ratio of wax to L-HPC of about 30:70; such as of about 35:65, such as of about 40:60, such as of about 41:59 w/w, such as of about 42:58 w/w, such as of about 43:57 w/w, such as of about 44:56 w/w, such as of about 45:55 w/w, such as of

about 46:54 w/w, such as of about 47:53 w/w, such as of about 48:52 w/w, such as of about 49:51 w/w, such as of about 50:50 w/w.

5 In some embodiments the delayed release layer and/or the barrier layer comprises 30 to 70% w/w of one or more L-HPC, such as of two L-HPC, such as 35 to 65% w/w, such as 40 to 60% w/w, such as 45 to 60% w/w, such as 45 to 55% w/w, such as 42 to 62% w/w, such as 47 to 57% w/w, such as about 52% w/w.

10 In some embodiments the one or more L-HPC has a hydroxypropyl content of about 11% (10.0-12.9%) and a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-21.

15 It is understood that reference to a L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), is a L-HPC with a hydroxypropyl content of about 11 **weight%** or 11% by weight (10.0-12.9 **weight%** or % by weight). This applies equally to any other L-HPC % hydroxypropyl content (i.e. weight%) as referred to herein throughout.

20 In some embodiments the one or more L-HPC has a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-32.

25 In some embodiments the one or more L-HPC has a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 130,000, and optionally a mean particle size of 55  $\mu\text{m}$  (45-65  $\mu\text{m}$ );, such as wherein said one or more L-HPC is LH-11.

In some embodiments the one or more L-HPC has a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 135,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-22.

30 In some embodiments the one or more L-HPC has a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 140,000, and optionally a mean particle size of 55  $\mu\text{m}$  (45-65  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-B1



In some embodiments the one or more L-HPC has a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 100,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-31.

- 5 In some embodiments the one or more L-HPC has a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 14% (13-15.9%); such as wherein said one or more L-HPC is NBD-020.

- 10 In some embodiments the one or more L-HPC has a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 11% (10-12.9%); such as wherein said one or more L-HPC is NBD-021.

- 15 In some embodiments the one or more L-HPC has a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 8% (7-9.9%); such as wherein said one or more L-HPC is NBD-022.

In some embodiments the one or more L-HPC is selected from LH-11, LH-21, LH-22, LH-B1, LH-31, LH-32, NBD-022, NBD-021 and NBD-020.

- 20 In a particular embodiment the one or more L-HPC has a hydroxypropyl content of about 11% (10.0-12.9%) and a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ). In a particular embodiment said one or more L-HPC is LH-21.

- 25 In a particular embodiment the one or more L-HPC has a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ). In a particular embodiment said one or more L-HPC is LH-32.

- 30 In some embodiments the delayed release layer and/or the barrier layer comprises a wax and two or more L-HPC, such as comprises a wax and two L-HPC.  
In some embodiments the delayed release layer and/or the barrier layer comprises a wax and two or more grades of L-HPC, such as comprises a wax and two grades of L-HPC.

In particular embodiments the delayed release layer and the barrier layer comprises a wax and two L-HPC. In some embodiments the two or more L-HPC in the delayed release layer and/or the barrier layer are individually selected from:

- 5 a. an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-21;
- 10 b. an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-32;
- 15 c. an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 130,000, and optionally a mean particle size of 55  $\mu\text{m}$  (45-65  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-11;
- 20 d. an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 135,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-22;
- 25 e. an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 140,000, and optionally a mean particle size of 55  $\mu\text{m}$  (45-65  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-B1;
- 30 f. an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 100,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-31;
- 35 g. an L-HPC with a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 14% (13-15.9%); such as wherein said one or more L-HPC is NBD-020;
- h. an L-HPC with a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 11% (10-12.9%); such as wherein said one or more L-HPC is NBD-021; and

- i. an L-HPC with L-HPC has a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 8% (7-9.9%); such as wherein said one or more L-HPC is NBD-022.

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In some embodiments the two or more grades of L-HPC include a coarse particle L-HPC and a medium particle L-HPC; such as a coarse particle L-HPC and a medium particle L-HPC selected from any one of the following combinations: LH-11 and LH-21, LH-11 and LH-22, LH-11 and NBD-022, LH-11 and NBD-021, LH-11 and NBD-020, LH-B1 and LH-21, LH-B1 and LH-22, LH-B1 and NBD-022, LH-B1 and NBD-021, and LH-B1 and NBD-020.

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In some embodiments the two or more grades of L-HPC include a coarse particle L-HPC and a micronized particle L-HPC; such as a coarse particle L-HPC and a micronized particle L-HPC selected from any one of the following combinations: LH-11 and LH-31, LH-11 and LH-32, LH-B1 and LH-31, LH-B1 and LH-32, NBD-021 and LH-32, NBD-020 and LH-32, LH-11 and LH-32, LH-21 and LH-32, LH-31 and LH-32, and LH-B1 and LH-32.

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In some embodiments the two or more grades of L-HPC include a medium particle L-HPC and a micronized particle L-HPC; such as a medium particle L-HPC and a micronized particle L-HPC selected from any one of the following combinations: LH-21 and LH-31, LH-22 and LH-31, NBD-022 and LH-31, NBD-021 and LH-31, NBD-020 and LH-31, LH-21 and LH-32, LH-22 and LH-32, NBD-022 and LH-32, NBD-021 and LH-32, and NBD-020 and LH-32.

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In some embodiments the two or more grades of L-HPC include a low level hydroxypropyl content L-HPC and a high level hydroxypropyl content L-HPC; such as a low level and a high level hydroxypropyl content L-HPC selected from any one of the following combinations: NBD-021 and NBD-022, NBD-020 and NBD-022, LH-11 and NBD-022, LH-21 and NBD-022, LH-31 and NBD-022, LH-B1 and NBD-022, NBD-021 and LH-22, NBD-020 and LH-22, LH-11 and LH-22, LH-21 and LH-22, LH-31 and LH-22, LH-B1 and LH-22.

In some embodiments the two or more grades of L-HPC include a low and a high level hydroxypropyl content L-HPC that are also a combination of a coarse and medium particle L-HPC; such as selected from any one of the following combinations: LH-11 and LH-22, LH11 and NBD-022, LH-B1 and LH-22, and LH-B1 and NBD-022.

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In some embodiments the two or more grades of L-HPC include a low and a high level hydroxypropyl content L-HPC that are also a combination of a medium and micronised particle L-HPC; such as selected from any one of the following combinations: LH-22 and LH-31, NBD-022 and LH-31, LH-21 and LH-32, NBD-021 and LH-32, and NBD-020 and LH 32.

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In a particular embodiments the two or more L-HPC are LH-21 and L-HPC LH-32.

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In a particular embodiment the two or more L-HPC are an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45 um (35-55 um); and an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20 um (17-23 um).

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In a particular embodiment the barrier layer comprises or consists of a wax and one or more L-HPC such as two L-HPC.

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In some embodiments the barrier layer comprises *i)* an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000 and optionally a mean particle size of 45 um (35-55 um); such as wherein said one or more L-HPC is LH-21; and *ii)* an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20 um (17-23 um); such as wherein said one or more L-HPC is LH-32; and wherein the *i)* L-HPC and the *ii)* L-HPC in the barrier layer is provided in a weight ratio of *i)* L-HPC to *ii)* L-HPC of 20:80 to 80:20 w/w, such as of 25:75 to 75:25 w/w, such as of 30:70 to 70:30 w/w, such as of 35:65 to 65:35 w/w, such as of 40:60 to 60:40 w/w; such as a weight ratio of *i)* L-HPC to *ii)* L-HPC about 25:75 to 45:55 w/w; such as of about 30:70 to 40:60 w/w;

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such as a weight ratio of *i)* L-HPC to *ii)* L-HPC of about 30:70, such as of about 31:69, such as of about 32:68 w/w, such as of about 33:67 w/w, such as of about 34:66 w/w, such as of about 35:65 w/w, such as of about 36:64 w/w, such as of about 37:63 w/w, such as of about 38:62 w/w, such as of about 39:61 w/w, such as of about 40:60 w/w.

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In a particular embodiments the delayed release layer comprises or consists of a wax and one or more L-HPC such as two L-HPC.

10 In some embodiments the delayed release layer comprises *i)* an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu$ m (35-55  $\mu$ m); such as wherein said one or more L-HPC is LH-21; and *ii)* an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu$ m (17-23  $\mu$ m); such as wherein said one or more L-HPC is

15 LH-32;

and wherein the *i)* L-HPC and the *ii)* L-HPC in the delayed release layer is provided in a weight ratio of *i)* L-HPC to *ii)* L-HPC of 30:70 to 70:30 w/w, such as of 35:65 to 65:35 w/w, such as of 40:60 to 60:40 w/w, such as of 45:55 to 55:45 w/w; such as a weight ratio of *i)* L-HPC to *ii)* L-HPC about 35:65 to 55:45 w/w; such as of

20 about 40:60 to 50:50 w/w; such as of about 40:60 to 50:50 w/w; such as a weight ratio of *i)* L-HPC to *ii)* L-HPC of about 35:65, such as of about 40:60, such as of about 41:59 w/w, such as of about 42:58 w/w, such as of about 43:57 w/w, such as of about 44:56 w/w, such as of about 45:55 w/w, such as of about 50:50 w/w.

25 Hydroxypropyl cellulose (HPC)

In some embodiments the delayed release layer and/or the barrier layer further comprises a HPC.

30 In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more binders, wherein said binder is HPC.

In some embodiments the delayed release layer and/or the barrier layer comprises or consists of a wax, one or more L-HPC such as two L-HPC, and a HPC.

In some embodiments the HPC has a viscosity of 2.0 to 50 mPa·s (at 20°C/2% aq. solution).

5 It is understood that reference to HPC with a viscosity of 2.0 to 50 mPa·s at 20°C/2% aq. solution, is HPC with a viscosity of 2.0 to 50 mPa·s at 20°C/2% **w/w** aq. solution, i.e. *weight/weight*, which in an aqueous solution is very similar to *weight/volume* (w/V). This applies equally to any other HPC viscosity (i.e. % **w/w** aq. solution) as referred to herein.

10 In some embodiments the delayed release layer and/or the barrier layer comprises a wax, one or more L-HPC such as two L-HPC, and a HPC with a viscosity of 2.0 to 50 mPa·s (at 20°C/2% aq. solution).

15 In some embodiments the delayed release layer and/or the barrier layer comprises a wax, one or more L-HPC such as two L-HPC, and a HPC, wherein the wax and the HPC are provided in a weight ratio of wax to HPC of 80:20 to 95:5 w/w; such as of 85:15 to 90:10 w/w; such as of about 85:15 w/w, such as of about 86:14 w/w, such as of about 87:13 w/w, such as of about 87.5:12.5 w/w, such as of about 88:12 w/w, such as of about 89:11 w/w, such as of about 90:10 w/w.

20 In some embodiments the delayed release layer and/or the barrier layer comprises a wax, one or more L-HPC such as two L-HPC, and a HPC, wherein the one or more L-HPC and the HPC are provided in a weight ratio of L-HPC to HPC of 80:20 to 95:5 w/w; such as of 85:15 to 90:10 w/w; such as of 85:15 to 95:15 w/w; such as of about 85:15 w/w, such as of about 86:14 w/w, such as of about 87:13 w/w, such as of about 88:12 w/w, such as of about 89:11 w/w, such as of about 90:10 w/w, such as of about 91:9 w/w, such as of about 92:8 w/w, such as of about 93:7 w/w, such as of about 94:6 w/w, such as of about 95:5 w/w.

30 In some embodiments the HPC of the present disclosure has a viscosity of 2.0 to 2.9 mPa·s (HPC-SSL); such as a viscosity of 3.0 to 5.9 mPa·s (HPC-SL); such as a viscosity of 6.0 to 10.0 mPa·s (HPC-L); such as a viscosity of 11 to 20 mPa·s (HPC-LM); such as a viscosity of 21 to 50 mPa·s (HPC-LMM) (at 20°C/2% aq. Solution).

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In a particular embodiment the HPC has a viscosity of 6.0 to 10.0 mPa·s (HPC-L).

In some embodiments the HPC has a molecular weight of 40,000 – 280,000; such as a molecular weight of about 40,000, such as of about 100,000, such as of about 140,000, such as of about 280,000, such as of about 180,000.

5

In a particular embodiment the HPC has a molecular weight of about 140,000.

In some embodiments the HPC has a viscosity of 2.0 to 50 mPa·s (at 20°C/2% aq. solution) and a molecular weight of 40,000 – 280,000.

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In some embodiments the HPC has a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution) and a molecular weight of about 140,000.

In some embodiments the HPC has a viscosity of 150 to 300 mPa·s (at 20°C/2% aq. solution) and a molecular weight of about 40,000.

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In some embodiments the HPC has a viscosity of 300 to 600 mPa·s (at 20°C/2% aq. solution) and a molecular weight of about 80,000.

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In some embodiments the HPC has a viscosity of 1,500 to 3,000 mPa·s (at 20°C/2% aq. solution) and a molecular weight of about 1,150,000.

In some embodiments the HPC is a HPC regular powder (40 mesh pass, D50 = 150-190 micrometres).

25

In some embodiments the HPC is a HPC fine powder (100 mesh pass, D50 = 80-110 micrometres) (HPC FP).

In some embodiments the delayed HPC is a HPC super fine powder (330 mesh pass, D50 = 20 micrometres).

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In preferred embodiments the HPC is a HPC fine powder (100 mesh pass, D50 = 80-110 micrometres), or HPC super fine powder (330 mesh pass, D50 = 20 micrometres).

In more preferred embodiments HPC is a HPC fine powder (100 mesh pass, D50 = 80-110 micrometres).

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In some embodiments the HPC has a viscosity of 2.0 to 50 mPa·s (at 20°C/2% aq. solution), a molecular weight of 40,000 – 280,000 and is a HPC fine powder (100 mesh pass, D50 = 80-110 micrometres).

5

In some embodiments the HPC with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution) and with a molecular weight of about 140,000 which is HPC fine powder (100 mesh pass, D50 = 80-110 micrometres).

10 In preferred embodiments the HPC is a fine powder HPC (100 mesh pass, D50 = 80-110 micrometres) with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution).

In some embodiments the delayed release layer and/or the barrier layer comprises 2 to 10% w/w HPC, such as 3 to 9% w/w HPC, such as 4 to 8% w/w HPC, such as 5 to 7% w/w HPC, such as about 6% w/w HPC.

15

In some embodiments the delayed release layer and/or the barrier layer comprises 2 to 3% w/w HPC, such as 3 to 4% w/w HPC, such as 4 to 5% w/w HPC, such as 5 to 6% w/w HPC, such as 6 to 7% w/w HPC, such as 7 to 8% w/w HPC, such as 8 to 9% w/w HPC, such as 9 to 10% w/w HPC.

20

In some embodiments the delayed release layer and/or the barrier layer comprises or consists of 35 to 65% w/w wax, 30 to 70% w/w L-HPC, and 2 to 10% w/w HPC.

25 In some embodiments the delayed release layer and/or the barrier layer comprises or consists of

- 35 to 65% w/w of a wax, such as 35 to 65% w/w of a wax, such as 35 to 60% w/w of a wax, such as 40 to 60% w/w of a wax, such as 42 to 50% w/w of a wax, such as about 42% w/w of a wax, such as about 50% w/w of a wax, and
- 30 to 70% w/w of one or more L-HPC, such as of two L-HPC, such as 35 to 65% w/w, such as 40 to 60% w/w, such as 45 to 60% w/w, such as 45 to 55% w/w, such as 42 to 62% w/w, such as 47 to 57% w/w, such as about 52% w/w, and

30



- 1 to 15 % w/w of a HPC, such as 1 to 10% w/w, such as 2 to 10% w/w, such as 3 to 9% w/w HPC, such as 4 to 8% w/w HPC, such as 5 to 7% w/w HPC, such as about 6% w/w HPC.

5 In some embodiments the composition of the barrier layer and the delayed release layer is the same.

In some embodiments the composition of the barrier layer and the delayed release layer are different. In some embodiments the barrier layer does not comprise a HPC. In  
10 some embodiments the delayed release layer comprises a HPC and the barrier layer does not comprise a HPC.

In some embodiments the delayed release layer and/or the barrier layer comprises 32-  
15 52% w/w of wax, 42-62% w/w of one or more L-HPC such as two L-HPC, and 1-15% w/w HPC;  
such as comprises 38-46% w/w of wax, 48-56% w/w of one or more L-HPC such as two L-HPC, and 2-10% w/w HPC;  
such as comprises 38-40, 40-41, 41-42, 42-43, 43-44, 44-46% w/w of wax, 48-50, 50-  
51, 51-52, 52-53, 53-54, 54-56% w/w of one or more L-HPC such as two L-HPC, and  
20 2-4, 4-5, 5-6, 6-7, 7-8, 8-10% w/w HPC.

In some embodiments the delayed release layer and/or barrier layer comprises 32-52% w/w of wax, 42-62% w/w of one or more L-HPC such as two L-HPC, and 1-15% w/w HPC;  
25 such as comprises 38-46% w/w of wax, 48-56% w/w of one or more L-HPC such as two L-HPC, and 2-10% w/w HPC;  
wherein said wax is selected from  
100% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; or  
30 100% w/w of a wax selected from a petroleum based wax such as microcrystalline wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid

such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol;

or

wherein said wax consist of 25-75% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and 25-75% w/w of a wax selected from a petroleum based wax such as microcrystalline wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol;

or

about 50% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and about 50% w/w of a wax selected from a petroleum based wax such as microcrystalline wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol.

In some embodiments the delayed release layer and/or the barrier layer comprises about 42% w/w of wax, about 52% w/w of one or more L-HPC such as two L-HPC, and about 6% w/w HPC.

In some embodiments the delayed release layer and/or the barrier layer comprises 38-46% w/w of a wax, such as about 42% w/w, wherein said wax is selected from 100% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; or 100% w/w of a wax selected from a petroleum based wax such as microcrystalline wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid

such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol;

or

- 5 wherein said wax consist of 25-75% w/w, such as about 50% w/w, of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and 25-75% w/w, such as about 50% w/w, of a wax selected from a petroleum based wax such as microcrystalline wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a
- 10 molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol; and
- 15 18-26% w/w, such as about 22% w/w, of an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); and
- 26-34% w/w, such as about 30% w/w, of an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); and
- 20 2-10% w/w, such as about 6% w/w, of a fine powder HPC (100 mesh pass, D50 = 80-110 micrometres) with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution).

- In some embodiments the delayed release layer and/or the barrier layer comprises
- 25 38-46% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof;
- 18-26% w/w of an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ );
- 26-34% w/w of an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a
- 30 molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); and
- 2-10% w/w of a fine powder HPC (100 mesh pass, D50 = 80-110 micrometres) with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution).

In some embodiments the delayed release layer and/or the barrier layer comprises 38-40, 40-42, 42-43, 43-44, 44-46% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; 18-20, 20-22, 22-23, 23-24, 24-26% w/w of an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ );  
26-28, 28-30, 30-31, 31-32, 32-34% w/w of an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); and  
2-4, 4-5, 5-6, 6-7, 7-8, 8-10% w/w of a fine powder HPC (100 mesh pass, D50 = 80-110 micrometres) with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution).

In some embodiments the delayed release layer and/or the barrier layer comprises about 42% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof;  
about 22% w/w of an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ );  
about 30% w/w of an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); and  
about 6% w/w of a fine powder HPC (100 mesh pass, D50 = 80-110 micrometres) with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution).

In some embodiments the barrier layer does not comprise a HPC, such as does not comprise a HPC with a viscosity of 2.0 to 50.0 mPa·s (at 20°C/2% aq. solution).

In some embodiments the barrier layer comprises or consists of 32-52% w/w of wax and 48-68% w/w of one or more L-HPC, such as two L-HPC;  
such as comprises or consists of 38-46% w/w of wax and 44-52% w/w of one or more L-HPC, such as two L-HPC;  
such as comprises or consists of 38-40, 40-41, 41-42, 42-43, 43-44, 44-46% w/w of wax and 44-46, 46-48, 48-50, 50-52% w/w of one or more L-HPC, such as two L-HPC.

In some embodiments the barrier layer comprises or consists of about 42% w/w of wax and about 58% w/w of one or more L-HPC, such as two L-HPC.

5 In some embodiments the barrier layer comprises or consists of 38-46% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof;  
16-24% w/w of an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45 um (35-55 um); and  
10 34-42% w/w of an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20 um (17-23 um).

15 In some embodiments the barrier layer comprises or consists of 38-40, 40-42, 42-43, 43-44, 44-46% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof;  
16-18, 18-20, 20-22, 22-23, 23-24% w/w of an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45 um (35-55 um); and  
20 34-36, 36-38, 38-40, 40-42% w/w of an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20 um (17-23 um).

25 In some embodiments the barrier layer comprises about 42% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof;  
about 19.5% w/w of an L-HPC with a hydroxypropyl content of about 11% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45 um (35-55 um), and  
30 about 38.5% w/w an L-HPC with a hydroxypropyl content of about 8% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20 um (17-23 um).

Other binders

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more binders, such as selected from L-HPC, HPC, isomalt, MCC, starch and pregelatinized starch.

5

In some embodiments the delayed release layer and the barrier layer comprises a wax and two or more binders, such as two binders, wherein said two or more binders are selected from from L-HPC, HPC, isomalt, MCC, starch and pregelatinized starch.

10

In some embodiments the delayed release layer and the barrier layer comprises a wax and two or more binders, wherein the delayed release layer and/or the barrier layer comprises said two binders in a ratio of binder to binder of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35, such as of about 30:70 to 70:30, such as of about 25:75 to 75:25.

15

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more binders, wherein said binder comprises or consist of isomalt. In some embodiments the delayed release layer and/or the barrier layer comprises a wax and isomalt. In some embodiments the delayed release layer and/or the barrier layer comprises a wax and isomalt, and optionally one or more L-HPC and/or HPC.

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax and isomalt in a ratio of wax to isomalt of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35, such as about 66.6:33.3.

25

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and binders isomalt and MCC.

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and binders isomalt and MCC in a ratio of wax to isomalt and MCC of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35;

30

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and isomalt and MCC in a ratio of about 50:25:25.

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In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more binder, wherein said binder comprises or consist of MCC. In

some embodiments the barrier layer comprises a wax and MCC. In some embodiments the barrier layer comprises a wax and MCC, and optionally one or more L-HPC and/or HPC.

- 5 In some embodiments the delayed release layer and/or the barrier layer comprises a wax and MCC in a ratio of wax to MCC of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35.

- 10 In some embodiments the delayed release layer and/or the barrier layer comprises or consist of a wax and 10 to 65% w/w of isomalt and/or MCC, such as 20 to 60% w/w isomalt and/or MCC, such as 25 to 50% w/w isomalt and/or MCC, such as about 25% w/w, such as about 50% w/w isomalt and/or MCC.

- 15 In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more binder, wherein said binder comprises or consist of starch and/or pregelatinized starch. In some embodiments the delayed release layer and/or the barrier layer comprises a wax and starch or pregelatinized starch. In some embodiments the delayed release layer and/or the barrier layer comprises a wax and starch or pregelatinized starch, and optionally one or more L-HPC and/or HPC.

- 20 In some embodiments the delayed release layer and/or the barrier layer comprises a wax and pregelatinized starch in a ratio of wax to pregelatinized starch of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35.

- 25 In some embodiments the delayed release layer and/or the barrier layer comprises a wax and 25 to 65% w/w pregelatinized starch, such as 25 to 35, such as 35 to 45, such as 45 to 55, such as 55 to 65% w/w pregelatinized starch.

- 30 In some embodiments the barrier layer comprises more than 30% w/w and less than 70% w/w of a wax, such as 35-65, such as 40-60, such as 45-65% w/w, such as about 50% w/w, wherein said wax is selected from  
100% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; or  
100% w/w of a wax selected from a petroleum based wax such as microcrystalline  
35 wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton

seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol;

or

wherein said wax consist of 25-75% w/w, such as about 50% w/w, of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and 25-75% w/w, such as about 50% w/w, of a wax selected from a petroleum based wax such as microcrystalline wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; and a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid;

and

wherein the barrier layer comprises more than 30% w/w and less than 70% w/w of a binder, such as 35-65, such as 40-60, such as 45-65% w/w, such as about 50% w/w of a binder, wherein said binder is selected from L-HPC, HPC, isomalt, MCC, HPMC, cellulose, Methylcellulose, Polymethacrylates, sodium CMC, PVP, starch, pregelatinized starch, sodium alginate and gelatin; such as selected from L-HPC, HPC, isomalt, MCC, and pregelatinized starch.

#### Fillers

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more fillers, such as selected from mannitol, sorbitol, xylitol, lactose, sucrose, calcium phosphate and calcium hydrogen phosphate dihydrate.

In some embodiments the delayed release layer and/or the barrier layer comprises a wax and one or more water-soluble fillers, such as selected from mannitol, sorbitol and lactose.



In some embodiments the delayed release layer comprises a wax and one or more fillers. In some embodiments the barrier layer comprises a wax but does not comprise one or more fillers.

- 5 In some embodiments the delayed release layer and/or the barrier layer comprises a wax and lactose. In some embodiments the delayed release layer and/or the barrier layer comprises a wax and lactose in a ratio of wax to lactose of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35.
- 10 In some embodiments the delayed release layer comprises a wax and mannitol and/or sorbitol. In some embodiments the delayed release layer and comprises a wax and mannitol and/or sorbitol in a ratio of wax to mannitol and/or sorbitol of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35.
- 15 In some embodiments the delayed release layer comprises a wax and 10 to 65% w/w of mannitol, sorbitol, and/or lactose, such as 20 to 60% w/w, such as 30 to 60% w/w, such as 40 to 60% w/w, such as about 50% w/w.
- 20 In some embodiments the delayed release layer comprises more than 30% w/w and less than 70% w/w of a wax, such as 35-65, such as 40-60, such as 45-65% w/w, such as about 50% w/w, wherein said wax is selected from  
100% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; or  
100% w/w of a wax selected from a petroleum based wax such as microcrystalline  
25 wax; a hydrogenated oil, such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such  
30 as stearyl alcohol;  
or  
wherein said wax consist of 25-75% w/w, such as about 50% w/w, of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and 25-75% w/w, such as about 50% w/w, of a wax selected from a  
35 petroleum based wax such as microcrystalline wax; a hydrogenated oil, such as

hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax, a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol; and

wherein the delayed release layer comprises more than 30% w/w and less than 70% w/w of a binder and/or a filler, such as 35-65, such as 40-60, such as 45-65% w/w, such as about 50% w/w of a binder and/or a filler,

wherein said binder is selected from L-HPC, HPC, isomalt, MCC, HPMC, cellulose, Methylcellulose, Polymethacrylates, sodium CMC, PVP, starch, pregelatinized starch, sodium alginate and gelatin; such as selected from L-HPC, HPC, isomalt, MCC, starch and pregelatinized starch, and wherein said filler is selected from mannitol, sorbitol, xylitol, lactose, sucrose, cellulose, glucose, calcium carbonate, calcium phosphate and calcium hydrogen phosphate dihydrate, such as wherein said filler is a water-soluble filler, such as wherein said filler is selected from mannitol, sorbitol and lactose.

#### Superdisintegrants

In some embodiments the delayed release layer and/or the barrier layer according to the present disclosure comprises a wax and one or more binders and/or fillers, and further comprises a disintegrant, such as a disintegrant selected from crospovidone, sodium starch glycolate and croscarmellose sodium. These disintegrants are also known as superdisintegrants.

Superdisintegrants are defined as highly effective disintegrants that, when used at low levels, provide rapid disintegration and dissolution.

In some embodiments the delayed release layer and/or the barrier layer according to the present disclosure comprises a wax and one or more binders, and crospovidone.

In some embodiments the delayed release layer and/or the barrier layer comprises 1% to 2% w/w of a disintegrant, such as about 2% to 3% w/w, such as about 3% to 4% w/w, such as about 4% to 5% w/w, such as about 5% to 6% w/w, such as about 6% to 7% w/w, such as about 7% to 8% w/w, such as about 8% to 9% w/w, such as about 9%

to 10% w/w of a disintegrant selected from crospovidone, sodium starch glycolate and croscarmellose sodium.

- 5 In some embodiments the delayed release layer and/or the barrier layer comprises 1% to 10% w/w of a disintegrant, such as about 2% to 8% w/w, such as about 3% to 7% w/w, such as about 4% to 6% w/w, such as about 5% w/w of a disintegrant selected from crospovidone, sodium starch glycolate and croscarmellose sodium.

#### Coating

- 10 In some embodiments the tablet formulation further comprises one or more coatings, such as an outer coating. The one or more coatings are in some embodiments applied to the outer surface of the tablet formulation, i.e. on the outer delayed release layer.

- 15 In some embodiments the triple-layer core further comprises one or more coatings. In some embodiments the first and/or second core layers further comprises one or more coatings. The one or more coatings are in some embodiments applied to the outer surface of the first and/or second core layer.

- 20 Tablet coating is the process where coating material is applied to the surface of the tablet to achieve the desired properties of dosage form over the uncoated variety. The coating may be applied to improve taste, odour, and colour of the drug, improve ease of swallowing by the patient, improve product stability or durability, to protect against the gastric environment and to improve mechanical resistance of the dosage form.

- 25 In some embodiments the tablet formulation comprises a film coating. Film coating is the deposition of a thin film of polymer (usually between 20 and 100  $\mu\text{m}$ ) applied mainly to tablets. Film-coating formula generally consists of polymers, plasticizer, colorants/opacifiers, solvents, etc.

- 30 In some embodiments the tablet formulation comprises a sugar coating. Unlike film coating, sugar coating is a more laborious multistep process, leading to final tablet weight increases of up to 30%–50%. The process of sugar coating involves various steps, i.e., sealing, sub-coating, smoothing, colouring, and polishing.

*Tablet dimensions*

Reference to *tablet* and *tablet formulation* is meant to encompass the final tablet formulation (core, or triple-layer core, with an outer delayed release layer).

5 In some embodiments the tablet formulation has a weight of 500-1000 mg, such as 500-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-1000 mg.

In some embodiments the tablet formulation is essentially round. Round is shaped like a circle or cylinder. In some embodiments the tablet formulation is essentially oval.

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In some embodiments the release of the two or more active agents is delayed for 3.5 to 4.5 hours, such as for about 4 hours, and said tablet has a weight of 600-800 mg, such as 650-750 mg, such as 675-750, such as 675-725 mg, such as 700-750 mg, such as wherein the tablet has a weight of about 685 mg, about 715 mg, about 745 mg.

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In some embodiments the release of the two or more active agents is delayed for 5.5 to 6.5 hours, such as for about 6 hours, and said tablet has a weight of 700-900 mg; such as 750-850 mg, such as about 750 mg, such as about 770 mg, such as about 770 mg, such as about 800 mg, such as about 825 mg, such as about 830 mg, such as about 850 mg.

20

In preferred embodiments the delayed release layer constitutes 50 to 75% w/w of the final tablet weight, such as 55 to 70% w/w, such as 59 to 68% w/w, such as 60 to 67% w/w; such as 50-55% w/w, such as 55-56, 56-57, 57-58, 58-59, 59-60, 60-61, 61-62, 62-63, 63-64, 64-65, 65-66, 66-67, 67-68, 68-69, 69-70 or 70-75% w/w of the final tablet weight.

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In some embodiments the delayed release layer constitutes about 58.0% w/w, about 58.5% w/w, about 59.0% w/w, about 59.5% w/w, about 60.0% w/w, about 60.5% w/w, about 61.0% w/w, about 61.5% w/w, about 62.0% w/w, about 62.5% w/w, about 63.0% w/w, about 63.5% w/w, about 64.0% w/w, about 64.5% w/w, about 65.0% w/w, about 65.5% w/w, about 66.0% w/w, about 66.5% w/w, about 67.0% w/w, about 67.5% w/w, about 68.0% w/w, about 68.5% w/w, about 69.0%, about 69.5% w/w, about 70.0% of the final tablet weight.

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In some embodiments the release of the two or more active agents is delayed for 3 to 5 hours, such as for 3.5 to 4.5 hours, such as for about 4 hours, and wherein said delayed release layer constitutes 59 to 63.5% w/w, such as 60 to 63% w/w of the final tablet weight;

5 such as wherein said delayed release layer constitutes 59.0 to 59.5% w/w, 59.5 to 60.0% w/w, 60.0-60.5% w/w, 60.5-61.0% w/w, 61.0-61.5% w/w, 61.5-62.0% w/w, 62.0-62.5% w/w, 62.5-63.0% w/w, 63.0 to 63.5% w/w of the final tablet weight;  
such as wherein said delayed release layer constitutes about 60.0% w/w, about 60.5% w/w, about 61.0% w/w, about 61.5% w/w, about 62.0% w/w, about 62.5% w/w, about  
10 63.0% w/w of the final tablet weight.

In some embodiments the release of the two or more active agents is delayed for 5 to 7 hours, such as for 5.5 to 6.5 hours, such as for about 6 hours, and wherein said delayed release layer constitutes 63.5 to 68% w/w, such as 64 to 67% w/w of the final  
15 tablet weight;

such as wherein said delayed release layer constitutes 63.5 to 64.0% w/w, 64.0-64.5% w/w, 64.5-65.0% w/w, 65.0-65.5% w/w, 65.5-66.0% w/w, 66.0-66.5% w/w, 66.5-67.0% w/w, 67.0 to 67.5% w/w, 67.5 to 68.0% w/w of the final tablet weight;  
such as wherein said delayed release layer constitutes about 64.0% w/w, about 64.5%  
20 w/w, about 65.0% w/w, about 65.5% w/w, about 66.0% w/w, about 66.5% w/w, about 67.0 w/w of the final tablet weight.

In some embodiments the barrier layer is of a certain minimum thickness to be able to control the release of the two or more active ingredients.

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In preferred embodiments the barrier layer constitutes 25 to 50% w/w of the combined weight of the core such as the triple-layer core, such as 25-30, 30-35, 35-40, 40-45, 45-50% w/w of the combined weight of the core; such as 30-40% w/w, such as 32-40% w/w; such as 30-32, 32-34, 34-36, 36-38, 38-40% w/w of the combined weight of the  
30 core; such as 34-38% w/w, such as 35-37% w/w of the combined weight of the core.

In some embodiments the barrier layer constitutes 5 to 25% w/w of the final tablet weight; such as 5-10, 10-15, 15-20, 20-25% w/w of the final tablet weight; such as 10 to 20% w/w, such as 10 to 17.5% w/w of the final tablet weight; such as about 12.5%  
35 w/w of the final tablet weight, such as about 14% w/w of the final tablet weight.

In some embodiments there is provided a tablet formulation for oral administration of two or more active agents, such as two active agents, the tablet comprising:

- i) A core, such as a triple-layer core, comprising or consisting of
  - 5           a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug,
  - 10           b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
  - 15           c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer comprising or consisting of more than 30% w/w and less than 70% w/w of a wax, and one or more binders; such as consisting of more than 30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of one or more binders,  
20           wherein the barrier layer constitutes 25 to 50% w/w of the combined weight of the core such as the triple-layer core,  
              and
- ii) A delayed release layer surrounding the core, said delayed release layer comprising or consisting of more than 30% w/w and less than 70% w/w of a wax, and one or more binders and/or fillers; such as consisting of more than 25           30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less than 70% w/w of one or more binders and/or fillers,  
              wherein the delayed release layer constitutes 50 to 75% w/w of the final tablet weight;  
30           wherein optionally the barrier layer constitutes 5 to 25% w/w of the final tablet weight;  
  
              wherein the release of the two or more active agents is delayed for 2 to 8 hours and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents in the first and second  
35           core, or core layer, is released within 5 to 80 minutes,

wherein optionally the pulse release of the second active agent is delayed for 10 to 120 minutes longer than the first active agent.

5 In some embodiments the release of the active agents is delayed for 3 to 5 hours, such as for 3.5 to 4.5 hours, such as for about 4 hours, and said barrier layer constitutes 13.25 to 25% w/w of the final tablet weight.

10 In some embodiments the release of the active agents is delayed for 5 to 7 hours, such as for 5.5 to 6.5 hours, such as for about 6 hours, and said barrier layer constitutes 5 to 13.25% w/w of the final tablet weight.

15 In some embodiment the release of the active agents is delayed for 3 to 5 hours, such as for 3.5 to 4.5 hours, such as for about 4 hours, and said delayed release layer constitutes 59 to 63.5% w/w of the final tablet weight.

In some embodiment the release of the active agents is delayed for 5 to 7 hours, such as for 5.5 to 6.5 hours, such as for about 6 hours, and said delayed release layer constitutes 63.5 to 68% w/w of the final tablet weight.

20 Without being bound by theory the tablet formulation in some embodiments has a certain dimension or thickness, which can vary depending on the final formulation. In particular formulating a smaller tablet may result in a less thick or tall tablet, and formulating a larger tablet may result in the tablet being thicker or taller.

25 Reference to dimension (final thickness) in this context refers to the thickness measured from the top side of the tablet formulation to the bottom side of the tablet formulation.

30 In some embodiments the tablet formulation has a dimension (final thickness) of 4 mm to 9 mm. In some embodiments the tablet formulation has a dimension (final thickness) of 5 mm to 8 mm.

In some embodiments the tablet formulation has a dimension (final thickness) of 5.5 mm to 7.5 mm, such as 5.5 - 6.0 mm, 6.0 - 6.5 mm, 6.5 - 7.0 mm, or 7.0 - 7.5 mm.

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In some embodiments the release of the two or more active agents is delayed for 3.5 to 4.5 hours, such as for about 4 hours, and wherein said tablet formulation has a dimension (final thickness) of 5 mm to 7 mm, such as 5.5 mm to 6.5 mm, such as 5.5-5.6, 5.6-5.7, 5.7-5.8, 5.8-5.9, 5.9-6.0, 6.0-6.1, 6.1-6.2, 6.2-6.3, 6.3-6.4, 6.4-6.5 mm;  
5 such as wherein the tablet formulation has a dimension (final thickness) of about 5.5 mm, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4 or about 6.5 mm.

In some embodiments the release of the two or more active agents is delayed for 5.5 to 6.5 hours, such as for about 6 hours, and wherein said tablet formulation has a  
10 dimension (final thickness) of 5.5 mm to 8.0 mm, such as 6.0 mm to 7.5 mm, such as 6.0-6.1, 6.1-6.2, 6.2-6.3, 6.3-6.4, 6.4-6.5, 6.5-6.6, 6.6-6.7, 6.7-6.8, 6.8-6.9, 6.9-7.0, 7.0-7.1, 7.1-7.2, 7.2-7.3, 7.3-7.4, 7.4-7.5 mm;  
such as wherein the tablet formulation has a dimension (final thickness) of about 6.0  
15 mm, about 6.1 mm, about 6.2 mm, about 6.3 mm, about 6.4 mm, about 6.5 mm, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4 or about 7.5 mm.

In some embodiments the delayed release layer substantially covers or coats all sides  
20 of the core or triple-layer core. In some embodiments the delayed release layer is essentially equally thick on all sides of the core or triple-layer core.

In some embodiments the delayed release layer is essentially equally thick on the top and bottom side of the core or triple-layer core. In some embodiments the delayed  
25 release layer is essentially equally thick on the planar side of the second core layer and the planar side of the first core layer.

In some embodiments the core, such as at the triple-layer core, is essentially  
30 symmetrically placed within the tablet formulation, i.e. within the delayed release layer.

In some embodiments the core, such as the triple-layer core, is asymmetrically placed within the tablet formulation, i.e. within the delayed release layer.

In some embodiments the delayed release layer is thicker on the planar side  
35 surrounding the second core, or second core layer, than the planar side surrounding



the first core, or first core layer. Reference to first core and first core layer, and second core and second core layer, may be used interchangeably herein.

5 In some embodiments the delayed release layer is 0.05 to 1.0 mm thicker on the planar side of the second core, or second core layer, than the planar side of the first core, or first core layer, such as 0.05 to 0.1 mm, such as 0.1 to 0.2 mm, such as 0.2 to 0.3 mm, such as 0.3 to 0.4 mm, such as 0.4 to 0.5 mm, such as 0.5 to 0.6 mm, such as 0.6 to 0.7 mm, such as 0.7 to 0.8 mm, such as 0.8 to 0.9 mm, such as 0.9 to 1.0 mm thicker; such as about 0.05 mm thicker, such as about 0.1 mm thicker, such as about 0.2 mm  
10 thicker, such as about 0.3 mm thicker, such as about 0.4 mm thicker such as about 0.5 mm thicker, such as about 0.6 mm thicker such as about 0.7 mm thicker, such as about 0.8 mm thicker such as about 0.9 mm thicker, such as about 1.0 mm thicker on the planar side of the second core, or second core layer than the planar side of the first core, or first core layer.

15 In some embodiments the delayed release layer is 0.25 to 10% thicker on the planar side of the second core, or second core layer, than the planar side of the first core, or first core layer, such as 0.25 to 0.5% thicker, such as 0.5 to 0.6% thicker, such as 0.6 to 0.7% thicker, such as 0.7 to 0.8% thicker, such as 0.8 to 0.9% thicker, such as 0.9 to  
20 1.0% thicker, such as 1.0 to 1.5% thicker, such as 1.5 to 2.0% thicker, such as 2.0 to 2.5% thicker, such as 2.5 to 3.0% thicker, such as 3.0 to 3.5% thicker, such as 3.5 to 4.0% thicker, such as 4.0 to 4.5% thicker, such as 4.5 to 5.0% thicker, such as 5.0 to 7.5% thicker, such as 7.5 to 10% thicker on the planar side of the second core, or second core layer than the planar side of the first core, or first core layer.

25 In some embodiments the delayed release layer is thinner on the planar side surrounding the first core, or first core layer, than the planar side of the second core, or second core layer; such as about 0.05 to 1.0 mm thinner on the planar side of the first core, or first core layer, than the planar side of the second core, or second core layer.

30 In some embodiments the delayed release layer is heavier or larger on the planar side of the second core layer than the planar side of the first core layer.

35 In some embodiments the delayed release layer weighs more on the planar side of the second core layer than the planar side of the first core layer.

In some embodiments the weight of the delayed release layer is higher on the planar side of the second core layer than the planar side of the first core layer.

- 5 In some embodiments the delayed release layer weighs 1 mg to 100 mg more on the planar side of the second core layer than the planar side of the first core layer, such as 1 to 50 mg more, 2.5 to 50 mg more, such as 2.5 to 25 mg more, such as 5 to 20 mg more,
- 10 such as 2.5 to 5 mg more, such as 5 to 10 mg more, such as 10 to 20 mg more, such as 20 to 25 mg more, such as 25 to 50 mg more, such as 50 to 75 mg more, such as 75 to 100 mg more,
- such as about 1 mg, such as about 2.5 mg, such as about 5 mg, such as about 10 mg, such as about 15 mg, such as about 20 mg, such as about 25 mg, such as about 30 mg, such as about 35 mg, such as about 40 mg, such as about 45 mg, such as about
- 15 50 mg more, such as about 75 mg more, such as about 100 mg more than the planar side of the second core layer than the planar side of the first core layer.

- In some embodiments the delayed release layer weighs at least about 0.25% more on the planar side of the second core layer than the planar side of the first core layer,
- 20 such as at least about 0.5% more, such as at least about 0.6% more, such as at least about 0.7% more, such as at least about 0.8% more, such as at least about 0.9% more, such as at least about 0.95% more, such as at least about 1.0% more, such as at least about 1.5% more, such as at least about 2.0% more, such as at least about 2.5% more, such as at least about 3.0% more, such as at least about 3.5%, such as at
- 25 least about 4.0%, such as at least about 4.5%, such as at least about 5.0% more on the planar side of the second core layer than the planar side of the first core layer.

- In some embodiments the delayed release layer weighs about 0.25% more on the planar side of the second core layer than the planar side of the first core layer,
- 30 such as about 0.5% more, such as about 0.6% more, such as about 0.7% more, such as about 0.8% more, such as about 0.9% more, such as about 0.95% more, such as about 1.0% more, such as about 1.5% more, such as about 2.0% more, such as about 2.5% more, such as about 3.0% more, such about 3.5% more, such as about 4.0% more, such about 4.5% more, such as about 5.0% more, such as about 7.5% more,

such as about 10% more on the planar side of the second core layer than the planar side of the first core layer.

5 In some embodiments the delayed release layer weighs 0.25 to 10% more, such as 0.25 to 5%, more, on the planar side of the second core layer than the planar side of the first core layer,  
such as 0.25 to 0.5% more, such as 0.5 to 0.6% more, such as 0.6 to 0.7% more, such as 0.7 to 0.8% more, such as 0.8 to 0.9% more, such as 0.9 to 1.0% more, such as 1.0 to 1.5% more, such as 1.5 to 2.0% more, such as 2.0 to 2.5% more, such as 2.5 to 3.0% more, such as 3.0 to 3.5% more, such as 3.5 to 4.0% more, such as 4.0 to 4.5% more, such as 4.5 to 5.0% more, such as 5.0 to 7.5% more, such as 7.5 to 10% more on the planar side of the second core layer than the planar side of the first core layer.

15 In preferred embodiments the planar side of the second core layer constitutes at least about 50.1% of the delayed release layer, such as constitutes at least about 50.2%, such as at least about 50.3%, such as at least about 50.4%, such as at least about 50.5%, such as at least about 50.6%, such as at least about 50.7%, such as at least about 50.8%, such as at least about 50.9%, such as at least about 51%, such as at least about 51.5%, such as at least about 52%, such as at least about 52.5%, such as at least about 53%, such as at least about 53.5%, such as at least about 54% such as at least about 54.5%, such as at least about 55%.

25 In preferred embodiments the planar side of the second core layer constitutes about 50.1% of the delayed release layer, such as about 50.2%, such as about 50.3%, such as about 50.4%, such as about 50.5%, such as about 50.6%, such as about 50.7%, such as about 50.8%, such as about 50.9%, such as about 51%, such as about 51.5%, such as about 52%, such as about 52.5%, such as about 53%, such as about 53.5%, such as about 54% such as about 54.5%, such as about 55%, such as about 56%, such as about 57%, such as about 58%, such as about 59%, such as about 60%.

30 In preferred some embodiments the planar side of the second core layer constitutes 50.1% to 60% of the delayed release layer, such as 50.1% to 55%, such as 50.1 to 50.2%, such as 50.2 to 50.3%, such as 50.3 to 50.4%, such as 50.4 to 50.5%, such as 50.5 to 50.6%, such as 50.6 to 50.7%, such as 50.7 to 50.8%, such as 50.8 to 50.9%,  
35 such as 50.9 to 51%, such as 51 to 51.5%, such as 51.5 to 52%, such as 52 to 52.5%,

such as 52.5 to 53%, such as 53 to 53.5%, such as 53.5 to 54%, such as 54 to 54.5%,  
such as 54.5 to 55%, such as 55 to 56%, such as 56 to 57%, such as 57 to 58%, such  
as 58 to 59%, such as 59 to 60%.

- 5 In some embodiments there is provided a tablet formulation for oral administration of  
two or more active agents, such as two active agents, the tablet comprising:
- 10 i) A core, such as a triple-layer core, comprising or consisting of
    - a. A first core, or first core layer, comprising an amount of a first active  
agent and one or more excipients, wherein said first active agent  
prevents peripheral metabolism of levodopa (L-DOPA);  
alternatively wherein said first active agent is selected from dopamine, a  
dopamine agonist, a dopamine precursor and a dopamine prodrug,
    - 15 b. A second core, or second core layer, comprising an amount of a second  
active agent and one or more excipients, wherein said second active  
agent is selected from dopamine, a dopamine agonist, a dopamine  
precursor and a dopamine prodrug, and
    - 20 c. A barrier layer interposed between the first and the second core, or first  
and second core layer, said barrier layer comprising or consisting of  
more than 30% w/w and less than 70% w/w of a wax, and one or more  
binders; such as consisting of more than 30% w/w and less than 70%  
w/w of a wax, and more than 30% w/w and less than 70% w/w of one or  
more binders,  
wherein the barrier layer constitutes 25 to 50% w/w of the combined  
weight of the core, such as the triple-layer core,  
25 and
  - 30 ii) A delayed release layer surrounding the core, said delayed release layer  
comprising or consisting of more than 30% w/w and less than 70% w/w of a  
wax, and one or more binders and/or fillers; such as consisting of more than  
30% w/w and less than 70% w/w of a wax, and more than 30% w/w and less  
than 70% w/w of one or more binders and/or fillers,  
wherein the delayed release layer constitutes 50 to 75% w/w of the final tablet  
weight;  
wherein the planar side of the second core layer constitutes 50.1% to 60% of  
the delayed release layer, such as 50.1% to 55%, alternatively wherein the

5 delayed release layer weighs 0.25 to 10%, such as 0.25 to 5%, more on the planar side of the second core layer than the planar side of the first core layer; wherein the release of the two or more active agents is delayed for 2 to 8 hours and thereafter the two or more active agents are pulse released, such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

In some embodiments there is provided a tablet formulation for oral administration of two or more active agents, such as two active agents, the tablet comprising:

- 10 i) A core, such as a triple-layer core, according to the present disclosure,  
ii) A delayed release layer comprising or consisting of more than 30% w/w and less than 70% w/w of a wax, and one or more binders and/or fillers, wherein the delayed release layer constitutes 50 to 75% w/w of the final tablet weight;
- 15 wherein the planar side of the second core layer constitutes 50.1% to 60% of the delayed release layer, such as 50.1% to 55%, alternatively wherein the delayed release layer weighs 0.25 to 10%, such as 0.25 to 5%, more on the planar side of the second core layer than the planar side of the first core layer; wherein the release of the two or more active agents is delayed for 2 to 8 hours,
- 20 and the pulse release of the second active agent is delayed for 10 to 120 minutes, such as 15 to 90 minutes, such as 15 to 60 minutes, longer than the first active agent; and thereafter the two or more active agents are pulse released such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

25

In some embodiments there is provided a tablet formulation for oral administration of two or more active agents, such as two active agents, the tablet comprising:

- 30 i) A core, such as a triple-layer core, according to the present disclosure,  
ii) A delayed release layer comprising or consisting of more than 30% w/w and less than 70% w/w of a wax, and one or more binders and/or fillers, wherein the delayed release layer constitutes 59 to 63.5% w/w of the final tablet weight;
- wherein the planar side of the second core layer constitutes 50.1% to 60% of the delayed release layer, such as 50.1% to 55%, alternatively wherein the

- 5 delayed release layer weighs 0.25 to 10%, such as 0.25 to 5%, more on the planar side of the second core layer than the planar side of the first core layer; wherein the release of the two or more active agents is delayed for 3 to 5 hours, and the pulse release of the second active agent is delayed for 15 to 90 minutes, such as 15 to 60 minutes, longer than the first active agent; and thereafter the two or more active agents are pulse released such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.
- 10 In some embodiments there is provided a tablet formulation for oral administration of two or more active agents, such as two active agents, the tablet comprising:
- i) A core, such as a triple-layer core, according to the present disclosure,
  - ii) A delayed release layer comprising or consisting of more than 30% w/w and less than 70% w/w of a wax, and one or more binders and/or fillers,
- 15 wherein the delayed release layer constitutes 63.5 to 68% w/w of the final tablet weight;
- wherein the planar side of the second core layer constitutes 50.1% to 60% of the delayed release layer, such as 50.1% to 55%, alternatively wherein the delayed release layer weighs 0.25 to 10%, such as 0.25 to 5%, more on the
- 20 planar side of the second core layer than the planar side of the first core layer; wherein the release of the two or more active agents is delayed for 5 to 7 hours, and the pulse release of the second active agent is delayed for 15 to 90 minutes, such as 15 to 60 minutes, longer than the first active agent; and thereafter the two or more active agents are pulse released such that at least 70% by weight of the
- 25 amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

#### *Tablet core / API*

30 The tablet formulation of the present disclosure comprises a core, such as a triple-layer core, surrounded by a delayed release layer. The first and the second core, or first and second core layers, of said core each comprise an active agent and one or more excipients.

35 An active agent of the present disclosure is also known as an active ingredient or active pharmaceutical ingredient (API), and may be used interchangeably herein. An

excipient may also be referred to as an inactive pharmaceutical ingredient. Excipients are substances other than the active pharmaceutical ingredient that produce the intended pharmaceutical effect, which are used in the formulation of a drug product.

- 5 The two or more active agents can be the same or different. In a preferred embodiment the two active agents are different. In some embodiments the two or more active agents are different derivatives of same active agent which have different properties, such as different solubility or different absorption profiles.

10 Active agent

- In some embodiments the first core or core layer comprises an amount of a first active agent, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); and the second core or core layer comprises an amount of a second active agent, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug.
- 15

- In some embodiments the first core or core layer comprises an amount of a first active agent, wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug; and the second core or core layer comprises an amount of a second active agent, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug.
- 20

- In some embodiments said first active agent that prevents peripheral metabolism of levodopa (L-DOPA) is a first active agent that prevents peripheral conversion of levodopa (L-DOPA) to dopamine. In some embodiments said first active agent prevents peripheral conversion of levodopa (L-DOPA) to dopamine by a DOPA decarboxylase.
- 25

- Reference to peripheral metabolism and peripheral conversion of levodopa entails metabolism or conversion outside the CNS.
- 30

- In some embodiments the first active agent prevents conversion of levodopa (L-DOPA) to dopamine by DOPA decarboxylase. In some embodiments the first active agent is a DOPA decarboxylase inhibitor.
- 35

In some embodiments the first active agent is a DOPA decarboxylase inhibitor, and the second active agent is a dopamine precursor or a dopamine prodrug.

- 5 In preferred embodiments the first active agent is a DOPA decarboxylase inhibitor, and the second active agent is levodopa (L-DOPA; 3,4-dihydroxyphenylalanine), or a pharmaceutically acceptable derivative of levodopa.

- 10 In some embodiments the DOPA decarboxylase inhibitor is selected from carbidopa, benserazide, methyl dopa and  $\alpha$ -Difluoromethyl-DOPA (DFMD), or a pharmaceutically acceptable derivative thereof.

- 15 Medicines containing carbidopa, either alone or in combination with L-DOPA, are branded as Lodosyn, Sinemet, Pharmacopa, Atamet, Stalevo and parcopa. Medicines containing benserazide either alone or in combination with L-DOPA are branded as Madopar, Prolopa, Modopar, Madopark, Neodopasol, EC-Doparyl, and others. Medicines containing methyl dopa are branded as Aldomet, Aldoril, Dopamet, Dopegyt, and others.

- 20 In some embodiments the DOPA decarboxylase inhibitor is carbidopa, or a pharmaceutically acceptable derivative thereof.

- 25 In more preferred embodiments of the present disclosure, the first active agent is carbidopa or a pharmaceutically acceptable derivative of carbidopa, and the second active agent is levodopa, or a pharmaceutically acceptable derivative of levodopa.

In some embodiments the first active agent prevents conversion of levodopa (L-DOPA) to 3-O-methyldopa (3-OMD) by catechol-O-methyltransferase (COMT)

- 30 In some embodiments the first active agent is a catechol-O-methyltransferase (COMT) inhibitor. In some embodiments the COMT inhibitor is selected from tolcapone, entacapone, opicapone, nitecapone and nebicapone

- 35 In some embodiments the first active agent is COMT inhibitor and the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.



In some embodiments the first active agent is a DOPA decarboxylase inhibitor and a COMT inhibitor, and wherein the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.

5

L-DOPA is sold as a psychoactive drug with the INN levodopa. In the human body L-DOPA is converted to dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC), also known as DOPA decarboxylase (DDC). Since L-DOPA is also converted to dopamine within the peripheral nervous system, causing excessive peripheral dopamine signaling and adverse effects, it is standard clinical practice to co-administer a peripheral DOPA decarboxylase inhibitor (DDCI), which potentiates the central effects of L-DOPA by decreasing the dose-dependency 4 to 5 fold.

In some embodiments said levodopa comprises levodopa and pharmaceutically acceptable derivatives of levodopa, including but not limited to levodopa prodrugs, such as selected from an ester, amide, dimeric amide, carrier-mediated, peptide transport-mediated, peptidyl, cyclic, chemical delivery systems and enzyme-model levodopa prodrugs; such as a levodopa prodrug selected from a levodopa ester, levodopa methyl ester and XP21279.

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In some embodiments said levodopa comprises pharmaceutically acceptable derivatives of levodopa, including but not limited to modified levodopa, such as deuterated levodopa and partially deuterated levodopa.

In some embodiments said levodopa comprises pharmaceutically acceptable derivatives of levodopa, including pharmaceutically acceptable salts, solvates, crystals and cocrystals.

In some embodiments the first active agent is levodopa, and the second active agent is a pharmaceutically acceptable derivative of levodopa.

30

In some embodiments the first active agent is levodopa, and the second active agent is a prodrug of levodopa.

In some embodiments the first active agent is a pharmaceutically acceptable derivative of levodopa, and the second active agent is levodopa.

5 In some embodiments the first active agent is a prodrug of levodopa, and the second active agent is levodopa.

10 In some embodiments said levodopa prodrug is selected from an ester, amide, dimeric amide, carrier-mediated, peptide transport-mediated, peptidyl, cyclic, chemical delivery systems and enzyme-model levodopa prodrugs; such as a levodopa prodrug selected from a levodopa ester, levodopa methyl ester and XP21279.

15 In some embodiments, the first active agent is levodopa or a pharmaceutically acceptable derivative thereof, and the second active agent is levodopa or a pharmaceutically acceptable derivative thereof, wherein said first and second agent are different derivatives of levodopa. In some embodiment the first active agent is levodopa or a pharmaceutically acceptable derivative thereof, and the second active agent is a levodopa prodrug, or a pharmaceutically acceptable derivative thereof. In some embodiment the first active agent is a levodopa prodrug or a pharmaceutically acceptable derivative thereof, and the second active agent is levodopa, or a  
20 pharmaceutically acceptable derivative thereof.

#### Other dopamine-active agents

In some embodiments the first active agent and/or the second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug.  
25 These may collectively be referred to as 'dopamine-active agents' herein.

A dopamine active agent is in some embodiments an agent that increases the dopamine concentration in the synaptic cleft.

30 In some embodiments the first active agent and/or the second active agent is dopamine, a dopamine precursor or a dopamine prodrug. A dopamine precursor is in some embodiments a substance that can be converted into dopamine in the body. Known dopamine precursors include L-phenylalanine, L-tyrosine and L-DOPA.

In some embodiments the first active agent and/or the second active agent is a dopamine precursor selected from L-phenylalanine, L-tyrosine and L-DOPA (levodopa), or a pharmaceutically acceptable derivative thereof. Levodopa is disclosed in detail elsewhere herein.

5

In some embodiments the first active agent and/or the second active agent is a dopamine agonist. A dopamine agonist may also be referred to as a dopamine receptor agonist. There are two families of dopamine receptors; D1-like and D2-like. In some embodiments the first active agent and/or the second active agent is a D2-like dopamine receptor agonist.

10

In some embodiments the first active agent and/or the second active agent is a dopamine agonist selected from a biased dopamine agonist, a partial dopamine agonist, a selective dopamine agonist, and a full dopamine agonist.

15

In some embodiments the first active agent and/or the second active agent is a dopamine agonist selected from bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapexin, Sifrol), ropinirole (Requip), piribedil (Pronora, Trivastal), cabergoline (Dostinex), apomorphine (Apokyn), dihydroergocryptine, propylnorapomorphine, lisuride, Ciladopa, dihydrexidine, dinapsoline, doxanthrine, epicriptine, quinagolide (Norprolac), rotigotine (Neupro), roxindole, sumanirole, fenoldopam, and any pharmaceutically acceptable derivatives thereof.

20

In some embodiments the first active agent and/or the second active agent is an indirect dopamine agonist. In some embodiments the indirect dopamine agonist is selected from a dopamine reuptake inhibitor / transporter blocker and a dopamine releasing agent.

25

In some embodiments the indirect dopamine agonist is selected from amphetamine, dextroamphetamine, Bupropion (Wellbutrin), Amineptine, nomifensine, Lisdexamfetamine, Methylphenidate (Ritalin) or dexamethylphenidate, methylenedioxypyrovalerone (MDPV; "Sonic"), ketamine, phencyclidine (PCP), Cathinone, Cocaine, amphetamine, Methamphetamine, methylenedioxymethamphetamine (MDMA), Phenethylamine, p-Tyramine, lisdexamfetamine (Vyvanse), phenmetrazine, pemoline, 4-methylaminorex (4-MAR),

30

benzylpiperazine, and Vesicular monoamine transporter 2 (VMAT2) inhibitors such as reserpine, tetrabenazine, and deserpidine.

*Core specifications*

5 In some embodiments the core, or triple-layer core, of the present disclosure comprises a first core or core layer, and a second core or core layer, wherein each of said two cores are tablet cores or dosage units each comprising an active agent and one or more excipients. In preferred embodiments said first core or core layer, a second core or core layer, are each immediate release cores. Immediate release cores or tablet  
10 cores / dosage units may be prepared by conventional methods, to achieve a pulse (burst/immediate) release of at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, within 5 to 80 minutes.

In some embodiments the core, or triple-layer core, of the present disclosure comprises  
15 a first core or core layer, and a second core or core layer, each comprising an amount of an active agent and one or more immediate release excipients.

In some embodiment the first core, or first core layer, and the second core, or second core layer, of the present disclosure each comprises 40-90% w/w of an active agent and 10-60% w/w of one or more excipients; such as comprises 30-80% w/w of an active agent and 20-70% w/w of one or more excipients;  
20 such as wherein the first core or core layer and the second core or core layer each comprises 30-35, 35-40, 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, 70-75, 75-80, 80-85, 85-90% w/w of an active agent and 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45,  
25 45-50, 50-55, 55-60, 60-65, 65-70% w/w of one or more excipients.

In some embodiments the first core or core layer comprises 30-70% w/w, such as 40-60% w/w of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof, and 30 to 70% w/w,  
30 such as 40-60% w/w of one or more excipients.

In some embodiments the first core or core layer comprises about 50% w/w of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof, and about 50% w/w of one or more  
35 excipients.

In some embodiments the first core or core layer comprises 2.5 to 250 mg of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof; such as comprises 2.5-5 mg, 5-10, 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-50, 50-60, 60-70, 70-75, 75-80, 80-90, 90-100, 100-125, 125-150, 150-200, 200-250 mg of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof. In some embodiments the first core or core layer comprises 10-100 mg, 10-75 mg, 10-50 mg, 10-40 mg or 15-35 mg of a first active agent, such as a DOPA decarboxylase inhibitor, such as carbidopa or a pharmaceutically acceptable derivative thereof.

In some embodiments the first core or core layer comprises about 25 mg of a first active agent, such as a DOPA decarboxylase inhibitor, such as carbidopa or a pharmaceutically acceptable derivative thereof.

In some embodiments the second core or core layer comprises 50-90% w/w, such as 60-90% w/w, such as 70-90% w/w of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, and 10-50% w/w, such as 10-40% w/w, such as 10-30% w/w of one or more excipients.

In some embodiments the second core or core layer comprises 50-80% w/w, such as 50-70% w/w, of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, and 20-50% w/w, such as 30-50% w/w of one or more excipients.

In some embodiments the second core or core layer comprises 60-80% w/w, such as 60-70% w/w, of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, and 20-40% w/w, such as 30-40% w/w of one or more excipients.

In some embodiments the second core or core layer comprises about 80% w/w of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, and about 20% w/w of one or more excipients.

In some embodiments the second core or core layer comprises about 66.67% w/w of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, and about 33.33% w/w of one or more excipients.

5 In some embodiments the second core or core layer comprises 10 to 1000 mg of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, such as comprises 10-20 mg, 20-25, 25-30, 30-40, 40-50, 50-60, 60-70, 70-75, 75-80, 80-90, 90-100, 100-125, 125-150, 150-175, 175-200, 200-250, 250-300, 300-400, 400-500, 500-750, 750-1000 mg of a second active agent, such as levodopa or a  
10 pharmaceutically acceptable derivative thereof; such as comprises 25-250 mg, 25-200 mg, 50-200 mg or 50-150 mg of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof.

15 In some embodiments the second core or core layer comprises about 100 mg of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof.

In some embodiments the first core or core layer and the second core or core layer comprises one or more excipients selected from a filler, a compressing agent, a  
20 disintegration agent, a lubricant and a binder.

In some embodiments the first core or core layer and the second core or core layer comprises a filler and/or a compressing agent, a disintegration agent and a lubricant; and optionally a binder.  
25

In some embodiments the first core or core layer and the second core or core layer comprises a filler and/or a compressing agent selected from isomalt, microcrystalline cellulose, calcium hydrogen phosphate, lactose, mannitol, sorbitol, cellulose, dextrose, starch, hydrolysed starch, and mixtures thereof.  
30

In some embodiments the first core or core layer and the second core or core layer comprises a disintegration agent selected from croscarmellose sodium, sodium starch glycolate, starch, starch derivatives, cellulose derivatives, bentonite, polyvinylpyrrolidone (PVP), and mixtures thereof.  
35

In some embodiments the first core or core layer and the second core or core layer comprises a lubricant selected from magnesium stearate, steric acid, talc, PEG, silica, colloidal silicas, silicone dioxide, and mixtures thereof.

5 In some embodiments the first core or core layer and the second core or core layer comprises a binder selected from methyl cellulose, polyvinylpyrrolidone (PVP), hydroxy propyl methyl cellulose, hydroxy propyl cellulose, gelatine, sorbitol, sodium alginate, and mixtures thereof

10 In some embodiments the first core or core layer and the second core or core layer comprises one or more excipients selected from microcrystalline cellulose, isomalt, croscarmellose sodium, sodium starch glycolate, and magnesium stearate

In some embodiments the first core or core layer and the second core or core layer  
15 comprises microcrystalline cellulose and/or isomalt.

In some embodiments the first core or core layer and the second core or core layer comprises microcrystalline cellulose and isomalt.

In some embodiments the first core or core layer and the second core or core layer  
20 comprises 15 to 50% w/w of filler and/or compressing agent, such as 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50% w/w filler and/or compressing agent.

In some embodiments the first core or core layer and the second core or core layer  
25 comprises 15 to 50% w/w of one or more filler and/or compressing agent selected from isomalt, microcrystalline cellulose, calcium hydrogen phosphate, lactose, mannitol, sorbitol, cellulose, dextrose, starch, hydrolysed starch, and mixtures thereof; such as comprises 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50% w/w of one or more filler and/or compressing agent selected from isomalt, microcrystalline cellulose, calcium  
30 hydrogen phosphate, lactose, mannitol, sorbitol, cellulose, dextrose, starch, hydrolysed starch, and mixtures thereof.

In some embodiments the first core or core layer and the second core or core layer  
35 comprises 15 to 50% w/w of microcrystalline cellulose and/or isomalt, such as 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50% w/w microcrystalline cellulose and/or isomalt.

In some embodiments the first core or core layer and the second core or core layer comprises 1.0 to 8.0% w/w of disintegration agent, such as 1.0-2.0, 2.0-3.0, 3.0-4.0, 4.0-5.0, 5.0-6.0, 6.0-7.0, 7.0-8.0% w/w of disintegration agent.

5

In some embodiments the first core or core layer and the second core or core layer comprises 1.0 to 10 % w/w, such as 1.0 to 8.0% w/w of one or more disintegration agent selected from croscarmellose sodium, sodium starch glycolate, starch, starch derivatives, cellulose derivatives, bentonite, polyvinylpyrrolidone (PVP), microcrystalline cellulose, and mixtures thereof, such as 1.0-2.0, 2.0-3.0, 3.0-4.0, 4.0-5.0, 5.0-6.0, 6.0-7.0, 7.0-8.0, 8.0-9.0, or 9.0-10% w/w of one or more disintegration agent selected from croscarmellose sodium, sodium starch glycolate, starch, starch derivatives, cellulose derivatives, bentonite, polyvinylpyrrolidone (PVP), microcrystalline cellulose, and mixtures thereof.

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In some embodiments the first core or core layer and the second core or core layer comprises 0.5 to 5.0% w/w croscarmellose sodium, such as 0.5-1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5, 2.5-3.0, 3.0-3.5, 3.5-4.0, 4.0-4.5, 4.5-5.0% w/w croscarmellose sodium.

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In some embodiments the first core or core layer and the second core or core layer comprises 0.5 to 5.0% w/w sodium starch glycolate, such as 0.5-1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5, 2.5-3.0, 3.0-3.5, 3.5-4.0, 4.0-4.5, 4.5-5.0% w/w sodium starch glycolate

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In some embodiments the first core or core layer and the second core or core layer comprises 1.0 to 10% w/w PVP, such as 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10% w/w PVP.

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In some embodiments the first core or core layer and the second core or core layer comprises 0.1 to 5.0% w/w of lubricant, such as 0.1-0.2, 0.2-0.3, 0.3-0.4, 0.4-0.5, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0, 2.0-2.25, 2.25-2.5, 2.5-2.75, 2.75-3.0, 3.0-3.5, 3.5-4.0, 4.0-4.5, 4.5-5.0 % w/w of lubricant.

35

In some embodiments the first core or core layer and the second core or core layer comprises 0.1 to 5.0% w/w of one or more lubricant selected from magnesium stearate, steric acid, talc, PEG, silica, colloidal silicas, silicone dioxide and mixtures thereof, such



as 0.1-0.2, 0.2-0.3, 0.3-0.4, 0.4-0.5, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0, 2.0-2.25, 2.25-2.5, 2.5-2.75, 2.75-3.0, 3.0-3.5, 3.5-4.0, 4.0-4.5, 4.5-5.0 % w/w of one or more lubricant selected from magnesium stearate, steric acid, talc, PEG, silica, colloidal silicas, and mixtures thereof.

5

In some embodiments the first core or core layer and the second core or core layer comprises 0.2 to 3.0% w/w magnesium stearate, such as 0.2-0.3, 0.3-0.4, 0.4-0.5, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0, 2.0-2.25, 2.25-2.5, 2.5-2.75, 2.75-3.0% w/w magnesium stearate

10

In some embodiments the first core or core layer and the second core or core layer comprises 0.2 to 2.0% w/w silicone dioxide, such as 0.2-0.3, 0.3-0.4, 0.4-0.5, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0% w/w silicone dioxide.

15

In some embodiments the first core or core layer comprises 40-60% w/w of a first active agent, such as a DOPA decarboxylase inhibitor, such as carbidopa or a pharmaceutically acceptable derivative thereof; 20-25% w/w microcrystalline cellulose, 20-25% w/w isomalt, 1-5% w/w croscarmellose sodium, 1-5% w/w sodium starch glycolate and 0.5-2.0 % w/w magnesium stearate.

20

In some embodiments the first core or core layer comprises about 50% w/w of a first active agent, such as a DOPA decarboxylase inhibitor, such as carbidopa or a pharmaceutically acceptable derivative thereof; about 22.22% w/w microcrystalline cellulose, about 22.22% w/w isomalt, about 2.22% w/w croscarmellose sodium, about 2.22% w/w sodium starch glycolate and about 1.12% w/w magnesium stearate.

25

In some embodiments the first core or core layer comprises 40-60% w/w of a first active agent, such as a DOPA decarboxylase inhibitor, such as carbidopa or a pharmaceutically acceptable derivative thereof; 15-25% w/w microcrystalline cellulose, 15-25% w/w isomalt, 1-8 % w/w PVP, 1-5% w/w croscarmellose sodium, 1-5% w/w sodium starch glycolate, 0.5-2.0 % w/w magnesium stearate and 0.1-1.0 % w/w silicon dioxide.

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In some embodiments the second core or core layer comprises 70-90% w/w of a second active agent, such as levodopa or a pharmaceutically acceptable derivative

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thereof; 5-14% w/w microcrystalline cellulose, 5-14% w/w isomalt, 0.2-2.0% w/w croscarmellose sodium, 0.2-2.0% w/w sodium starch glycolate and 0.1-1.5 w/w magnesium stearate.

5 In some embodiments the second core or core layer comprises about 80% w/w of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof; about 8.89% w/w microcrystalline cellulose, about 8.89% w/w isomalt, about 0.89% w/w croscarmellose sodium, about 0.89% w/w sodium starch glycolate and about 0.45% w/w magnesium stearate.

10 In some embodiments the second core or core layer comprises 60-75% w/w of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof; 7-17% w/w microcrystalline cellulose, 7-17% w/w isomalt, 1-8% w/w PVP, 0.5-5.0% w/w croscarmellose sodium, 0.1-1.5% w/w magnesium stearate and 0.1-1.0% w/w silicon dioxide.

15 In some embodiments the second core or core layer comprises about 66.67% w/w of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof; about 12.92% w/w microcrystalline cellulose, about 12.92% w/w isomalt, about 4% w/w PVP, about 2% w/w croscarmellose sodium, about 1% w/w magnesium stearate and about 0.5% w/w silicon dioxide.

20 In some embodiments the dimension (thickness) of the core, or triple-layer core, comprising a first and second core, or first and second core layer, and a barrier layer, is 2.5 mm to 6.0 mm, such as 3.0 mm to 5.5 mm, such as 3.0-3.5 mm, 3.5-4.0 mm, 4.0-4.1 mm, 4.1-4.2 mm, 4.2-4.3 mm, 4.3-4.4 mm, 4.4-4.5 mm, 4.5-5.0, 5.0-5.5 mm. In some embodiments the dimension (thickness) of the core comprising a first and second core, or core layer, and a barrier layer, is about 4.0 mm, about 4.1 mm, about 4.2 mm, about 4.3 mm, about 4.4 mm, or about 4.5 mm.

30

#### *Method of manufacture*

It is an aspect to provide a method of making a tablet formulation according to the present disclosure, the method comprising the steps of:

35 a) the first active agent and the one or more excipients are mixed or granulated together and compressed to form a first core layer;

- 5                   b) the second active agent and the one or more excipients are mixed or granulated together and compressed to form a second core layer;
- c) one or more wax and one or more binders such as L-HPC are mixed and melted to form granules and the resulting mixture interposed between the first and the second core layer to form a barrier layer, forming a triple-layer core,
- 10                  d) one or more wax and one or more binders, such as one or more L-HPC, and optionally a HPC, are mixed and melted to form granules and the resulting mixture compressed around the outer surface of the triple-layer core so as to form a delayed release layer.

In some embodiments there is provided a method of making a tablet formulation according to the present disclosure, the method comprising:

- 15           i)       manufacturing a triple-layer core tablet comprising the steps of:
- a) the second active agent and the one or more excipients are mixed or granulated together and placed into a tablet-press die to form a second core layer;
- b) one or more wax and one or more binders, such as one or more L-HPC, are mixed and melted to form granules and the resulting mixture placed on top of the second core layer to form a barrier layer,
- 20           c) the first active agent and the one or more excipients are mixed or granulated together and placed on top of the second core layer to form a first core layer,
- d) the tablet (tablet core) is compressed, such as compressed at 10-14 kN, such as at about 11-13 kN, such as about 10 kN, such as about 12 kN, such as about 14 kN, to produce a triple-layer core,
- 25           ii)     manufacturing a tablet formulation comprising the triple-layer core in an outer delayed release layer (tablet-in-tablet), the method comprising the steps of:
- 30           e) one or more wax and one or more binders, such as one or more L-HPC, and optionally a HPC, are mixed and melted to form granules and optionally mixed prior to use,
- f) resulting mixture of step e) is placed into a tablet-press die,
- 35           g) the triple-layer core of step d) is centralized in the tablet-press die, in the mixture of step f),

- h) resulting mixture of step e) is placed into a tablet-press die, added over the core of step g),
- i) compressing the tablet (tablet-in-tablet), such as compressing at 6-10 kN, such as at 8-12 kN, such as about 8 kN, such as about 10 kN, such as about 12 kN, to produce a tablet formulation.

5

In some embodiments the release of the two or more active agents is delayed for 3.5 to 4.5 hours, such as for about 4 hours, and wherein said tablet formulation in step i) is compressed at 6-10 kN, such as at 7-9 kN, such as at 7.5-9.5 kN, such as about 7 kN, such as about 8 kN, such as about 9 kN.

10

In some embodiments the release of the two or more active agents is delayed for 5.5 to 6.5 hours, such as for about 6 hours, and wherein said tablet formulation in step i) is compressed at 8-12 kN, such as at 9-11 kN, such as at 9.5-10.5 kN, such as about 9 kN, such as about 10 kN, such as about 11 kN.

15

In some embodiments the tablet-press die of step i) a) is an 8.0 mm die and punch set. In some embodiments the tablet-press die of step i) a) is an 8.0 mm FBE die and punch set. In some embodiments the tablet-press die of step ii) f) is an 12.0 mm die and punch set. In some embodiments the tablet-press die of step ii) f) is an 12.0 mm round biconvex R24 die and punch set.

20

#### *Treatment*

Oral levodopa typically provides robust dependable relief of symptoms when it is first started. However, after taking the medicine for many months or years, most patients with Parkinson's disease begin to develop a fluctuating response to levodopa.

25

Fluctuating responses are divided into "ON" time, when the medication is working well and controlling Parkinson's symptoms, and "OFF" time when the medication fails or is delayed in working and Parkinson's disease symptoms are poorly controlled. Morning akinesia is one form of "OFF" episode, and is often referred to as 'Early morning OFF' (EMO). Motor symptoms of morning akinesia include tremor, slowness, muscle stiffness, freezing and falls, and difficulty in moving and walking in the morning. Non-motor symptom of EMO include anxiety, low mood, paraesthesia, pain, dribbling and urgency.

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In some embodiments the tablet formulation according to the present disclosure is capable of one or more of improving the night time sleeping pattern in a patient with Parkinson's disease; reducing sleep disorders involved in triggering early morning OFF periods; providing over-night levodopa coverage for a patient with Parkinson's disease;  
5 reducing OFF-time in a patient with Parkinson's disease; reducing dopaminergic nocturnal decline; increase ON-time in a patient with Parkinson's disease; and/or reducing motor symptoms and/or nonmotor symptoms in a patient with Parkinson's disease.

10 It is an aspect to provide a tablet formulation according to the present disclosure for use in the treatment of morning akinesia, such as for use in the treatment of morning akinesia in a patient with Parkinson's disease.

Reference to morning akinesia may be used herein interchangeably with EMO (early morning OFF), morning immobility and morning hypomobility.  
15

It is an aspect to provide a tablet formulation according to the present disclosure for use in the treatment of morning immobility and/or morning hypomobility, such as for use in the treatment of morning immobility and/or morning hypomobility in a patient with  
20 Parkinson's disease.

It is an aspect to provide a tablet formulation according to the present disclosure for use in the treatment of EMO (early morning OFF), such as for use in the treatment of EMO in a patient with Parkinson's disease.  
25

It is an aspect to provide a tablet formulation according to the present disclosure for use in the treatment of one or more motor symptoms and/or nonmotor symptoms in a patient with Parkinson's disease with early morning OFF/morning akinesia.

30 In some embodiments the tablet formulation according to the present disclosure is for use in the treatment of early morning OFF/morning akinesia in a patient with Parkinson's disease presenting with one or more motor symptoms selected from tremor, slowness, muscle stiffness, freezing and falls, and difficulty in moving and walking in the morning.

35

In some embodiments the tablet formulation according to the present disclosure is for use in the treatment of early morning OFF/morning akinesia in a patient with Parkinson's disease presenting with one or more non-motor symptoms selected from anxiety, low mood, paraesthesia, pain, dribbling and urgency.

5

It is also an aspect to provide a tablet formulation according to the present disclosure for use in the treatment of nocturnal symptoms in a patient with Parkinson's disease.

Reference to nocturnal symptoms may be used herein interchangeably with nocturnal akinesia and nocturnal immobility.

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It is thus an aspect to provide a tablet formulation according to the present disclosure for use in the treatment of nocturnal akinesia and/or nocturnal immobility in a patient with Parkinson's disease.

15

In some embodiments is provided a tablet formulation for oral administration of two or more active agents, for use in the treatment of morning akinesia and/or nocturnal symptoms, such as in a patient with Parkinson's disease, the tablet comprising:

- 20 i) A core, such as a triple-layer core, comprising or consisting of
  - a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA); such as wherein said first active agent comprises a DOPA decarboxylase inhibitor; such as carbidopa or a pharmaceutically acceptable derivative thereof,
  - 25 b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is levodopa, or a pharmaceutically acceptable derivative thereof, and
  - 30 c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer comprising or consisting of a wax and one or more binders and/or fillers,
- and
- ii) A delayed release layer surrounding the core, said delayed release layer comprising or consisting of a wax and one or more binders and/or fillers,

wherein the release of the two or more active agents is delayed for 2 to 10 hours, and thereafter the two or more active agents are pulse released such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

5

In some embodiments said nocturnal symptoms in a patient with Parkinson's disease are motor symptoms.

10

In some embodiments said nocturnal symptoms in a patient with Parkinson's disease are selected from motor complications, immobility episodes, nocturnal immobility, tremor.

15

It is an aspect to provide a tablet formulation according to the present disclosure for use in the treatment of nocturnal akinesia and/or nocturnal immobility and/or nocturnal hypomobility, such as for use in the treatment of nocturnal akinesia and/or nocturnal immobility and/or nocturnal hypomobility in a patient with Parkinson's disease.

20

In some embodiments said nocturnal symptoms in a patient with Parkinson's disease are non-motor symptoms such as anxiety, depression, pain, urinary urge, dribbling of saliva, low mood, limb paresthesia, dizziness, post-prandial bloating, abdominal discomfort, early satiety, nausea, vomiting, weight loss, and malnutrition.

#### *Administration and dosage*

25

The tablet formulation disclosed herein is preferably administered to individuals in need of treatment in pharmaceutically effective doses. A therapeutically effective amount of a compound or active pharmaceutical ingredient is an amount sufficient to cure, prevent, reduce the risk of, alleviate or partially arrest the clinical manifestations of a given disease and its complications. The amount that is effective for a particular therapeutic purpose will depend on the severity and the sort of the disease as well as on the weight and general state of the subject.

30

The tablet formulation according to the present disclosure may be administered one or several times per day, such as 1 to 4 times per day, such as 1 to 3 times per day, such as 1 to 2 times per day, preferably once a day. In a particular embodiment, the

composition is administered once a day, such as twice per day, for example 3 times per day, such as 4 times per day.

5 In one embodiment the tablet formulation of the present disclosure is administered prior to sleep.

In one embodiment the tablet formulation of the present disclosure is administered once daily prior to sleep.

In one embodiment the tablet formulation of the present disclosure is administered before bedtime.

10 In one embodiment the tablet formulation of the present disclosure is administered once daily before bedtime.

In one embodiment the tablet formulation of the present disclosure is administered 4 to 0 hours prior to sleep / before bedtime, such as 4 hours to 3½ hours, such as 3½ hours to 3 hours, such as 3 hours to 2½ hours, such as 2½ hours to 2 hours, such as 2 hours to 1½ hours, such as 1½ hours to 1 hour, such as 1 hour to 45 minutes, such as 45 minutes to 30 minutes, such as 30 minutes to 20 minutes, such as 20 minutes to 15 minutes, such as 15 minutes to 10 minutes, such as 10 minutes to 5 minutes, such as 5 minutes to 1 minute, such as 1 minute to 0 minutes prior to sleep / before bedtime.

20 Administration may occur for a limited time or administration may be chronic such as chronic from the onset of diagnosis, such as throughout the lifetime of the individual or as long as the individual will benefit therefrom i.e. when a disease is present or while having an increased risk of developing a disease.

25 The concentration of each of the active agents in the present pharmaceutical composition are optimized to achieve an appropriate dosage of each drug. Levodopa is often administered at an initial dosage and later administered at a maintenance dosage.

30 In one embodiment said levodopa, or pharmaceutically acceptable derivative thereof, is administered at a dosage of 10 to 5000 mg/day, such as 10-25 mg/day, such as 25-50 mg/day, such as 50-75 mg/day, such as 75-100 mg/day, such as 100-150 mg/day, such as 150-200 mg/day, such as 200-250 mg/day, such as 250-500 mg/day, such as 500-750 mg/day, such as 750-1000 mg/day, such as 1000-1500 mg/day, such as 35



1500-2000 mg/day, such as 2000-2500 mg/day, such as 2500-3000 mg/day, such as 3000-4000 mg/day, such as 4000-5000 mg/day. In one embodiment said levodopa, or pharmaceutically acceptable derivative thereof, is administered at a dosage of 25 to 250 mg/day, such as 25-200 mg/day, such as 50-200 mg/day, such as 50-150 mg/day, such as 75-125 mg/day, such as about 100 mg/day.

In one embodiment said levodopa, or pharmaceutically acceptable derivative thereof, is administered at a daily dosage of 0.01 to 100 mg/kg bodyweight, such as 0.1 to 10 mg/kg bodyweight, such as 0.1 to 1 mg/kg bodyweight, such as 1 to 2 mg/kg bodyweight, such as 2 to 3 mg/kg bodyweight, such as 3 to 4 mg/kg bodyweight, such as 4 to 5 mg/kg bodyweight, such as 5 to 6 mg/kg bodyweight, such as 6 to 7 mg/kg bodyweight, such as 7 to 8 mg/kg bodyweight, such as 8 to 9 mg/kg bodyweight, such as 9 to 10 mg/kg bodyweight.

In one embodiment said levodopa, or pharmaceutically acceptable derivative thereof, is administered at 10-1000 mg or 10-500 mg per dosage, such as at 10-25 mg, 25-50 mg, 50-75mg, 75-100 mg, 100-125 mg, 125-150 mg, 150-175 mg, 175-200 mg, 200-250 mg, 250-500 mg per dosage. In one embodiment said levodopa, or pharmaceutically acceptable derivative thereof, is administered at 25-250 mg per dosage, such as at 50-200 mg per dosage, such as at 50-150 mg per dosage, such as at 75-125 mg per dosage. In one embodiment said levodopa, or pharmaceutically acceptable derivative thereof, is administered at about 100 mg per dosage.

In one embodiment said carbidopa, or pharmaceutically acceptable derivative thereof, is administered at a dosage of 5 to 1000 mg/day, such as 5-10 mg/day, such as 10-25 mg/day, such as 25-50 mg/day, such as 50-75 mg/day, such as 75-100 mg/day, such as 100-150 mg/day, such as 150-200 mg/day, such as 200-250 mg/day, such as 250-500 mg/day, such as 500-750 mg/day, such as 750-1000 mg/day. In one embodiment said carbidopa, or pharmaceutically acceptable derivative thereof, is administered at a dosage of 5 to 200 mg/day, such as 10-100 mg/day, such as 10-75 mg/day, such as 10-50 mg/day, such as about 25 mg/day.

In one embodiment said levodopa, or pharmaceutically acceptable derivative thereof, is administered at a daily dosage of 0.01 to 100 mg/kg bodyweight, such as 0.1 to 10 mg/kg bodyweight, such as 0.1 to 0.5 mg/kg bodyweight, such as 0.5 to 1 mg/kg

bodyweight such as 1 to 2 mg/kg bodyweight, such as 2 to 3 mg/kg bodyweight, such as 3 to 4 mg/kg bodyweight, such as 4 to 5 mg/kg bodyweight, such as 5 to 6 mg/kg bodyweight, such as 6 to 7 mg/kg bodyweight, such as 7 to 8 mg/kg bodyweight, such as 8 to 9 mg/kg bodyweight, such as 9 to 10 mg/kg bodyweight.

5

In one embodiment said carbidopa, or pharmaceutically acceptable derivative thereof, is administered at 5-150 mg per dosage, such as at 10-20 mg, 20-25 mg, 25-30 mg, 30-40 mg, 40-50 mg, 50-60 mg, 60-70 mg, 70-80 mg, 80-90 mg, 90-100 mg, 100-125 mg, 125-150 mg per dosage. In one embodiment said carbidopa, or pharmaceutically acceptable derivative thereof, is administered at 10-50 mg per dosage. In one embodiment said carbidopa, or pharmaceutically acceptable derivative thereof, is administered at about 25 mg per dosage.

10

In some embodiments is provided a tablet formulation according to the present disclosure for use in the treatment of morning akinesia and/or nocturnal symptoms, such as in a patient with Parkinson's disease, the tablet comprising:

15

i) A core, such as a triple-layer core, comprising or consisting of

20

i) A first core, or first core layer, comprising 5 to 150 mg of carbidopa, or a pharmaceutically acceptable derivative thereof, and one or more excipients,

ii) A second core, or second core layer, comprising 1 to 1000 mg levodopa, or a pharmaceutically acceptable derivative thereof, and one or more excipients,

25

iii) A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer comprising or consisting of a wax and one or more binders and/or fillers,

and

ii) A delayed release layer surrounding the core, said delayed release layer comprising or consisting of a wax and one or more binders and/or fillers,

30

wherein the release of the two or more active agents is delayed for 2 to 10 hours, and thereafter the two or more active agents are pulse released such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

In some embodiments said first core, or first core layer, comprises 5 to 150 mg, such as at 10-20 mg, 20-25 mg, 25-30 mg, 30-40 mg, 40-50 mg, 50-60 mg, 60-70 mg, 70-80 mg, 80-90 mg, 90-100 mg, 100-125 mg, 125-150 mg carbidopa, or a pharmaceutically acceptable derivative thereof. In one embodiment said first core, or first core layer,  
5 comprises 10 to 50 mg carbidopa, or a pharmaceutically acceptable derivative thereof, such as about 25 mg carbidopa, or a pharmaceutically acceptable derivative thereof.

In some embodiments said second core, or second core layer, comprises 10-1000 mg, such as 10-500 mg, such as at 10-25 mg, 25-50 mg, 50-75mg, 75-100 mg, 100-125  
10 mg, 125-150 mg, 150-175 mg, 175-200 mg, 200-250 mg, 250-500 mg levodopa, or a pharmaceutically acceptable derivative thereof.

In one embodiment second first core, or second core layer, comprises 25 to 250 mg levodopa, or a pharmaceutically acceptable derivative thereof, such as about 50 to 200  
15 mg, 50 to 150 mg, 75 to 125 mg levodopa, such as about 100 mg or a pharmaceutically acceptable derivative thereof.

## ITEMS

- 20 1. A tablet formulation for oral administration of two or more active agents, the tablet comprising:
- i) A core, such as a triple-layer core, comprising or consisting of
- a. A first core, or first core layer, comprising an amount of a first active agent and one or more excipients, wherein said first active agent  
25 prevents peripheral metabolism of levodopa;
- b. A second core, or second core layer, comprising an amount of a second active agent and one or more excipients, wherein said second active agent is levodopa, or a pharmaceutically acceptable derivative thereof;  
and
- 30 c. A barrier layer interposed between the first and the second core, or first and second core layer, said barrier layer comprising a wax and one or more L-HPC,
- and
- ii) A delayed release layer surrounding the core and comprising a wax and one  
35 or more L-HPC,

wherein the release of the two or more active agents is delayed for 2 to 10 hours, and thereafter the two or more active agents are pulse released such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.

5

2. The tablet formulation according to item 1, wherein the first active agent is a DOPA decarboxylase inhibitor and/or a COMT inhibitor, and the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.

10

3. The tablet formulation according to any one of the preceding items, wherein the first active agent is carbidopa or a pharmaceutically acceptable derivative thereof, and the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.

15

4. The tablet formulation according to any one of the preceding items, wherein the release of the two or more active agents is delayed for 2 to 10 hours after oral administration of the tablet to a subject.

20

5. The tablet formulation according to any one of the preceding items, wherein the release of the two or more active agents is delayed for 2 to 10 hours after placing the tablet in an aqueous solution, such as placing the tablet in an aqueous solution comprising 0.1 N HCl at 37°C +/- 0.5°C, optionally in 500 ml at 50 rpm as measured by the USP 2 paddle method.

25

6. The tablet formulation according to any one of the preceding items, wherein at least 70%, at least 80%, at least 90%, or at least 95% by weight of the amount of the two or more active agents is released within 5 to 80 minutes as measured by the USP 2 paddle method at about 50 rpm in about 500 ml of an aqueous solution comprising 0.1 N HCl at 37°C +/- 0.5°C.

30

7. The tablet formulation according to any one of the preceding items, wherein the release of the two or more active agents is delayed for about 3 to 5 hours, such as for about 3.5 to 4.5 hours, such as for about 4 hours; or wherein the release of the two or more active agents is delayed for about 5 to 7 hours, such as for about 5.5 to 6.5 hours, such as for about 6 hours.

35

- 5           8. The tablet formulation according to any one of the preceding items, wherein the release of the two or more active agents is delayed for 2 to 10 hours and the release of the second active agent is delayed 10 to 120 minutes longer than the release of the first active agent.
- 10           9. The tablet formulation according to any of the preceding claims, wherein the delayed release layer comprises a wax, two or more such as two L-HPC and a HPC; and the barrier layer comprises or consist of a wax and two or more such as two L-HPC.
- 15           10. The tablet formulation according to any of the preceding items, wherein the delayed release layer comprises a HPC with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% w/w aq. solution) and with a molecular weight of about 140,000, optionally which is HPC fine powder (100 mesh pass, D50 = 80-110 micrometres).
- 20           11. The tablet formulation according to any of the preceding items, wherein the one or more L-HPC has a hydroxypropyl content of about 11% by weight (10.0-12.9% by weight), a molecular weight of about 120,000, and optionally a mean particle size of 45 µm (35-55 µm); such as wherein said one or more L-HPC is LH-21; and/or
- 25           wherein the one or more L-HPC has a hydroxypropyl content of about 8% by weight (7.0-9.9% by weight), a molecular weight of about 115,000, and optionally a mean particle size of 20 µm (17-23 µm); such as wherein said one or more L-HPC is LH-32.
- 30           12. The tablet formulation according to any of the preceding items, wherein the wax is selected from a glyceryl ester, microcrystalline wax, a hydrogenated castor oil, carnauba wax and beeswax, and any combination of waxes; such as wherein the glyceryl ester is glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof.
- 35           13. The tablet formulation according to any of the preceding items, wherein the delayed release layer constitutes 50 to 75% w/w of the final tablet weight and

- 5 the delayed release layer weighs at least about 0.25% more on the planar side of the second core layer than the planar side of the first core layer, such as at least about 0.5% more, such as at least about 0.6% more, such as at least about 0.7% more, such as at least about 0.8% more, such as at least about 0.9% more, such as at least about 0.95% more, such as at least about 1.0% more on the planar side of the second core layer than the planar side of the first core layer.
- 10 14. The tablet formulation according to any of the preceding items, wherein the barrier layer constitutes 25 to 50% w/w of the combined weight of the core such as the triple-layer core; and/or wherein the barrier layer constitutes 5 to 25% w/w of the final tablet weight.
- 15 15. A tablet formulation according to any one of the preceding items for use in the treatment of morning akinesia and/or nocturnal akinesia in a patient with Parkinson's disease.

## Examples

### Example 1

5 Development of a delayed release dual pulse tablet containing two active ingredients (API); Carbidopa (CD) and Levodopa (LD). The release of the two APIs is preferably separated in time so that Carbidopa is released from the tablet before Levodopa is released. During development, a range of different prototype formulations were assessed to determine a reproducible release profile (see Fig. 1):

10 *Prototype 1:* A bilayer core tablet containing, in each layer, Carbidopa and Levodopa surrounded by an outer erodible barrier layer, EBL, functioning as a *delayed release layer*.

*Prototype 2:* A triple-layer core tablet containing Carbidopa and Levodopa surrounded by an outer erodible barrier layer, EBL, functioning as a *delayed release layer*. The core has an additional *barrier layer* between the two API core layers to achieve a difference in release time of the Carbidopa and Levodopa. The composition of the additional barrier layer is in some embodiments different from the outer erodible barrier layer (delayed release layer).

20 *Prototype 3:* A core with two core tablets containing Carbidopa and Levodopa, respectively, are compressed within the erodible barrier layer (delayed release layer), mimicking a triple-layer core. The outer erodible barrier layer is found also between the two core tablets.

*Prototype 4:* A four-layer core tablet containing Carbidopa and Levodopa surrounded by an outer erodible barrier layer, EBL, functioning as a *delayed release layer*, having an additional *barrier layer* between the two API layers (as prototype 2) as well as an additional barrier layer on the Levodopa side of the core.

30 *Prototype 5:* A first core tablet where Levodopa is compressed within an additional barrier layer and a second core tablet comprising Carbidopa placed on top of the first core; both cores surrounded by an outer erodible barrier layer, EBL, functioning as a *delayed release layer*. The additional barrier layer between the levodopa tablet and the carbidopa tablet, and the levodopa tablet and the carbidopa tablet, mimics a triple-layer core.

35 Based on the observations and dissolution release patterns observed, prototype-2 was chosen for further investigation. Two different formulations were used as the barrier

layer between the APIs and both composition and weight of this layer explored as a parameter for the control of release of API, among other parameters. Following successful development of the four-hour delay tablet based on prototype 2, a prototype tablet with a six-hour delay was developed. The longer delay or lag time was achieved  
5 mainly by increasing the weight of the outer layer surrounding the core tablet (the delayed release layer).

*In vitro dissolution studies*

The prototype 4- and 6-hour tablet is expected to be dosed at night prior to sleep.  
10 Therefor the in-vitro dissolution studies were performed at a pH similar to the gastric pH at night. The release profiles for each of the prototype tablets was determined by dissolution in pH 1.2 media. This is not strictly necessary as the erosion of the outer erodible barrier layer works independently of pH.

15 *UV dissolution*

CD and LD were shown to have very similar UV absorbance profiles. The absorbance of LD, however, is much higher than CD, making it possible to use dissolution with UV absorbance as a rapid means of identifying the time for onset of release of both API. The dissolution test was performed using a USP II dissolution apparatus (USP 2  
20 paddle method). The apparatus (Automated Lab Systems, UK) consists of a closed loop with an in-line UV PGI T70+ spectrophotometer for automated dissolution testing. During testing samples were collected with 5-minute intervals to measure absorbance, allowing accurate detection of the API, and enabling rapid generation of data.

| Parameters         | Value         |
|--------------------|---------------|
| Apparatus          | USP II Paddle |
| Media              | pH1.2         |
| Media volume       | 500 mL total  |
| Paddle speed (rpm) | 50            |
| Temperature        | 37 ± 0.5°C    |
| Cell pathlength    | 1 mm          |
| Sampling time      | 5 min         |
| Wavelength         | 220nm         |
| Analysis           | UV Vis        |

25

*HPLC dissolution*

To confirm that the dissolution method was accurately reflecting the release of the two API's, an HPLC dissolution (with manual sampling for HPLC analysis) was run and the results correlated with the in-line UV results from the same dissolution. Prototype 2



- tablets with a 4-hour release time were chosen for method evaluation. Small aliquots of media were removed from the in-line dissolution apparatus at the required sampling times and analysed via HPLC. Due to removal of media and slight adjustment to the remaining concentrations, % release values are approximate. The correlated results demonstrate that the in-line UV dissolution selected delay times for CD and LD match those achieved through HPLC analysis, and as such the UV dissolution method could be utilised in the development stages for rapid screening.

#### Results – Tablet development

- All initial prototypes included a CD dose of 25 mg and a LD dose of 100 mg:

| Tablet design    | Barrier layer – between CD/LD cores (mg) | Erodible layer (TinT; Top/Bottom, mg)                          | Observations                                                                                 |
|------------------|------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Prototype-1      | NA                                       | 160 / 120                                                      | Distinct release of LD and CD not observed                                                   |
| Prototype-2 (1)  | 30 (Formulation 1)                       | 180 / 140                                                      | Distinct release of LD and CD observed                                                       |
| Prototype-3      | NA                                       | NA                                                             | Distinct release of LD and CD observed, however this is technically difficult to manufacture |
| Prototype-4      | 70-100                                   | 140 / 240                                                      | Distinct release of LD and CD not observed                                                   |
| Prototype-5      | NA                                       | 100 / 100 (intermediate)<br>170 / 200 (6-h)<br>130 / 160 (4-h) | Distinct release of LD and CD not observed                                                   |
| Prototype-2 (2)  | 50 (Formulation 1)                       | 260 / 260                                                      | Distinct release of LD and CD observed                                                       |
| Prototype-2 (3)  | 70 (Formulation 1)                       | 200 / 200 (4h)<br>240 / 240 (6h)                               | Release profile shows clear difference between CD and LD release.                            |
| Prototype-2 (3B) | 70 (Formulation 1)                       | 210 / 210 (4h)                                                 | Release profile shows clear difference between CD and LD release                             |

Dissolution release times for prototype tablets. pH 1.2 HCl, USP II paddles, 500 ml, 50 rpm, 220 nm, 37.0 ± 0.5 °C, n=1-3. CD and LD release time is based on the UV absorbances:

|                 | CD release time | LD release time | Delay difference |
|-----------------|-----------------|-----------------|------------------|
| Prototype-1     | 65              | 70              | 5                |
| Prototype-2 (1) | 100             | 110             | 10               |
| Prototype-3     | 15              | 20              | 5                |
| Prototype-4     | 135             | 135             | 0                |

|                                |                                                             |                                                             |                                                    |
|--------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------|
|                                | 175<br>160<br>240<br>240                                    | 175<br>160<br>245<br>245                                    | 0<br>0<br>5<br>5                                   |
| Prototype-5                    | 60<br>90                                                    | 75<br>105                                                   | 15<br>15                                           |
| Prototype-2 (2)                | 385<br>375                                                  | 405<br>395                                                  | 20<br>20                                           |
| Prototype-2 (3)<br>4hr target  | 325<br>310<br>320                                           | 355<br>350<br>340                                           | 30<br>40<br>20                                     |
| Prototype-2 (3)<br>6hr target  | 235<br>230                                                  | 270<br>250                                                  | 35<br>20                                           |
| Prototype-2 (3B)<br>4hr target | 220<br>235<br>225<br>225<br>195<br>235<br>210<br>200<br>230 | 240<br>265<br>255<br>275<br>230<br>260<br>260<br>205<br>245 | 20<br>30<br>30<br>50<br>35<br>25<br>50<br>05<br>15 |

Triplicates of prototype-2 (3B) showed a variable dissolution pattern such as either one or two tablets release both APIs simultaneously and variable in delay difference in both APIs.

- 5 The barrier layer 'formulation 1' is identical to the outer erodible barrier layer and contains a low fine powder hydroxypropyl cellulose (HPC Nisso LFP), which acts a binder. A barrier layer 'formulation 2' without HPC LFP was manufactured for use in the core tablet between the CD and LD core layers (Prototype-2 (4); 110 mg barrier layer, 200/200 mg outer layer; half-dose tablet). A robust and repeatable dissolution
- 10 profile was observed:

|          | CD release start | LD release start | Delay difference |
|----------|------------------|------------------|------------------|
| Repeat-1 |                  |                  |                  |
| Average  | 233.33           | 282.5            | 49.17            |
| Min      | 185              | 270              | 25               |
| Max      | 245              | 290              | 50               |
| Repeat-2 |                  |                  |                  |
| Average  | 230.83           | 287.5            | 56.67            |
| Min      | 195              | 260              | 30               |
| Max      | 265              | 310              | 100              |

Prototypes were further developed to achieve a 4-hour delayed release dual pulse tablet (25 mg CD, 100 mg LD), testing core thickness and the barrier layer formulation in between the CD/LD cores (TinT = Tab-in-Tab):

| Tablet design   | Barrier layer –<br>between CD/LD<br>cores (mg) | Erodible barrier layer<br>(TinT; Top/Bottom, mg) | Observations                                 |
|-----------------|------------------------------------------------|--------------------------------------------------|----------------------------------------------|
| Prototype-2 (5) | 110 (Formulation 2)                            | 230 / 230                                        |                                              |
| Prototype-2 (6) | 90 (Formulation 1)                             | 200 / 200                                        | Some simultaneous<br>release of the two APIs |
| Prototype-2 (7) | 110 (Formulation 1)                            | 240 / 250                                        |                                              |
| Prototype-2 (8) | 85 (Formulation 1)                             | 240 / 240                                        |                                              |
| Prototype-2 (9) | 100 (Formulation 2)                            | 220 / 220                                        | A robust dissolution<br>profile is achieved. |
|                 | Do                                             | Do                                               | Repeat-2                                     |
|                 | Do                                             | Do                                               | Repeat-3                                     |

- 5 A 25/100 mg CD/LD tablet was compressed using barrier layer Formulation-2 (100 mg) in between CD and LD to an 8 mm round flat tablet (Prototype-2 (9)). The excipient blend used for the LD layer was 25 mg instead of 50 mg (used for previous optimisation) to reduce the core tablet thickness further in conjunction with higher compression force at 12 KN. Final Tab-in-Tab was compressed to a 12 mm round
- 10 biconvex R24 diameter tablet at 8 KN compression force. The resulting dissolution profile showed a robust and reproducible release pattern:

|         | CD release (min) | LD release (min) | Difference (min) |
|---------|------------------|------------------|------------------|
| 1       | 280              | 305              | 25               |
| 2       | 270              | 315              | 45               |
| 3       | 210              | 255              | 45               |
| 4       | 245              | 260              | 15               |
| 5       | 245              | 295              | 50               |
| 6       | 280              | 310              | 30               |
| Average | 255              | 290              | 35               |
| Min.    | 210              | 255              | 15               |
| Max.    | 280              | 315              | 50               |

*Dissolution profile for 4-h dual pulse released tablets analysed by UV. Dissolution conditions are pH 1.2 HCl, USP II paddles, 500 ml, 50 rpm, 220 nm, 37.0 ± 0.5 °C, n=6. (The quantification in the tablet is based on UV, they were confirmed by HPLC and matches with the UV profile).*

- 5 A 6-hour delayed release dual pulse tablet was developed by changing the weight of the outer erodible barrier layer around the core tablet to achieve a longer lag time. For 6-h delayed release Tab-in-Tabs, 10 KN compression force was used to obtain a suitable size tablet. Variations in the weight of the outer erodible barrier layer for the Tab-in-Tab were investigated to achieve the target delay time. A robust and reproducible release pattern was achieved (UV dissolution profile):

| Tablet design    | Barrier layer – <i>between CD/LD cores</i> (mg) | Erodible barrier layer (TinT; Top/Bottom, mg) | Observations                             |
|------------------|-------------------------------------------------|-----------------------------------------------|------------------------------------------|
| Prototype-2 (10) | 100 (Formulation 2)                             | 285 / 285                                     | Adjustments to achieve target delay time |
| Prototype-2 (11) | 100 (Formulation 2)                             | 280 / 280                                     | Do                                       |
| Prototype-2 (12) | 100 (Formulation 2)                             | 260 / 260                                     | Do                                       |
| Prototype-2 (13) | 100 (Formulation 2)                             | 265 / 285                                     | Do                                       |
| Prototype-2 (14) | 100 (Formulation 2)                             | 275 / 285                                     | Do                                       |
| Prototype-2 (15) | 100 (Formulation 2)                             | 250 / 260                                     | Do                                       |
| Prototype-2 (16) | 100 (Formulation 2)                             | 260 / 265                                     | Do                                       |
|                  | Do                                              | Do                                            | Repeat-2                                 |
|                  | Do                                              | Do                                            | Repeat-3                                 |

*Dissolution profile for 6-hour delayed release tablets; pH 1.2 HCl, USP II paddles, 500 ml, 50 rpm, 220 nm, 37.0 ± 0.5 °C, n=6*

|         | CD release (min) | LD release (min) | Difference (min) |
|---------|------------------|------------------|------------------|
| 1       | 350              | 380              | 30               |
| 2       | 360              | 395              | 35               |
| 3       | 335              | 360              | 25               |
| 4       | 315              | 350              | 35               |
| 5       | 350              | 370              | 20               |
| 6       | 315              | 350              | 35               |
| Average | 337.5            | 367.5            | 30               |
| Min.    | 315              | 350              | 20               |
| Max.    | 360              | 395              | 35               |

- 10 *Dissolution profile for 6-h dual pulse released tablets analysed by UV. Dissolution conditions are pH 1.2 HCl, USP II paddles, 500 ml, 50 rpm, 220 nm, 37.0 ± 0.5 °C, n=6. (The quantification in the tablet is based on UV, they were confirmed by HPLC and matches with the UV profile).*

The below table illustrates the composition of a Dual Pulse tablet releasing 25mg of Carbidopa after a 4-hour delay followed by 100mg of Levodopa after a further 0.5-1 hour delay:

| Component                               | Material                                       | %/Component | Mg/tab | %/tab | Component weight    |
|-----------------------------------------|------------------------------------------------|-------------|--------|-------|---------------------|
| Outer erodible barrier layer            | Glyceryl behenate                              | 42.00       | 184.80 | 25.85 | 440 mg (220/220 mg) |
|                                         | Hydroxypropyl Cellulose (Nisso HPC L FP)       | 6.00        | 26.40  | 3.69  |                     |
|                                         | Low-substituted hydroxypropylcellulose (LH-21) | 22.00       | 96.80  | 13.54 |                     |
|                                         | Low-substituted hydroxypropylcellulose (LH-32) | 30.00       | 132.00 | 18.46 |                     |
| Barrier layer (between CD core/LD core) | Glyceryl behenate                              | 42.00       | 42.00  | 5.87  | 100 mg              |
|                                         | Low-substituted hydroxypropylcellulose (LH-21) | 19.52       | 19.52  | 2.73  |                     |
|                                         | Low-substituted hydroxypropylcellulose (LH-32) | 38.48       | 38.48  | 5.38  |                     |
| Carbidopa core                          | Carbidopa                                      | 50.00       | 25.00  | 3.50  | 50 mg               |
|                                         | Microcrystalline cellulose                     | 22.22       | 11.11  | 1.55  |                     |
|                                         | Isomalt                                        | 22.22       | 11.11  | 1.55  |                     |
|                                         | Croscarmellose sodium                          | 2.22        | 1.11   | 0.16  |                     |
|                                         | Sodium starch glycolate                        | 2.22        | 1.11   | 0.16  |                     |
|                                         | Magnesium stearate                             | 1.12        | 0.56   | 0.08  |                     |
| Levodopa core                           | Levodopa                                       | 80.00       | 100.00 | 13.99 | 125 mg              |
|                                         | Microcrystalline cellulose                     | 8.89        | 11.11  | 1.55  |                     |
|                                         | Isomalt                                        | 8.89        | 11.11  | 1.55  |                     |
|                                         | Croscarmellose sodium                          | 0.89        | 1.11   | 0.16  |                     |
|                                         | Sodium starch glycolate                        | 0.89        | 1.11   | 0.16  |                     |
|                                         | Magnesium stearate                             | 0.45        | 0.56   | 0.08  |                     |
| Final weight                            |                                                |             |        |       | 715 mg              |
| Final thickness                         |                                                |             |        |       | 5.80mm to 6.10 mm   |

5

The below table illustrates the composition of a Dual Pulse tablet releasing 25mg of Carbidopa after a 6-hour delay followed by 100mg of Levodopa after a further 0.5-1 hour delay:

| Component                               | Material                                       | %/Component | Mg/tab | %/tab | Component weight    |
|-----------------------------------------|------------------------------------------------|-------------|--------|-------|---------------------|
| Outer erodible barrier layer            | Glyceryl behenate                              | 42.00       | 220.5  | 27.56 | 525 mg (260/265 mg) |
|                                         | Hydroxypropyl Cellulose (Nisso HPC L FP)       | 6.00        | 31.5   | 3.94  |                     |
|                                         | Low-substituted hydroxypropylcellulose (LH-21) | 22.00       | 115.5  | 14.44 |                     |
|                                         | Low-substituted hydroxypropylcellulose (LH-32) | 30.00       | 157.5  | 19.69 |                     |
| Barrier layer (between CD core/LD core) | Glyceryl behenate                              | 42.00       | 42.00  | 5.25  | 100 mg              |
|                                         | Low-substituted hydroxypropylcellulose (LH-21) | 19.52       | 19.52  | 2.44  |                     |
|                                         | Low-substituted hydroxypropylcellulose (LH-32) | 38.48       | 38.48  | 4.81  |                     |
| Carbidopa core                          | Carbidopa                                      | 50.00       | 25.00  | 3.13  | 50 mg               |
|                                         | Microcrystalline cellulose                     | 22.22       | 11.11  | 1.39  |                     |
|                                         | Isomalt                                        | 22.22       | 11.11  | 1.39  |                     |
|                                         | Croscarmellose sodium                          | 2.22        | 1.11   | 0.14  |                     |
|                                         | Sodium starch glycolate                        | 2.22        | 1.11   | 0.14  |                     |
|                                         | Magnesium stearate                             | 1.12        | 0.56   | 0.07  |                     |
| Levodopa core                           | Levodopa                                       | 80.00       | 100.00 | 12.50 | 125 mg              |
|                                         | Microcrystalline cellulose                     | 8.89        | 11.11  | 1.39  |                     |
|                                         | Isomalt                                        | 8.89        | 11.11  | 1.39  |                     |
|                                         | Croscarmellose sodium                          | 0.89        | 1.11   | 0.14  |                     |
|                                         | Sodium starch glycolate                        | 0.89        | 1.11   | 0.14  |                     |
|                                         | Magnesium stearate                             | 0.45        | 0.56   | 0.07  |                     |
| Final weight                            |                                                |             |        |       | 800 mg              |
| Final thickness                         |                                                |             |        |       | 6.4 – 6.8 mm        |

The barrier layer in between the CD and LD cores is a factor that impact release rate.

#### Tablet manufacturing

A common excipient blend was used in the development of both the Levodopa and

5 Carbidopa components of the tablet prototypes:

| Ingredient – Excipient blend | w / w (%)    |
|------------------------------|--------------|
| Microcrystalline Cellulose   | 44.444       |
| Isomalt                      | 44.444       |
| Croscarmellose Sodium        | 4.444        |
| Sodium Starch Glycolate      | 4.444        |
| <u>Magnesium Stearate</u>    | <u>2.222</u> |
| Total                        | 100          |

The API:excipient blend ratios were designed to have a high drug loading to allow the tablet to remain as small as possible:

| Ingredient – CD core | w / w (%) | Quantity Per Tablet (mg) |
|----------------------|-----------|--------------------------|
| CD                   | 50        | 25                       |
| Excipient Blend      | 50        | 25                       |
| Total                | 100       | 50                       |

  

| Ingredient – LD core | w / w (%) | Quantity Per Tablet (mg) |
|----------------------|-----------|--------------------------|
| LD                   | 80        | 100                      |
| Excipient Blend      | 20        | 25                       |
| Total                | 100       | 125                      |

5

The formulations used to achieve the delay times are shown below. Formulation 1 was utilised as the outer erodible barrier layer and allowed for the 4 or 6 hours delays to be achieved. Formulation 2 was positioned between the API layers (as a barrier layer) allowing for the short delay between release in some prototypes.

10

| Ingredient - w/w (%)                            | Formulation-1 | Formulation-2 |
|-------------------------------------------------|---------------|---------------|
| Glyceryl Dibehenate (GB)                        | 42            | 42            |
| HPC Nisso L FP                                  | 6             | -             |
| Low substituted hydroxypropyl cellulose (LH-21) | 22            | 19.52         |
| Low substituted hydroxypropyl cellulose (LH-32) | 30            | 38.48         |
| Total                                           | 100           | 100           |

The method for manufacture of the barrier layer granules is as follows: All excipients were weighed, combined, and mixed via a tumbling method for 10 minutes. The pre-mixed blend was heated to 90 °C and mixed prior to sizing through a 1 mm sieve and allowed to cool.

15

Core tableting

The manufacturing parameters for the 4-hour core tablets can be found in the below.

20

Carbidopa blend preparation:  
An equal weight of Carbidopa and Excipient blend was weighed and mixed.  
Levodopa blend preparation:  
Levodopa and excipient blend was weighed in a 4:1 (Levodopa: excipient blend) ratio and mixed.

25

Core Tablet manufacturing process

A triple layer core tablet, comprising the levodopa blend, the Formulation 1 or 2 granules and the carbidopa blend was manufactured using conventional tableting techniques and compressed at 12kN. The resulting tablet weight (range: 255 mg – 295 mg), and tablet thickness (range: 4.15 – 4.35 mm) were recorded.

5

Following successful development of the four-hour tablet, a second prototype tablet with a six-hour lag time was developed. The longer lag time was achieved by increasing the weight of outer barrier layer (delayed release layer) around the core tablet.

10

Manufacturing Process for final 4-h delayed release (prototype-2) Tablet-in-Tablet: 220 mg of formulation-1 was weighed and added to the die and the core tablet positioned before adding 220 mg of formulation-1 and compressing at 8 kN. The resulting tablet weight (range: 685 mg – 745 mg) and tablet thickness (range: 5.80 mg – 6.10 mg) was recorded.

15

Manufacturing Process for final 6-h delayed release (prototype-2) Tablet-in-Tablet: 265 mg of formulation-1 granules were weighed and added to the die and the core tablet was positioned before adding 260 mg of formulation-1 and compressing at 10 kN. The resultant tablet weight (range: 770 mg – 830 mg) and tablet thickness (range: 6.3 mg – 6.9 mg) was recorded.

20

### **Example 2**

Dual pulse Carbidopa and Levodopa tablets intended for improved management of nocturnal immobility and morning akinesia in individuals with Parkinson's disease have been developed, one with a four-hour lag time before onset of release of the Carbidopa and one with a six-hour lag time before onset of release of the Carbidopa. The two prototype tablets have been assessed in a clinical proof of principle study against the comparator product, half Sinemet, to confirm tablet performance and determine pharmacokinetics.

25

30

#### *Phase 1a study*

Two prototype delayed release, dual pulse carbidopa and levodopa tablets were tested in a Phase 1 exploratory pharmacoscintigraphic single centre, open-label, crossover study in healthy volunteers.

35



*Test item 1:* Carbidopa release start at 4 hrs after oral administration, levodopa release start at 4½ hrs after oral administration.

5      *Test item 2:* Carbidopa release start at 6 hrs after oral administration, levodopa release start at 6½ hrs after oral administration.

The study was a single centre, phase 1, three arm, open label cross-over, overnight study in 19 healthy male volunteers, with the following treatments:

- 10      A. **Treatment A:** One radiolabelled dual pulse tablet containing 25mg carbidopa and 100mg levodopa designed to release carbidopa at 4 hours post dose with a second pulse of levodopa 0.5-1 hours later.
- 15      B. **Treatment B:** One radiolabelled dual pulse tablet containing 25mg carbidopa and 100mg levodopa designed to release carbidopa at 6 hours post dose with a second pulse of levodopa 0.5-1 hours later.
- 15      C. **Treatment C:** One currently marketed extended-release formulation containing 25mg carbidopa and 100mg levodopa (Half Sinemet CR 25mg/100mg Prolonged release tablet).

20      Treatment A and B were radiolabelled to contain a total dose of approximately 4 MBq <sup>99m</sup>Tc-DTPA at time of dosing. Each subject received one dose of Treatment A at Assessment Visit 1 and one dose of Treatment B at Assessment Visit 2. Each subject received one dose of Treatment C at Assessment Visit 3.

25      Each treatment was administered orally with 240 mL room temperature noncarbonated water. Subjects were dosed in the fed state (standard dinner served at approximately 2 hours before dosing).

30      The primary objective of the study was to evaluate the absorption (PK) of levodopa and carbidopa from two delayed pulsatile release formulations and correlate with scintigraphic time and site of release.

Secondary objectives was to compare the PK performance of the levodopa and carbidopa time delayed tablets with a commercially available marketed product; to determine the gastrointestinal transit parameters of the delayed release tablets;

and to evaluate the safety and tolerability of 25mg carbidopa and 100mg levodopa administered by a dual pulse tablet.

Pharmacokinetic (PK) parameters of carbidopa and levodopa (pharmacokinetic endpoints) include: Maximum Concentration (C<sub>max</sub>), Time of Maximum Concentration (T<sub>max</sub>), Lag Time (T<sub>lag</sub>), Area Under the Curve from time 0 to 24 hours (AUC<sub>last</sub>), Area Under the Curve from time 0 to infinity (AUC<sub>0-inf</sub>), Terminal First Order Rate constant (K), and Terminal Elimination Half Life (t<sub>1/2</sub>). PK parameters were derived by non-compartmental analysis methods performed using Phoenix WinNonlin software (v8.4, Certara USA, Inc., USA).

The following pharmacokinetic parameters were determined for each subject, analyte and study regimen as applicable:

| Parameter                             | Definition                                                                                                               |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| T <sub>max</sub>                      | Time of maximum observed concentration                                                                                   |
| t <sub>lag</sub>                      | Lag time                                                                                                                 |
| C <sub>max</sub>                      | Maximum observed concentration                                                                                           |
| AUC <sub>last</sub>                   | Area under the curve from 0 time to the last measurable concentration                                                    |
| AUC <sub>0-inf</sub>                  | Area under the curve from 0 time extrapolated to infinity                                                                |
| t <sub>1/2</sub>                      | Apparent elimination half-life                                                                                           |
| λ <sub>z</sub>                        | Slope of the apparent elimination phase                                                                                  |
| AUC <sub>0-24</sub>                   | Area under the curve from 0 time extrapolated to 24 hours                                                                |
| F <sub>rel</sub> C <sub>max</sub>     | Relative bioavailability ratio of C <sub>max</sub> calculated as Test [Treatment A or B]/Reference [Treatment C]*100     |
| F <sub>rel</sub> AUC <sub>0-24</sub>  | Relative bioavailability ratio of AUC <sub>0-24</sub> calculated as Test [Treatment A or B]/Reference [Treatment C]*100  |
| F <sub>rel</sub> AUC <sub>0-inf</sub> | Relative bioavailability ratio of AUC <sub>0-inf</sub> calculated as Test [Treatment A or B]/Reference [Treatment C]*100 |

#### Scintigraphic imaging

Each subject had external anatomical markers containing a maximum of 0.02 MBq <sup>99m</sup>Tc taped to the right side of the chest and back to allow accurate alignment of sequential images. Anterior abdominal images of 25 seconds duration each were taken every 30 min until max 12 hr post-dose. Scintigraphic images were analysed using the WebLink image analysis program. The individual anterior images were assessed by two trained analysts. GI transit parameters and Time and site of onset of radiolabel release and complete tablet disintegration was recorded.

Example scintigraphic images showing the GI transit and radiolabel release from a subject dosed with treatment A and treatment B, respectively, is shown in Fig. 2 and 3 (overlaid onto a standard stomach outline to illustrate the positional progress of the radiolabelled tablet(s) over time).

PK Results and conclusions

The study was designed primarily to evaluate the absorption of levodopa and carbidopa from delayed, dual pulse release tablets and correlate with scintigraphic time and site of release. Secondary objectives included comparing the PK performance of levodopa and carbidopa in two forms of the dual pulse tablets with a commercially available extended release formula tablet. The study was also designed to evaluate the safety and tolerability of the dual pulse tablets.

Following a single oral dose of delayed release dual pulse tablets containing levodopa and carbidopa in Treatment A and B, plasma concentrations of levodopa and carbidopa first appear in the plasma at a later timepoint than when following a single oral dose of currently marketed extended release formula levodopa carbidopa tablets (Treatment C). These figures indicate the dual pulse release tablets (Treatment A and B) have a delayed release compared to the currently marketed extended release formula tablets (Treatment C):

- The observed median Tmax of levodopa was 6.00 h in Treatment A, 7.00 h in Treatment B and 2.50 h in Treatment C respectively.

An informal levodopa relative bioavailability comparison (Frel) of Treatment A with Treatment C showed a geometric mean ratio of 105 %, 76.4 % and 95.8 % for Cmax, AUClast and AUC0-inf respectively, suggesting a strong comparability of the delivery of levodopa in Treatment A and C.

An informal levodopa relative bioavailability comparison (Frel) of Treatment B with Treatment C showed a geometric mean ratio of 105 %, 79.8 % and 80.7 % for Cmax, AUClast and AUC0-inf respectively, suggesting a strong comparability of the delivery of levodopa in Treatment B and C.

The observed plasma elimination half-life of levodopa was similar across the three treatments at 1.89 h, 1.54 h and 1.85 h for Treatments A, B and C respectively.

5 The observed plasma elimination half-life of carbidopa was similar across the three treatments at 1.99 h, 1.95 h and 2.40 h for Treatments A, B and C respectively.

10 The low variability associated with the determination of half-life as well as all subjects conforming to the criteria ( $R^2 > 0.8$ ) gives confidence in the reliability of the determined pharmacokinetic values observed. Robust estimation of AUC<sub>0-inf</sub> values were also achieved in most subjects.

### **Example 3**

#### *Phase 1b study*

15 A pharmacoscintigraphic single-centre, open-label, randomised, 3-way cross-over study in patients with Parkinson's disease will be conducted to evaluate the delayed release, dual pulse carbidopa and levodopa tablets (the two prototypes described in Example 2 above).

20 The two formulations are designed to be taken at bedtime and will release a pulse of carbidopa about 4 hours or 6 hours after dose followed by a second delayed pulse of levodopa 30-60 minutes later with the objective of achieving clinically relevant therapeutic plasma levels of levodopa during the late night and/or early morning hours prior to waking.

25 A phase Ia pharmacoscintigraphic study in healthy volunteers has been completed demonstrating successful targeted release of carbidopa/levodopa at the intended time points and clinically relevant plasma levels of levodopa (cf. Example 2 herein), supportive of this treatment concept. This study aims to confirm the phase Ia results in the targeted patient population.

30

#### Primary Objective

- To evaluate the PKs of levodopa and carbidopa from the two delayed release tablets

and correlate with scintigraphic time and site of release in patients with Parkinson's disease.

Secondary Objective(s)

- To compare the PKs of the levodopa and carbidopa delayed release tablets with an immediate release product (Sinemet IR) in patients with Parkinson's disease
- To determine the gastrointestinal transit parameters of the tablets in patients with Parkinson's disease
- To evaluate the safety and tolerability of the tablets in patients with Parkinson's disease.

Approximately 15 patients with Parkinson's disease will be enrolled with the aim of achieving 12 evaluable participants. The participant included in this trial should already be on therapy with levodopa for  $\geq 3$  years and currently receiving  $\geq 3$  daily doses.

Eligible, enrolled participants will attend for three overnight visits on each of which they will receive a single dose of one of three different treatments. Participants will be randomised to sequence of treatments. Dosing will be separated by a minimum of 3 days to allow sufficient washout of radiolabel. A follow up visit will be conducted within 7-14 days of the last treatment visit. On treatment visits, participants will be dosed at approximately 9 pm. Pre-existing treatment regimen doses can be taken as normal up to and including at 5 pm.

- A. **Treatment A** - One radiolabelled dual pulse tablet containing 25mg carbidopa and 100mg levodopa designed to release carbidopa at 4 hours post dose with a second pulse of levodopa 0.5-1 hours later.
- B. **Treatment B** - One radiolabelled dual pulse tablet containing 25mg carbidopa and 100mg levodopa designed to release carbidopa at 4 hours post dose with a second pulse of levodopa 0.5-1 hours later.
- C. **Treatment C** - (reference therapy): One tablet of a currently marketed immediate-release product containing 25mg carbidopa and 100mg levodopa (SINEMET® Plus 25 mg/100 mg Tablets).

The tablets in Treatments A and B will be radiolabelled to contain a total dose of approximately 4 MBq  $^{99m}\text{Tc}$ -DTPA at time of dosing. Each treatment will be

administered orally with 240 mL room temperature noncarbonated water. Participants will be dosed in the fed state (2 hours post standardised dinner).

5 Anterior abdominal images of 25 seconds duration each will be taken every 30 min until 12 hr postdose. Scintigraphic images will be analysed using the WebLink image analysis program.

10 At each treatment visit, blood samples will be drawn by suitably trained site staff at appropriate timepoints to allow an assessment of carbidopa and levodopa concentrations in plasma.

**Example 4**

15 Further to Example 1 the inventors tested additional excipients in the outer delayed release layer, and in the barrier layer, of the dual pulse tablets.

For the delayed release layer, the data demonstrates that the glyceryl ester wax (glyceryl dibehenate) as used in Example 1 can be exchanged or supplemented with another wax or wax-like solid, while retaining a delay of release in a dissolution assay and subsequent burst release. Also, the data demonstrates that the delayed release layer should comprise more than about 30% w/w and below about 70% w/w of a wax.

All percentages in the below tables are % w/w:

| Formulation Batch   |                   | A      | B      | C      | D      | E      |
|---------------------|-------------------|--------|--------|--------|--------|--------|
| Ingredients         | Brand name        | %      | %      | %      | %      | %      |
| Glyceryl Dibehenate | Compritol 888 ATO | 30.00  | 50.00  | 70.00  | 70.00  | 30.00  |
| MCC                 | Avicel PH200      | 70.00  | 50.00  | 30.00  | 25.00  | 65.00  |
| Crospovidone        | XL                | -      | -      | -      | 5.00   | 5.00   |
| Total               |                   | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| Any delay? Y / N    |                   | N      | Y      | N      | N      | N      |
| Any burst? Y / N    |                   | Y      | N      | N      | N      | Y      |

| Formulation Batch         |                   | F      | G      | H      | I      |
|---------------------------|-------------------|--------|--------|--------|--------|
| Ingredients               | Brand name        | %      | %      | %      | %      |
| Glyceryl Dibehenate       | Compritol 888 ATO | 50.00  | 70.00  | 50.00  | 50.00  |
| Starch                    | -                 | 50.00  | 30.00  | -      | 25.00  |
| Isomalt                   | -                 |        |        | 50.00  | 25.00  |
| Total                     |                   | 100.00 | 100.00 | 100.00 | 100.00 |
| Any delay observed? Y / N |                   | N      | N      | Y      | Y      |
| Any burst observed? Y / N |                   | N      | N      | (Y)    | Y      |

| Formulation Batch         |                   | J      | K      | L      | M      | N      | O      | P      | Q      |
|---------------------------|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Ingredients               | Brand name        | %      | %      | %      | %      | %      | %      | %      | %      |
| Glyceryl Dibehenate       | Compritol 888 ATO | 50.00  | 50.00  | -      | 21.00  | -      | 21.00  | 50.00  | 50.00  |
| Isomalt                   |                   | 25.00  | 25.00  | -      | -      | -      | -      | -      | -      |
| Crospovidone              | XL-               | -      | 5.00   | -      | -      | -      | -      | -      | -      |
| MCC                       | Avicel PH200      | 25.00  | 25.00  | -      | -      | -      | -      | -      | -      |
| HCO                       | Kolliwax®         | -      | -      | 42.00  | 21.00  | -      | -      | -      | -      |
| Montan SX Wax             |                   | -      | -      | -      | -      | 42.00  | 21.00  | -      | -      |
| HPC L FP                  |                   | -      | -      | 6.00   | 6.00   | 6.00   | 6.00   | -      | -      |
| LH-21                     |                   | -      | -      | 22.00  | 22.00  | 22.00  | 22.00  | -      | -      |
| LH-32                     |                   | -      | -      | 30.00  | 30.00  | 30.00  | 30.00  | -      | -      |
| Mannitol                  |                   | -      | -      | -      | -      | -      | -      | 50.00  | -      |
| Sorbitol                  |                   | -      | -      | -      | -      | -      | -      | -      | 50.00  |
| Total                     |                   | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| Any delay observed? Y / N |                   | Y      | Y      | Y      | Y      | (Y)    | (Y)    | Y      | Y      |
| Any burst observed? Y / N |                   | Y      | (Y)    | Y      | Y      | (Y)    | (Y)    | Y      | (Y)    |

| Formulation Batch            |                   | R     | S     | T     | U     | V     |
|------------------------------|-------------------|-------|-------|-------|-------|-------|
| Ingredients                  | Brand name        | %     | %     | %     | %     | %     |
| Glyceryl Dibehenate          | Compritol 888 ATO | -     | 21.00 | 21.00 | 21.00 | 50.00 |
| Candelilla Wax               | -                 | 42.00 | 21.00 | -     | -     | -     |
| Hydrogenated Cotton Seed Oil | Lubritab®         | -     | -     | 21.00 | -     | -     |

|                           |   |        |        |        |        |        |
|---------------------------|---|--------|--------|--------|--------|--------|
| Microcrystalline Wax      | - | -      | -      | -      | 21.00  | -      |
| Lactose                   |   | -      | -      | -      | -      | 50.00  |
| HPC L FP                  | - | 6.00   | 6.00   | 6.00   | 6.00   | -      |
| LH-21                     | - | 22.00  | 22.00  | 22.00  | 22.00  | -      |
| LH-32                     | - | 30.00  | 30.00  | 30.00  | 30.00  | -      |
| Total                     |   | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| Any delay observed? Y / N |   | Y      | Y      | Y      | Y      | (Y)    |
| Any burst observed? Y / N |   | Y      | Y      | (Y)    | Y      | Y      |

| Formulation Batch                                           |                   | X      | Y      | Z      | AA     | BB     | CC     | DD     |
|-------------------------------------------------------------|-------------------|--------|--------|--------|--------|--------|--------|--------|
| Ingredients                                                 | Brand name        | %      | %      | %      | %      | %      | %      | %      |
| Glyceryl Dibehenate                                         | Compritol 888 ATO | 21.00  | -      | 21.00  | -      | 21.00  | -      | 21.00  |
| Beeswax                                                     | -                 | 21.00  | -      | -      | -      | -      | -      | -      |
| PEG 3000                                                    | -                 | -      | 42.00  | 21.00  | -      | -      | -      | -      |
| Cetostearyl Alcohol (50:50 Cetyl Alcohol : Stearyl Alcohol) | Kolliwax® CSA 50  | -      | -      | -      | 42.00  | 21.00  | -      | -      |
| Cetostearyl Alcohol (70:30 Cetyl Alcohol : Stearyl Alcohol) | Kolliwax® CSA 70  | -      | -      | -      | -      | -      | 42.00  | 21.00  |
| HPC L FP                                                    | -                 | 6.00   | 6.00   | 6.00   | 6.00   | 6.00   | 6.00   | 6.00   |
| LH-21                                                       | -                 | 22.00  | 22.00  | 22.00  | 22.00  | 22.00  | 22.00  | 22.00  |
| LH-32                                                       | -                 | 30.00  | 30.00  | 30.00  | 30.00  | 30.00  | 30.00  | 30.00  |
| Total                                                       |                   | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| Any delay observed? Y / N                                   |                   | Y      | Y      | Y      | (Y)    | N      | N      | N      |
| Any burst observed? Y / N                                   |                   | (Y)    | Y      | Y      | N      | N      | N      | N      |



| Formulation Batch       |                   | EE     | FF     | GG     | HH     | II     | JJ     | KK     |
|-------------------------|-------------------|--------|--------|--------|--------|--------|--------|--------|
| Ingredients             | Brand name        | %      | %      | %      | %      | %      | %      | %      |
| Glyceryl Dibehenate     | Compritol 888 ATO | -      | 21.00  | -      | 21.00  | -      | 21.00  | 21.00  |
| Carnauba Wax            | -                 | 42.00  | 21.00  | -      | -      | -      | -      | -      |
| Stearic / Palmitic Acid | Kolliwax® S       | -      | -      | 42.00  | 21.00  | -      | -      | -      |
| Cetyl Alcohol           | Kolliwax® CA      | -      | -      | -      | -      | 42.00  | 21.00  | -      |
| Glycerol Monostearate   | Kolliwax® GMS II  | -      | -      | -      | -      | -      | -      | 21.00  |
| HPC L FP                | -                 | 6.00   | 6.00   | 6.00   | 6.00   | 6.00   | 6.00   | 6.00   |
| LH-21                   | -                 | 22.00  | 22.00  | 22.00  | 22.00  | 22.00  | 22.00  | 22.00  |
| LH-32                   | -                 | 30.00  | 30.00  | 30.00  | 30.00  | 30.00  | 30.00  | 30.00  |
| Total                   |                   | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| Any Delay? Y / N        |                   | Y      | Y      | Y      | Y      | (Y)    | N      | Y      |
| Any burst? Y / N        |                   | Y      | Y      | Y      | Y      | (Y)    | N      | (Y)    |

| Formulation Batch     |                   | LL     | MM     | NN     | OO     | PP     | QQ     |
|-----------------------|-------------------|--------|--------|--------|--------|--------|--------|
| Ingredients           | Brand name        | %      | %      | %      | %      | %      | %      |
| Glyceryl Dibehenate   | Compritol 888 ATO | -      | -      | 21.00  | -      | 21.00  | 50.00  |
| Palmitic Acid (98 %)  | -                 | 42.00  | -      | -      | -      | -      | -      |
| Stearyl Alcohol       | Kolliwax® SA      | -      | 42.00  | 21.00  | -      | -      | -      |
| PEG 20,000            | -                 | -      | -      | -      | 42.00  | 21.00  | -      |
| Pregelatinised Starch | Lycatab®          | -      | -      | -      | -      | -      | 50.00  |
| HPC L FP              | -                 | 6.00   | 6.00   | 6.00   | 6.00   | 6.00   | -      |
| LH-21                 | -                 | 22.00  | 22.00  | 22.00  | 22.00  | 22.00  | -      |
| LH-32                 | -                 | 30.00  | 30.00  | 30.00  | 30.00  | 30.00  | -      |
| Total                 |                   | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| Any Delay? Y / N      |                   | Y      | Y      | Y      | Y      | Y      | Y      |
| Any burst? Y / N      |                   | Y      | Y      | Y      | Y      | Y      | Y      |

| Formulation Batch          |                         | RR     | SS     | TT     | UU     | VV     | XX     | YY     |
|----------------------------|-------------------------|--------|--------|--------|--------|--------|--------|--------|
| Ingredients                | Brand name              | %      | %      | %      | %      | %      | %      | %      |
| Glyceryl Dibehenate        | Compritol 888 ATO       | 42.00  | 42.00  | 42.00  | 42.00  | 42.00  | 42.00  | 42.00  |
| HPC L FP                   | -                       | -      | -      | -      | 58.00  | -      | -      | -      |
| HPC                        | Klucel™ ELF Pharm       | 6.00   | -      | -      | -      | 58.00  | -      | -      |
| HPC                        | Klucel™ EXF Ultra Pharm | -      | 6.00   | -      | -      | -      | 58.00  | -      |
| HPC                        | Klucel™ Xtend HXF Pharm | -      | -      | 6.00   | -      | -      | -      | 58.00  |
| LH-21                      | -                       | 22.00  | 22.00  | 22.00  | -      | -      | -      | -      |
| LH-32                      | -                       | 30.00  | 30.00  | 30.00  | -      | -      | -      | -      |
| Total                      |                         | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |
| Any Delay / Release? Y / N |                         | Y      | Y      | Y      | N      | N      | Y      | N      |
| Any burst? Y / N           |                         | Y      | Y      | Y      | N      | N      | (Y)    | N      |

| Grade (X = fine) | Average MW | Typical Viscosity (mPa's) |
|------------------|------------|---------------------------|
| ELF Pharm        | 40,000     | 150 – 300                 |
| EXF Ultra Pharm  | 80,000     | 300 – 600                 |
| HPC L FP         | 140,000    | 6 – 10                    |
| Xtend HXF Pharm  | 1,150,000  | 1,500 – 3,000             |

- 5 For the barrier layer, the following formulations (same numbering as above tables) were tested for ability to delay carbidopa (CD) and levodopa (LD). The data demonstrates that formulations comprising as wax 100% montan wax or 50% stearyl

alcohol (with 50% glyceryl dibehenate) are inferior; and formulations comprising a wax and 100% filler which is mannitol or sorbitol does not work, in the barrier layer:

| Formulation | H | J | K | N | O | P | Q | 27 |
|-------------|---|---|---|---|---|---|---|----|
| CD-LD delay | Y | Y | Y | N | Y | N | N | Y  |

| Formulation | Z | EE | FF | LL | NN | OO | PP | QQ |
|-------------|---|----|----|----|----|----|----|----|
| CD-LD delay | Y | Y  | Y  | Y  | N  | Y  | Y  | Y  |

5

**Example 5**

Additional carbidopa and levodopa tablet cores (or core layers) were manufactured with the following components:

10 Carbidopa-containing core (in triple-layer core):

| Material                   | Brand             | %/Component | Mg/tab | %/batch |
|----------------------------|-------------------|-------------|--------|---------|
| Carbidopa                  | Emprove Essential | 50.00       | 25.00  | 100.00  |
| Microcrystalline cellulose | Avicel PH102      | 20.06       | 10.03  | 40.12   |
| Isomalt                    | Galen IQ 720      | 20.06       | 10.03  | 40.12   |
| PVP                        | K30               | 4.00        | 2.00   | 8.00    |
| Croscarmellose sodium      | Ac-Di-Sol SD711   | 2.19        | 1.10   | 4.38    |
| Sodium starch glycolate    | Explotab          | 2.19        | 1.10   | 4.38    |
| Silicon dioxide            | Syloid            | 0.50        | 0.25   | 1.00    |
| Magnesium stearate         | -                 | 1.00        | 0.50   | 2.00    |

Levodopa-containing core (in triple-layer core):

| Material                   | Brand             | %/Component | Mg/tab | %/batch |
|----------------------------|-------------------|-------------|--------|---------|
| levodopa                   | Emprove Essential | 66.67       | 100.01 | 133.34  |
| Microcrystalline cellulose | Avicel PH102      | 12.92       | 19.37  | 25.83   |
| Isomalt                    | Galen IQ 720      | 12.92       | 19.37  | 25.83   |
| PVP                        | K30               | 4.00        | 6.00   | 8.00    |
| Croscarmellose sodium      | Ac-Di-Sol SD711   | 2.00        | 3.00   | 4.00    |
| Silicon dioxide            | Syloid            | 0.50        | 0.75   | 1.00    |
| Magnesium stearate         | -                 | 1.00        | 1.50   | 2.00    |

15

## CLAIMS

1. A tablet formulation for oral administration of two or more active agents, the tablet comprising:
- 5 i) A core comprising or consisting of
- a. A first core comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA);
- alternatively wherein said first active agent is selected from dopamine, a
- 10 dopamine agonist, a dopamine precursor and a dopamine prodrug,
- b. A second core comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
- 15 c. A barrier layer interposed between the first and the second core, said barrier layer comprising or consisting of a wax and one or more binders and/or fillers,
- and
- ii) A delayed release layer surrounding the core, said delayed release layer
- 20 comprising or consisting of a wax and one or more binders and/or fillers,
- wherein the release of the two or more active agents is delayed for 2 to 10 hours, and thereafter the two or more active agents are pulse released such that at least 70% by weight of the amount of the two or more active agents in the first and second core, or core layer, is released within 5 to 80 minutes.
- 25
2. The tablet formulation according to claim 1, wherein the tablet is for oral administration of two active agents, such as wherein said first core or first core layer comprises an amount of a single first active agent and said second core or second core layer comprises an amount of a single second active agent.
- 30
3. The tablet formulation according to any one of the preceding claims, the tablet comprising:
- i) A triple-layer core comprising or consisting of

- 5 a. A first core layer comprising an amount of a first active agent and one or more excipients, wherein said first active agent prevents peripheral metabolism of levodopa (L-DOPA);  
alternatively wherein said first active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug,
- 10 b. A second core layer comprising an amount of a second active agent and one or more excipients, wherein said second active agent is selected from dopamine, a dopamine agonist, a dopamine precursor and a dopamine prodrug, and
- 15 c. A barrier layer interposed between the first and the second core layer, said barrier layer comprising a wax and one or more binders and/or fillers.
- 20 4. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for 2 to 10 hours after oral administration of the tablet to a subject.
- 25 5. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for 2 to 10 hours after placing the tablet in an aqueous solution;  
such as placing the tablet in an aqueous solution comprising about 0.1 N HCl at 37°C +/- 0.5°C, optionally in about 500 ml at about 50 rpm;  
such as placing the tablet in an aqueous solution at pH 1.2 HCl at 37°C +/- 0.5°C, optionally in about 500 ml at about 50 rpm.
- 30 6. The tablet formulation according to any of the preceding claims, wherein at least 70%, at least 80%, at least 90%, or at least 95% by weight of the amount of the two or more active agents in the first and second core, or first and second core layer, is released within 5 to 80 minutes as measured by the USP 2 paddle method at about 50 rpm in about 500 ml of an aqueous solution comprising about 0.1 N HCl at 37°C +/- 0.5°C; or of an aqueous solution at pH 1.2 HCl at 37°C +/- 0.5°C.
- 35 7. The tablet formulation according to any of the preceding claims, wherein at least 70% by weight of the amount of the two or more active agents is released

within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.

- 5 8. The tablet formulation according to any of the preceding claims, wherein at least 80% by weight of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.
- 10 9. The tablet formulation according to any of the preceding claims, wherein at least 90% by weight, such as at least 95% by weight, of the amount of the two or more active agents is released within 5 to 80 minutes, such as within 5 to 60 minutes, such as within 5 to 45 minutes, such as within 5 to 30 minutes, such as within 5 to 15 minutes.
- 15 10. The tablet formulation according to any one of the preceding claims, wherein the two or more active agents are pulse released essentially at the same time.
- 20 11. The tablet formulation according to any one of the preceding claims, wherein the second active agent is pulse released after the first active agent is pulse released, such as pulse released 10 to 120 minutes after the first active agent is pulse released.
- 25 12. The tablet formulation according to any one of the preceding claims, wherein pulse release of the second active agent starts after the pulse release of the first active agent starts, such as wherein pulse release of the second active agent starts 10 to 120 minutes, such as 15 to 90 minutes, such as 15 to 60 minutes, such as 15 to 45 minutes; such as 30 to 60 minutes after the pulse release of the first active agent start.
- 30 13. The tablet formulation according to any of the preceding claims, wherein pulse release of the second active agent starts 10 to 15 minutes, such as 15 to 20 minutes, such as 20 to 25 minutes, such as 25 to 30 minutes, such as 30 to 35 minutes, such as 35 to 40 minutes, such as 40 to 45 minutes, such as 45 to 50 minutes, such as 50 to 55 minutes, such as 55 to 60 minutes, such as 60 to 70 minutes, such as 70 to 80 minutes, such as 80 to 90 minutes, such as 90 to 100
- 35

minutes, such as 100 to 110 minutes, such as 110 to 120 minutes after the pulse release of the first active agent starts.

- 5 14. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for 2 to 10 hours and the release of the second active agent is delayed 10 to 120 minutes longer than the release of the first active agent, such as delayed 15 to 90 minutes longer, such as 15 to 60 minutes longer, such as 15 to 45 minutes longer; such as 30 to 60 minutes longer than the release of the first active agent.
- 10 15. The tablet formulation according to any of the preceding claims, wherein the release of the second active agent is delayed 10 to 15 minutes longer, such as 15 to 20 minutes longer, such as 20 to 25 minutes longer, such as 25 to 30 minutes longer, such as 30 to 35 minutes longer, such as 35 to 40 minutes longer, such as 40 to 45 minutes longer, such as 45 to 50 minutes longer, such as 50 to 55 minutes longer, such as 55 to 60 minutes longer, such as 60 to 70 minutes longer, such as 70 to 80 minutes longer, such as 80 to 90 minutes longer, such as 90 to 100 minutes longer, such as 100 to 110 minutes longer, such as 110 to 120 minutes longer than the release of the first active agent.
- 20 16. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for about 2 hours, such as for about 2.5 hours, such as for about 3 hours, such as for about 3.5 hours, such as for about 4 hours, such as for about 4.5 hours, such as for about 5 hours, such as for about 5.5 hours, such as for about 6 hours, such as for about 6.5 hours, such as for about 7 hours, such as for about 7.5 hours, such as for about 8 hours, such as for about 8.5 hours, such as for about 9 hours, such as for about 9.5 hours, such as for about 10 hours.
- 25 17. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for 2 to 2.5 hours, such as for 2.5 to 3 hours, such as for 3 to 3.5 hours, such as for 3.5 to 4 hours, such as for 4 to 4.5 hours, such as for 4.5 to 5 hours, such as for 5 to 5.5 hours, such as for 5.5 to 6 hours, such as for 6 to 6.5 hours, such as for 6.5 to 7 hours, such

as for 7 to 7.5 hours, such as for 7.5 to 8 hours, such as for 8 to 8.5 hours, such as for 8.5 to 9 hours, such as for 9 to 9.5 hours, such as for 9.5 to 10 hours.

5 18. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for 3 to 10 hours, such as for 3 to 9 hours, such as for 3 to 8 hours, such as for 3 to 7 hours.

10 19. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for at least about 3 hours, such as at least about 3.5 hours, such as at least about 4 hours.

15 20. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for about 3 to 5 hours, such as for about 3.5 to 4.5 hours, such as for about 4 hours.

21. The tablet formulation according to any one of the preceding claims, wherein the release of the two or more active agents is delayed for about 5 to 7 hours, such as for about 5.5 to 6.5 hours, such as for about 6 hours.

20 22. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises more than 30% w/w of a wax.

25 23. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises at least 31% w/w of a wax, such as at least 32% w/w of a wax, such as at least 33% w/w of a wax, such as at least 34% w/w of a wax, such as at least 35% w/w of a wax, such as at least 36% w/w of a wax, such as at least 37% w/w of a wax, such as at least 38% w/w of a wax, such as at least 39% w/w of a wax, such as at least 40% w/w of a wax, such as at least 42% w/w of a wax.

30 24. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises more than 30% w/w of a wax and less than 70% w/w of a wax.

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25. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises 32 to 68% w/w of a wax, such as 35 to 65% w/w of a wax, such as 35 to 60% w/w of a wax, such as 40 to 60% w/w of a wax, such as 42 to 50% w/w of a wax, such as about 42% w/w of a wax, such as about 50% w/w of a wax.
26. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises a wax, which is a single wax or a combination of two or more waxes.
27. The tablet formulation according to any of the preceding claims, wherein the wax is selected from a glyceryl ester, a petroleum based wax (paraffin wax), a saturated solid triglyceride such as a hydrogenated oil, a long chain saturated carboxylic acid, saturated long chain monoglyceride, a long chain alcohol, a plant wax, an animal wax, montan wax, a PEG with a molecular weight of at least 1000, and any combination of waxes.
28. The tablet formulation according to any of the preceding claims, wherein the wax is a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof; such as wherein said wax consist of 100% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof.
29. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of 25 to 75% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and comprises 25 to 75% w/w of one or more other waxes.
30. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of a petroleum based wax, such as microcrystalline wax; such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and microcrystalline wax; in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

31. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of a saturated solid triglyceride, such as a hydrogenated oil, such as selected from hydrogenated castor oil and hydrogenated cottonseed oil;  
5 such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and hydrogenated castor oil or hydrogenated cottonseed oil in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.
32. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of a plant wax, such as a plant wax selected from carnauba wax, candelilla wax, jojoba oil and ouricury wax;  
15 such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and a plant wax selected from carnauba wax, candelilla wax, jojoba oil and ouricury wax in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.
33. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of an animal wax, such as an animal wax selected from bees wax, spermaceti and lanolin;  
20 such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and an animal wax selected from bees wax, spermaceti and lanolin in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.
34. The tablet formulation according to any of the preceding claims, wherein said wax comprises montan wax; such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate,  
30 and any mixture thereof, and montan wax in a 95:5 to 50:50 ratio, such as a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.
35. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of a long chain saturated carboxylic acid, such as  
35 selected from stearic acid, palmitic acid, and stearic/palmitic acid,

5 such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and a long chain saturated carboxylic acid selected from stearic acid, palmitic acid and stearic/palmitic acid in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

10 36. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of a saturated long chain monoglyceride such as glycerol monostearate, such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and a saturated long chain monoglyceride such as glycerol monostearate in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

15 37. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of a long chain alcohol, such as stearyl alcohol, such as comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture thereof, and a long chain alcohol such as stearyl alcohol in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

20 38. The tablet formulation according to any of the preceding claims, wherein said wax comprises or consist of a PEG (polyethylene glycol) with a molecular weight of at least 1000 (PEG1000), such as a PEG with a molecular weight of at least 1,450 (PEG1450), such as a PEG with a molecular weight of at least 1,500 (PEG1500), such as a PEG with a molecular weight of at least 3,000 (PEG3000);  
25 such as a PEG with a molecular weight of 1000 to 100,000, such as 1,450 to 75,000, such as 3,000 to 50,00, such as 1,000 to 20,000, such as 1,450 to 20,000, such as 3,000 to 20,000.

30 39. The tablet formulation according to any of the preceding claims, wherein said wax comprises a combination of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, and glyceryl tribehenate, and any mixture

thereof, and a PEG with a molecular weight of at least 1000, in a 25:75 to a 75:25 ratio, such as about a 50:50 ratio.

- 5                   40. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises or consists of a wax and one or more binders and/or fillers, such as comprises or consist of more than 30% w/w and less than 70% w/w of a wax and more than 30% w/w and less than 70% w/w of one or more binders and/or fillers;
- 10                   such as wherein the delayed release layer comprises a wax and one or more binders and one or more fillers, or a wax and one or more binders, or a wax and one or more fillers, such as wherein the barrier layer comprises or consist of a wax and one or more binders.
- 15                   41. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises one or more binders selected from L-HPC, HPC, isomalt, microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC), cellulose, methylcellulose,
- 20                   polymethacrylates, sodium carboxymethyl cellulose (sodium CMC), polyvinyl pyrrolidone (PVP), starch, pregelatinized starch, sodium alginate and gelatin.
42. The tablet formulation according to any of the preceding claims, wherein the delayed release layer comprises one or more binders selected from L-HPC,
- 25                   HPC, isomalt, MCC, starch and pregelatinized starch.
43. The tablet formulation according to any of the preceding claims, wherein the barrier layer comprises one or more binders selected from L-HPC, HPC, isomalt, MCC and pregelatinized starch.
- 30                   44. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and the barrier layer comprises or consists of a wax and one or more L-HPC, such as two L-HPC.

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45. The tablet formulation according to any of the preceding claims, wherein the one or more L-HPC has a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-21.

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46. The tablet formulation according to any of the preceding claims, wherein the one or more L-HPC has a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-32.

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47. The tablet formulation according to any of the preceding claims, wherein the one or more L-HPC has a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 130,000, and optionally a mean particle size of 55  $\mu\text{m}$  (45-65  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-11.

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48. The tablet formulation according to any of the preceding claims, wherein the one or more L-HPC has a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 135,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-22.

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49. The tablet formulation according to any of the preceding claims, wherein the one or more L-HPC has a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 140,000, and optionally a mean particle size of 55  $\mu\text{m}$  (45-65  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-B1.

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50. The tablet formulation according to any of the preceding claims, wherein the one or more L-HPC has a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 100,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); such as wherein said one or more L-HPC is LH-31.

51. The tablet formulation according to any of the preceding claims, wherein the one or more L-HPC has a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 14 weight% (13-15.9%); such as wherein said one or more L-HPC is NBD-020; or

wherein the one or more L-HPC has a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 11 weight% (10-12.9%); such as wherein said one or more L-HPC is NBD-021; or

5 wherein the one or more L-HPC has a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ), a 90% cumulative particle size of 70-130  $\mu\text{m}$ , and a hydroxypropyl content of about 8 weight% (7-9.9%); such as wherein said one or more L-HPC is NBD-022.

10 52. The tablet formulation according to any of the preceding claims, wherein the wax and the one or more L-HPC are provided in a weight ratio of wax to L-HPC of 30:70 to 70:30 w/w, such as of 35:65 to 65:35 w/w, such as of 40:60 to 60:40 w/w, such as of 45:55 to 55:45 w/w;  
such as a weight ratio of wax to L-HPC of about 35:65 to 55:45 w/w; such as of  
15 about 40:60 to 50:50 w/w; such as of about 60:40 to 50:50 w/w;  
such as a weight ratio of wax to L-HPC of about 30:70; such as of about 35:65, such as of about 40:60 w/w, such as of about 41:59 w/w, such as of about 42:58 w/w, such as of about 43:57 w/w, such as of about 44:56 w/w, such as of about 45:55 w/w, such as of about 46:54 w/w, such as of about 47:53 w/w, such  
20 as of about 48:52 w/w, such as of about 49:51 w/w, such as of about 50:50 w/w.

53. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises or consists of a wax and two L-HPC.

25

54. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises a wax and an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); and  
30 an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ).

55. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises 30 to 70% w/w of one or more L-HPC, such as of two L-HPC, such as 35 to 65% w/w, such as 40 to 60% w/w, such as 45 to 60% w/w, such as 45 to 55% w/w, such as 42 to 62% w/w, such as 47 to 57% w/w, such as about 52% w/w of one or more L-HPC, such as two L-HPC.
56. The tablet formulation according to any of the preceding claims, wherein the barrier layer comprises *i)* an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu$ m (35-55  $\mu$ m); such as wherein said one or more L-HPC is LH-21; and *ii)* an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu$ m (17-23  $\mu$ m); such as wherein said one or more L-HPC is LH-32; and wherein the *i)* L-HPC and the *ii)* L-HPC in the barrier layer is provided in a weight ratio of *i)* L-HPC to *ii)* L-HPC of 20:80 to 80:20 w/w, such as of 25:75 to 75:25 w/w, such as of 30:70 to 70:30 w/w, such as of 35:65 to 65:35 w/w, such as of 40:60 to 60:40 w/w; such as a weight ratio of *i)* L-HPC to *ii)* L-HPC about 25:75 to 45:55 w/w; such as of about 30:70 to 40:60 w/w; such as a weight ratio of *i)* L-HPC to *ii)* L-HPC of about 30:70, such as of about 31:69, such as of about 32:68 w/w, such as of about 33:67 w/w, such as of about 34:66 w/w, such as of about 35:65 w/w, such as of about 36:64 w/w, such as of about 37:63 w/w, such as of about 38:62 w/w, such as of about 39:61 w/w, such as of about 40:60 w/w.
57. The tablet formulation according to any of the preceding claims, wherein the delayed release layer comprises *i)* an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu$ m (35-55  $\mu$ m); such as wherein said one or more L-HPC is LH-21; and *ii)* an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu$ m (17-23  $\mu$ m); such as wherein said one or more L-HPC is LH-32;

- and wherein the *i)* L-HPC and the *ii)* L-HPC in the delayed release layer is provided in a weight ratio of *i)* L-HPC to *ii)* L-HPC of 30:70 to 70:30 w/w, such as of 35:65 to 65:35 w/w, such as of 40:60 to 60:40 w/w, such as of 45:55 to 55:45 w/w;
- 5        such as a weight ratio of *i)* L-HPC to *ii)* L-HPC about 35:65 to 55:45 w/w; such as of about 40:60 to 50:50 w/w; such as of about 40:60 to 50:50 w/w; such as a weight ratio of *i)* L-HPC to *ii)* L-HPC of about 35:65, such as of about 40:60, such as of about 41:59 w/w, such as of about 42:58 w/w, such as of about 43:57 w/w, such as of about 44:56 w/w, such as of about 45:55 w/w, such as of about 50:50 w/w.
- 10
58. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer further comprises a HPC (hydroxypropyl cellulose).
- 15
59. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises or consists of a wax, two or more L-HPC and a HPC.
- 20
60. The tablet formulation according to any of the preceding claims, wherein said HPC has a viscosity of 2.0 to 50 mPa·s (at 20°C/2% w/w aq. solution); such as a HPC with a viscosity of 2.0 to 2.9 mPa·s (HPC-SSL); such as a HPC with a viscosity of 3.0 to 5.9 mPa·s (HPC-SL); such as a HPC with a viscosity of 6.0 to 10.0 mPa·s (HPC-L);
- 25        such as a HPC with a viscosity of 11 to 20 mPa·s (HPC-LM); such as a HPC with a viscosity of 21 to 50 mPa·s (HPC-LMM).
61. The tablet formulation according to any of the preceding claims, wherein said HPC is a HPC with a molecular weight of 40,000 – 280,000; such as a HPC
- 30        with a molecular weight of about 40,000, such as a molecular weight of about 100,000, such as a molecular weight of about 140,000, such as a molecular weight of about 180,000, such as a molecular weight of about 280,000.
62. The tablet formulation according to any of the preceding claims, wherein the
- 35        HPC is a HPC regular powder (40 mesh pass, D50 = 150-190 micrometres), a



HPC fine powder (100 mesh pass, D50 = 80-110 micrometres), or a HPC super fine powder (330 mesh pass, D50 = 20 micrometres); preferably a HPC fine powder (100 mesh pass, D50 = 80-110 micrometres).

- 5            63. The tablet formulation according to any of the preceding claims, wherein the HPC has a viscosity of 2.0 to 50 mPa·s (at 20°C/2% w/w aq. solution), a molecular weight of 40,000 – 280,000 and is a HPC fine powder (100 mesh pass, D50 = 80-110 micrometres).
- 10           64. The tablet formulation according to any of the preceding claims, wherein the HPC has a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% w/w aq. solution) and a molecular weight of about 140,000 which is HPC fine powder (100 mesh pass, D50 = 80-110 micrometres).
- 15           65. The tablet formulation according to any of the preceding claims, wherein the HPC is selected from a HPC with a viscosity of 150 to 300 mPa·s (at 20°C/2% w/w aq. solution) and a molecular weight of about 40,000; a HPC with a viscosity of 300 to 600 mPa·s (at 20°C/2% w/w aq. solution) and a molecular weight of about 80,000; and a HPC with a viscosity of 1,500 to 3,000 mPa·s (at
- 20           20°C/2% w/w aq. solution) and a molecular weight of about 1,150,000.
66. The tablet formulation according to any of the preceding claims, wherein delayed release layer and/or the barrier layer comprises 1 to 15% w/w HPC, such as 1 to 10% w/w HPC, such as 2 to 10% w/w HPC, such as 3 to 9% w/w
- 25           HPC, such as 4 to 8% w/w HPC, such as 5 to 7% w/w HPC, such as about 6% w/w HPC.
67. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises 32-52% w/w of wax,
- 30           42-62% w/w of one or more L-HPC such as two L-HPC, and 1-15% w/w HPC; such as comprises 38-46% w/w of wax, 48-56% w/w of one or more L-HPC such as two L-HPC, and 2-10% w/w HPC;
- such as comprises 38-40, 40-41, 41-42, 42-43, 43-44, 44-46% w/w of wax, 48-50, 50-51, 51-52, 52-53, 53-54, 54-56% w/w of one or more L-HPC such as two
- 35           L-HPC, and 2-4, 4-5, 5-6, 6-7, 7-8, 8-10% w/w HPC.

- 5 68. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises about 42% w/w of wax, about 52% w/w of one or more L-HPC such as two or more L-HPC, and about 6% w/w HPC.
- 10 69. The tablet formulation according to any of the preceding claims, wherein the wax is selected from  
100% w/w of a wax selected from a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; a petroleum based wax such as microcrystalline wax; a hydrogenated oil such as hydrogenated castor oil and hydrogenated cotton seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax; a PEG having a molecular weight of at least 1000; a saturated long chain  
15 monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol.
- 20 70. The tablet formulation according to any of the preceding claims, wherein said wax consist of 25-75% w/w, such as about 50% w/w, of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof, and 25-75% w/w, such as about 50% w/w, of a wax selected from a petroleum based wax such as microcrystalline wax; a hydrogenated oil such as hydrogenated castor oil and hydrogenated cotton  
25 seed oil; a plant wax such as carnauba wax and candelilla wax; an animal wax such as beeswax; a PEG having a molecular weight of at least 1000; a saturated long chain monoglyceride such as glycerol monostearate; a long chain saturated carboxylic acid such as stearic acid and/or palmitic acid; Montan wax; and a long chain alcohol such as stearyl alcohol.
- 30 71. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises 38-46% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof;

- 18-26% w/w of an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ );
- 26-34% w/w of an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); and
- 2-10% w/w of a fine powder HPC (100 mesh pass, D50 = 80-110 micrometres) with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% aq. solution).
72. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises about 42% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof;
- about 22% w/w of an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ );
- about 30% w/w of an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ); and
- about 6% w/w of a fine powder HPC (100 mesh pass, D50 = 80-110 micrometres) with a viscosity of 6.0 to 10.0 mPa·s (at 20°C/2% w/w aq. solution).
73. tablet formulation according to any of the preceding claims, wherein the barrier layer does not comprise a HPC, such as does not comprise a HPC with a viscosity of 2.0 to 50.0 mPa·s (at 20°C/2% aq. solution).
74. The tablet formulation according to any of the preceding claims, wherein the barrier layer comprises or consists of 32-52% w/w of wax and 48-68% w/w of one or more L-HPC, such as two L-HPC;
- such as comprises or consists of 38-46% w/w of wax and 44-52% w/w of one or more L-HPC, such as two L-HPC;
- such as comprises or consists of about 42% w/w of wax and about 58% w/w of one or more L-HPC, such as two L-HPC.

75. The tablet formulation according to any of the preceding claims, wherein the barrier layer comprises or consists of 38-46% w/w of a glyceryl ester selected from glyceryl behenate, glyceryl dibehenate, glyceryl tribehenate, and any mixture thereof; 16-24% w/w of an L-HPC with a hydroxypropyl content of about 11 weight% (10.0-12.9%), a molecular weight of about 120,000, and optionally a mean particle size of 45  $\mu\text{m}$  (35-55  $\mu\text{m}$ ); and 34-42% w/w of an L-HPC with a hydroxypropyl content of about 8 weight% (7.0-9.9%), a molecular weight of about 115,000, and optionally a mean particle size of 20  $\mu\text{m}$  (17-23  $\mu\text{m}$ ).
76. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises a wax and isomalt in a ratio of wax to isomalt of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35, such as about 66.6:33.3, such as wherein the delayed release layer and/or the barrier layer comprises a wax and MCC in a ratio of wax to MCC of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35; such as wherein the delayed release layer and/or the barrier layer comprises a wax and isomalt and MCC in a ratio of wax to isomalt and MCC of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35; such as wherein the delayed release layer and/or the barrier layer comprises a wax and isomalt and MCC in a ratio of about 50:25:25.
77. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer comprises a wax and starch or pregelatinized starch; such as comprises a wax and pregelatinized starch in a ratio of wax to pregelatinized starch of about 50:50, such as of about 40:60 to 60:40, such as of about 35:65 to 65:35.
78. The tablet formulation according to any of the preceding claims, wherein the delayed release layer comprises one or more fillers selected from mannitol, sorbitol, xylitol, lactose, sucrose, cellulose, glucose, calcium carbonate, calcium phosphate and calcium hydrogen phosphate dihydrate; such as comprises one or more water-soluble fillers selected from mannitol, sorbitol and lactose;

such as comprises 10 to 65% w/w of mannitol, sorbitol, and/or lactose, such as 20 to 60% w/w, such as 30 to 60% w/w, such as 40 to 60% w/w, such as about 50% w/w.

- 5           79. The tablet formulation according to any of the preceding claims, wherein the delayed release layer and/or the barrier layer further comprises a disintegrant selected from crospovidone, sodium starch glycolate and croscarmellose sodium;
- 10           such as comprises 1% to 10% w/w of said disintegrant, such as about 2% to 8% w/w, such as about 3% to 7% w/w, such as about 4% to 6% w/w, such as about 5% w/w of said disintegrant.
- 15           80. The tablet formulation according to any of the preceding claims, wherein the delayed release layer constitutes 50 to 75% w/w of the final tablet weight; such as 55 to 70% w/w, such as 59 to 68% w/w, such as 60 to 67% w/w, such as 50-55% w/w, such as 55-56, 56-57, 57-58, 58-59, 59-60, 60-61, 61-62, 62-63, 63-64, 64-65, 65-66, 66-67, 67-68, 68-69, 69-70 or 70-75% w/w of the final tablet weight;
- 20           such as wherein the delayed release layer constitutes about 58.0% w/w, about 58.5% w/w, about 59.0% w/w, about 59.5% w/w, about 60.0% w/w, about 60.5% w/w, about 61.0% w/w, about 61.5% w/w, about 62.0% w/w, about 62.5% w/w, about 63.0% w/w, about 63.5% w/w, about 64.0% w/w, about 64.5% w/w, about 65.0% w/w, about 65.5% w/w, about 66.0% w/w, about 66.5% w/w, about 67.0% w/w, about 67.5% w/w, about 68.0% w/w, about 68.5% w/w, about 69.0%, about 69.5% w/w, about 70.0% of the final tablet weight.
- 25           81. The tablet formulation according to any of the preceding claims, wherein the delayed release layer delays the release of the two or more active agents for 3 to 5 hours, such as for 3.5 to 4.5 hours a, such as for about 4 hours, and wherein said delayed release layer constitutes 59 to 63.5% w/w, such as 60 to 63% w/w of the final tablet weight;
- 30           such as 59.0-59.5% w/w, 59.5-60.0% w/w, 60.0-60.5% w/w, about 60.5-61.0% w/w, about 61.0-61.5% w/w, about 61.5-62.0% w/w, about 62.0-62.5% w/w, 62.5-63.0% w/w , 63.0 to 63.5% w/w of the final tablet weight;
- 35

such as about 60.0% w/w, about 60.5% w/w, about 61.0% w/w, about 61.5% w/w, about 62.0% w/w, about 62.5% w/w, about 63.0% w/w of the final tablet weight.

- 5           82. The tablet formulation according to any of the preceding claims, wherein the delayed release layer delays the release of the two or more active agent for 5 to 7 hours, such as for 5.5 to 6.5 hours, such as for about 6 hours, and wherein said delayed release layer constitutes 63.5 to 68% w/w, such as 64 to 67% w/w of the final tablet weight;
- 10           such as 63.5 to 64.0% w/w, 64.0-64.5% w/w, 64.5-65.0% w/w, 65.0-65.5% w/w, 65.5-66.0% w/w, 66.0-66.5% w/w, 66.5-67.0% w/w, 67.0 to 67.5% w/w, 67.5 to 68.0% w/w of the final tablet weight;
- such as about 64.0% w/w, about 64.5% w/w, about 65.0% w/w, about 65.5% w/w, about 66.0% w/w, about 66.5% w/w, about 67.0 w/w of the final tablet
- 15           weight.
83. The tablet formulation according to any of the preceding claims, wherein the barrier layer constitutes 25 to 50% w/w of the combined weight of the core such as the triple-layer core, such as 25-30, 30-35, 35-40, 40-45, 45-50% w/w of the
- 20           combined weight of the core; such as about 30-40% w/w, such as about 30-32, 32-34, 34-36, 36-38, 38-40% w/w of the combined weight of the core; such as about 32-33, 33-34, 34-35, 35-36, 36-37, 37-38% w/w, such as 34-38% w/w, such as about 35-37% w/w of the combined weight of the core.
84. The tablet formulation according to any of the preceding claims, wherein the barrier layer constitutes 5 to 25% w/w of the final tablet weight; such as 5-10, 10-15, 15-20, 20-25% w/w of the final tablet weight; such as 10 to 20% w/w, such as 10 to 17.5% w/w of the final tablet weight; such as about 12.5% w/w of
- 25           the final tablet weight, such as about 14% w/w of the final tablet weight.
- 30           85. The tablet formulation according to any of the preceding claims, wherein the release of the active agents is delayed for 3 to 5 hours, such as for 3.5 to 4.5 hours, such as for about 4 hours, and said barrier layer constitutes 13.25 to 25% w/w of the final tablet weight.
- 35

- 5 86. The tablet formulation according to any of the preceding claims, wherein the release of the active agents is delayed for 5 to 7 hours, such as for 5.5 to 6.5 hours, such as for about 6 hours, and said barrier layer constitutes 5 to 13.25% w/w of the final tablet weight.
- 10 87. The tablet formulation according to any of the preceding claims, wherein the delayed release is essentially equally thick on all sides of the core, such as triple-layer core, such as essentially equally thick on the planar side of the second core or core layer, and the planar side of the first core or core layer.
- 15 88. The tablet formulation according to any of the preceding claims, wherein the core or triple-layer core is essentially symmetrically placed within the tablet formulation, i.e. within the delayed release layer.
- 20 89. The tablet formulation according to any of the preceding claims, wherein the core or triple-layer core is asymmetrically placed within the tablet formulation, i.e. within the delayed release layer.
- 25 90. The tablet formulation according to any of the preceding claims, wherein the delayed release layer is 0.25 to 10% thicker, such as 0.25 to 5% thicker, on the planar side of the second core or core layer than the planar side of the first core or core layer, such as 0.25 to 0.5% thicker, such as 0.5 to 0.6% thicker, such as 0.6 to 0.7% thicker, such as 0.7 to 0.8% thicker, such as 0.8 to 0.9% thicker, such as 0.9 to 1.0% thicker, such as 1.0 to 1.5% thicker, such as 1.5 to 2.0% thicker, such as 2.0 to 2.5% thicker, such as 2.5 to 3.0% thicker, such as 3.0 to 3.5% thicker, such as 3.5 to 4.0% thicker, such as 4.0 to 4.5% thicker, such as 4.5 to 5.0% thicker, such as 5.0 to 7.5% thicker, such as 7.5 to 10% thicker on the planar side of the second core or core layer than the planar side of the first core or core layer.
- 30 91. The tablet formulation according to any of the preceding claims, wherein the delayed release layer weighs 0.25 to 10% more, such as 0.25 to 5%, more, on the planar side of the second core or core layer than the planar side of the first core or core layer,

- such as 0.25 to 0.5% more, such as 0.5 to 0.6% more, such as 0.6 to 0.7% more, such as 0.7 to 0.8% more, such as 0.8 to 0.9% more, such as 0.9 to 1.0% more, such as 1.0 to 1.5% more, such as 1.5 to 2.0% more, such as 2.0 to 2.5% more, such as 2.5 to 3.0% more, such as 3.0 to 3.5% more, such as 3.5 to 4.0% more, such as 4.0 to 4.5% more, such as 4.5 to 5.0% more, such as 5.0 to 7.5% more, such as 7.5 to 10% more on the planar side of the second core or core layer than the planar side of the first core or core layer.
- 5
92. The tablet formulation according to any of the preceding claims, wherein the planar side of the second core layer constitutes 50.1% to 60% of the delayed release layer, such as 50.1% to 55%, such as 50.1 to 50.2%, such as 50.2 to 50.3%, such as 50.3 to 50.4%, such as 50.4 to 50.5%, such as 50.5 to 50.6%, such as 50.6 to 50.7%, such as 50.7 to 50.8%, such as 50.8 to 50.9%, such as 50.9 to 51%, such as 51 to 51.5%, such as 51.5 to 52%, such as 52 to 52.5%, such as 52.5 to 53%, such as 53 to 53.5%, such as 53.5 to 54%, such as 54 to 54.5%, such as 54.5 to 55%, such as 55 to 56%, such as 56 to 57%, such as 57 to 58%, such as 58 to 59%, such as 59 to 60%.
- 10
- 15
93. The tablet formulation according to any one of the preceding claims, wherein the first active agent prevents conversion of levodopa (L-DOPA) to dopamine by DOPA decarboxylase.
- 20
94. The tablet formulation according to any one of the preceding claims, wherein the first active agent is a DOPA decarboxylase inhibitor.
- 25
95. The tablet formulation according to any one of the preceding claims, wherein the first active agent is a DOPA decarboxylase inhibitor and wherein the second active agent is a dopamine precursor or a dopamine prodrug.
- 30
96. The tablet formulation according to any one of the preceding claims, wherein the first active agent is a DOPA decarboxylase inhibitor and wherein the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.
- 35
97. The tablet formulation according to any one of the preceding claims, wherein the DOPA decarboxylase inhibitor is selected from carbidopa, benserazide,



methyl dopa and  $\alpha$ -difluoromethyl-DOPA (DFMD), and a pharmaceutically acceptable derivative thereof.

5 98. The tablet formulation according to any one of the preceding claims, wherein the DOPA decarboxylase inhibitor is carbidopa, or a pharmaceutically acceptable derivative thereof.

10 99. The tablet formulation according to any one of the preceding claims, wherein the first active agent is carbidopa, or a pharmaceutically acceptable derivative thereof, and wherein the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.

15 100. The tablet formulation according to any one of the preceding claims, wherein the first active agent prevents conversion of levodopa (L-DOPA) to 3-O-methyldopa (3-OMD) by catechol-O-methyltransferase (COMT); such as wherein the first active agent is a catechol-O-methyltransferase (COMT) inhibitor; such as wherein the COMT inhibitor is selected from tolcapone, entacapone, opicapone, nitecapone and nebicapone.

20 101. The tablet formulation according to any one of the preceding claims, wherein the first active agent is a COMT inhibitor and wherein the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.

25 102. The tablet formulation according to any one of the preceding claims, wherein the first active agent is a combination of a DOPA decarboxylase inhibitor and a COMT inhibitor, and the second active agent is levodopa, or a pharmaceutically acceptable derivative thereof.

30 103. The tablet formulation according to any one of the preceding claims, wherein said levodopa comprises levodopa and pharmaceutically acceptable derivatives of levodopa, including but not limited to levodopa prodrugs, such as selected from an ester, amide, dimeric amide, carrier-mediated, peptide transport-mediated, peptidyl, cyclic, chemical delivery systems and enzyme-models prodrugs; such as a levodopa prodrug selected from a levodopa ester, 35 levodopa methyl ester and XP21279.

104. The tablet formulation according to any one of the preceding claims,  
wherein said levodopa comprises pharmaceutically acceptable derivatives of  
levodopa, including but not limited to modified levodopa, such as deuterated  
5 levodopa and partially deuterated levodopa.
105. The tablet formulation according to any one of the preceding claims,  
wherein the first active agent is levodopa, and wherein the second active agent  
is a pharmaceutically acceptable derivative of levodopa, such as a levodopa  
10 prodrug or modified levodopa; or  
wherein the first active agent is a pharmaceutically acceptable derivative of  
levodopa, such as a levodopa prodrug or modified levodopa, and wherein the  
second active agent is levodopa.
106. The tablet formulation according to any one of the preceding claims,  
wherein the first active agent and/or the second active agent is a dopamine  
precursor; such as selected from L-phenylalanine, L-tyrosine and L-DOPA  
(levodopa), or a pharmaceutically acceptable derivative thereof
107. The tablet formulation according to any one of the preceding claims,  
wherein the first active agent and/or the second active agent is a dopamine  
agonist; such as selected from a biased dopamine agonist, a partial dopamine  
agonist, a selective dopamine agonist, and a full dopamine agonist; such as a  
20 dopamine agonist selected from bromocriptine (Parlodel), pergolide (Permax),  
pramipexole (Mirapex, Sifrol), ropinirole (Requip), piribedil (Pronora, Trivastal),  
cabergoline (Dostinex), apomorphine (Apokyn), dihydroergocryptine,  
25 propylnorapomorphine, lisuride, Ciladopa, dihydrexidine, dinapsoline,  
doxanthrine, epicriptine, quinagolide (Norprolac), rotigotine (Neupro), roxindole,  
sumanirole, fenoldopam, and any pharmaceutically acceptable derivatives  
30 thereof.
108. The tablet formulation according to any one of the preceding claims,  
wherein the first active agent and/or the second active agent is an indirect  
dopamine agonist; such as an indirect dopamine agonist selected from a  
35 dopamine reuptake inhibitor / transporter blocker and a dopamine releasing

agent; such as an indirect dopamine agonist selected from amphetamine, dextroamphetamine, Bupropion (Wellbutrin), Amineptine, nomifensine, Lisdexamfetamine, Methylphenidate (Ritalin) or dexamethylphenidate, methylenedioxypyrovalerone (MDPV; "Sonic"), ketamine, phencyclidine (PCP), Cathinone, Cocaine, amphetamine, Methamphetamine, methylenedioxymethamphetamine (MDMA), Phenethylamine, p-Tyramine, lisdexamfetamine (Vyvanse), phenmetrazine, pemoline, 4-methylaminorex (4-MAR), benzyloxyphenylamine, and Vesicular monoamine transporter 2 (VMAT2) inhibitors such as reserpine, tetrabenazine, and deserpidine.

109. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer each comprises 40-90% w/w of an active agent, and 10-60% w/w of one or more excipients; such as comprises 30-80% w/w of an active agent and 20-70% w/w of one or more excipients;

such as wherein the first core or core layer and the second core or core layer each comprises 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, 70-75, 75-80, 80-85, 85-90% w/w of an active agent and 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50, 50-55, 55-60% w/w of one or more excipients.

110. The tablet formulation according to any of the preceding claims, wherein the first core or core layer comprises 30-70% w/w, such as 40-60% w/w of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof, and 30-70% w/w, such as 40-60% w/w of one or more excipients; such as comprises about 50% w/w of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof, and about 50% w/w of one or more excipients.

111. The tablet formulation according to any of the preceding claims, wherein the first core or core layer comprises 2.5 to 250 mg of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof; such as comprises 2.5-5 mg, 5-10, 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-50, 50-60, 60-70, 70-75, 75-80, 80-90, 90-100, 100-125, 125-150, 150-200, 200-250 mg of a first active agent, such as a

5 DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof; such as comprises 10-100 mg, 10-75 mg, 10-50 mg, 10-40 mg or 15-35 mg, such as about 25 mg of a first active agent, such as a DOPA decarboxylase inhibitor such as carbidopa, or a pharmaceutically acceptable derivative thereof.

10 112. The tablet formulation according to any of the preceding claims, wherein the second core or core layer comprises 50-90% w/w, such as 60-90% w/w, such as 70-90% w/w of a second active agent, such as levodopa, or a pharmaceutically acceptable derivative thereof, and 10-50% w/w, such as 10-40% w/w, such as 10-30% w/w of one or more excipients; such as comprises 50-80% w/w, such as 50-70% w/w, of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, and 20-50% w/w, such as 30-50% w/w of one or more excipients; 15 such as comprises 60-80% w/w, such as 60-70% w/w, of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, and 20-40% w/w, such as 30-40% w/w of one or more excipients.

20 113. The tablet formulation according to any of the preceding claims, wherein the second core or core layer comprises 10 to 1000 mg of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof, such as comprises 10-20 mg, 20-25, 25-30, 30-40, 40-50, 50-60, 60-70, 70-75, 75-80, 80-90, 90-100, 100-125, 125-150, 150-175, 175-200, 200-250, 250-300, 300-400, 400-500, 500-750, 750-1000 mg of a second active agent, such as 25 levodopa or a pharmaceutically acceptable derivative thereof; such as comprises 25-250 mg, 25-200 mg, 50-200 mg, or 50-150 mg, such as about 100 mg of a second active agent, such as levodopa or a pharmaceutically acceptable derivative thereof.

30 114. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises one or more excipients, such as one or more immediate release excipients, such as one or more excipients selected from a filler, a compressing agent, a disintegration agent, a lubricant and a binder.

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115. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises a filler and/or compressing agent selected from isomalt, microcrystalline cellulose, calcium hydrogen phosphate, lactose, mannitol, sorbitol, cellulose, dextrose, starch, hydrolysed starch, and mixtures thereof.
116. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises a compressing agent, such as microcrystalline cellulose.
117. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises a disintegration agent selected from croscarmellose sodium, sodium starch glycolate, starch, starch derivatives, cellulose derivatives, bentonite, polyvinylpyrrolidone (PVP), and mixtures thereof.
118. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises a lubricant selected from magnesium stearate, steric acid, talc, PEG, silica, colloidal silicas, silicone dioxide, and mixtures thereof.
119. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises a binder selected from methyl cellulose, polyvinylpyrrolidone (PVP), hydroxy propyl methyl cellulose, hydroxy propyl cellulose, gelatine, sorbitol, sodium alginate, and mixtures thereof.
120. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises one or more excipients selected from microcrystalline cellulose, isomalt, croscarmellose sodium, sodium starch glycolate, and magnesium stearate.
121. The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises

microcrystalline cellulose and/or isomalt, such as comprises microcrystalline cellulose and isomalt.

- 5           122.       The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises 15 to 50% w/w of filler and/or compressing agent, such as 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50% w/w filler and/or compressing agent.
- 10           123.       The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises 15 to 50% w/w of microcrystalline cellulose and/or isomalt, such as 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50% w/w microcrystalline cellulose and/or isomalt.
- 15           124.       The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises 1.0 to 8.0% w/w of disintegration agent, such as 1.0-2.0, 2.0-3.0, 3.0-4.0, 4.0-5.0, 5.0-6.0, 6.0-7.0, 7.0-8.0% w/w of disintegration agent.
- 20           125.       The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises 0.5 to 5.0% w/w croscarmellose sodium, such as 0.5-1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5, 2.5-3.0, 3.0-3.5, 3.5-4.0, 4.0-4.5, 4.5-5.0% w/w croscarmellose sodium.
- 25           126.       The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises 0.5 to 5.0% w/w sodium starch glycolate, such as 0.5-1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5, 2.5-3.0, 3.0-3.5, 3.5-4.0, 4.0-4.5, 4.5-5.0% w/w sodium starch glycolate.
- 30           127.       The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises 1.0 to 10% w/w PVP, such as 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10% w/w PVP.
- 35           128.       The tablet formulation according to any of the preceding claims, wherein the first core or core layer and the second core or core layer comprises 0.1 to 5.0% w/w of lubricant, such as 0.1-0.2, 0.2-0.3, 0.3-0.4, 0.4-0.5, 0.5-0.75, 0.75-

1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0, 2.0-2.25, 2.25-2.5, 2.5-2.75, 2.75-3.0, 3.0-3.5, 3.5-4.0, 4.0-4.5, 4.5-5.0 % w/w of lubricant.

129. The tablet formulation according to any of the preceding claims, wherein  
5 the first core or core layer and the second core or core layer comprises 0.2 to 3.0% w/w magnesium stearate, such as 0.2-0.3, 0.3-0.4, 0.4-0.5, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0, 2.0-2.25, 2.25-2.5, 2.5-2.75, 2.75-3.0% w/w magnesium stearate; and/or  
10 comprises 0.2 to 2.0% w/w silicone dioxide, such as 0.2-0.3, 0.3-0.4, 0.4-0.5, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0% w/w silicone dioxide.

130. The tablet formulation according to any of the preceding claims, wherein  
the first core or core layer comprises 40-60% w/w of a first active agent, 20-  
25% w/w microcrystalline cellulose, 20-25% w/w isomalt, 1-5% w/w  
15 croscarmellose sodium, 1-5% w/w sodium starch glycolate and 0.5-2.0 % w/w magnesium stearate.

131. The tablet formulation according to any of the preceding claims, wherein  
the first core or core layer comprises 40-60% w/w of a first active agent; 15-  
20 25% w/w microcrystalline cellulose, 15-25% w/w isomalt, 1-8 % w/w PVP, 1-5% w/w croscarmellose sodium, 1-5% w/w sodium starch glycolate, 0.5-2.0 % w/w magnesium stearate and 0.1-1.0 % w/w silicon dioxide.

132. The tablet formulation according to any of the preceding claims, wherein  
the second core or core layer comprises 70-90% w/w of a second active agent,  
25 5-14% w/w microcrystalline cellulose, 5-14% w/w isomalt, 0.2-2.0% w/w croscarmellose sodium, 0.2-2.0% w/w sodium starch glycolate and 0.1-1.5 w/w magnesium stearate.

133. The tablet formulation according to any of the preceding claims, wherein  
30 the second core or core layer comprises 60-75% w/w of a second active agent; 7-17% w/w microcrystalline cellulose, 7-17% w/w isomalt, 1-8% w/w PVP, 0.5-5.0% w/w croscarmellose sodium, 0.1-1.5% w/w magnesium stearate and 0.1-1.0% w/w silicon dioxide.

134. The tablet formulation according to any of the preceding claims, wherein the barrier layer constitutes 25 to 50% w/w of the combined weight of the core such as the triple-layer core, such as 30 to 40% w/w, such as 34 to 38% w/w of the combined weight of the core.

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135. The tablet formulation according to any of the preceding claims, wherein the barrier layer constitutes 5 to 25% w/w of the final tablet weight; such as 5-10, 10-15, 15-20, 20-25% w/w of the final tablet weight; such as 10 to 20% w/w, such as 10 to 17.5% w/w of the final tablet weight; such about 12.5% w/w of the final tablet weight, such as about 14% w/w of the final tablet weight.

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136. The tablet formulation according to any of the preceding claims, wherein the tablet has a dimension (final thickness) of 5.0 mm to 8.0 mm, such as 5.5 mm to 7.5 mm, such as 5.5 - 6.0, 6.0 - 6.5, 6.5 - 7.0, 7.0 - 7.5 mm.

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137. The tablet formulation according to any of the preceding claims, wherein the tablet has a weight of 500-1000 mg, such as 500-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-1000 mg.

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138. The tablet formulation according to any of the preceding claims further comprising one or more coatings, such as a film coating.

139. A tablet formulation according to any one of the preceding claims for use in the treatment of morning akinesia.

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140. A tablet formulation according to any one of the preceding claims for use in the treatment of morning akinesia in a patient with Parkinson's disease.

141. A tablet formulation according to any one of the preceding claims for use in the treatment of nocturnal symptoms in a patient with Parkinson's disease, such as one or more nocturnal symptoms selected from motor complications, immobility episodes, nocturnal immobility, nocturnal hypomobility, nocturnal akinesia and/or tremor.

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