

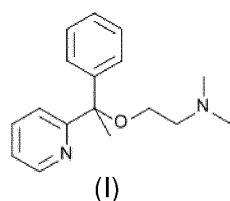
Title

A multiple unit oral dosage form of doxylamine succinate and pyridoxine hydrochloride free of titanium dioxide

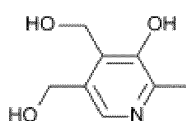
The present invention relates to a multiple unit oral dosage form comprising a capsule shell, a first plurality of modified release units of doxylamine or a pharmaceutically acceptable salt thereof and a second plurality of modified release units of pyridoxine or a pharmaceutically acceptable salt thereof, characterized in that said capsule shell does not contain titanium dioxide. It also relates to multiple unit oral dosage form wherein the capsule shell comprises at least one capsule shell material, preferably at least one capsule shell material and at least one organic colourant

Background Art

Doxylamine is the International Non-proprietary Name of (*RS*)-*N,N*-dimethyl-2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethanamine having the CAS number 469-21-6. Doxylamine is the first-generation of antihistamine that competitively, reversibly and non-specifically blocks H1 receptors and is also a non-specific antagonist that can block other receptors such as central or peripheral muscarinic receptors, with marked anticholinergic activity. It is commonly used in form of a salt and particularly in form of its succinate salt (cf. European Pharmacopoeia 10.0. doxylamine hydrogen succinate monograph pp.2476-2477) The structure of doxylamine corresponds to the formula (I):



On the other hand, pyridoxine also known as vitamin B₆ is the International Non-proprietary Name of 4,5-Bis(hydroxymethyl)-2-methylpyridin-3-ol having the CAS number 65-23-6. Pyridoxine is a water-soluble vitamin factor whose active form is pyridoxal phosphate. It acts as an enzyme co-factor in numerous biochemical reactions involved in the digestive breakdown of proteins and amino acids and, to a lesser extent, lipids and carbohydrates. It is also involved in the metabolism of unsaturated fatty acids and it is also a coenzyme for transaminases and decarboxylases allowing the conversion of tryptophan into nicotinic acid. Pyridoxine is commonly used in form of a salt and particularly in form of its hydrochloride salt (cf. European Pharmacopoeia 10.0. pyridoxine hydrochloride monograph pp.3676-3677). The structure of pyridoxine corresponds to the formula (II):



(II)

Doxylamine is commonly used by itself as a short-term sedative and also in combination with other drugs to provide night-time allergy and cold relief. Doxylamine is also used in combination with the analgesics paracetamol (acetaminophen) and codeine as an analgesic/calmativ preparation, and is prescribed in combination with pyridoxine to prevent morning sickness in pregnant women.

Modified release oral dosage forms of doxylamine succinate and pyridoxine hydrochloride with different pharmacokinetic and pharmacological properties have been disclosed in the state of the art.

Oral dosage forms of doxylamine succinate and pyridoxine hydrochloride with different pharmacokinetic and pharmacological properties have been disclosed in the

state of the art, for example in WO2013123569 and WO2021191268, all of them including titanium dioxide (TiO₂).

Besides gastro-resistant tablets of doxylamine succinate and pyridoxine hydrochloride containing TiO₂ are marketed with the name Xonvea®.

Furthermore, hard capsules containing TiO₂ in the capsule shell and filled with modified release pellets of doxylamine succinate and modified release pellets of pyridoxine hydrochloride are marketed with the name Cariban®, that is used is used for the symptomatic treatment of nausea and vomiting.

Titanium dioxide (TiO₂) is a naturally occurring mineral that is used in many industries (e.g. food, cosmetic, pharmaceutical and paint etc.) as a white colorant and opacifying agent. The pharmaceutical industry has been using TiO₂, as opacifier, in the coating of tablets, films of capsule shells or packaging material, to avoid degradation of medicine components induced by radiation or heat.

The ubiquitous use of titanium oxide is due to critical functions resulting from the fact that it has the following properties: it is an inert substance, it gives a consistent and homogeneous coloring and it provides radiation protection.

In particular, it is known in the art that the presence of titanium dioxide in the external coating film of tablets or pellets and in the capsule helps to protect the active ingredients against UV light, humidity and heat. It was considered an essential component of the protective layer which aids in preserving the safety, efficacy and quality of the product over its shelf life by supporting the physical and chemical integrity of the product (Handbook of Pharmaceutical Excipients, 9th edition, pages 1081-1084, 19 May 2020; EMA/504010/2021, 8 September 2021).

However, due to recent restrictions (Commission Regulation (EU) 2022/63 on TiO₂) in the Food sector on the use of titanium dioxide (TiO₂) and the possible future

extension of this restriction to the Pharma sector, there is the need of obtaining pharmaceutical forms free of TiO_2 .

Therefore, from what is known in the art, there is still the need of providing a modified release oral dosage form comprising a capsule shell free of TiO_2 and containing both active ingredients doxylamine and pyridoxine, which nevertheless exhibits an appropriate stability profile and a physical integrity for being used in therapy.

Summary of the invention

The inventors have surprisingly found that the absence of TiO_2 in the capsule shells of the multiple unit oral dosage forms of the present invention does not seem to have a negative influence either on the photo-stability or on the shelf-life stability at $25^\circ\text{C}/60\%\text{RH}$ and $30^\circ\text{C}/65\%\text{RH}$ of the multiple units contained within them.

Moreover, they have unexpectedly discovered that is not necessary to include any alternative opacifier in the capsule shell, such as a calcium salt, a barium salt, zinc oxide and/or magnesium oxide, instead of TiO_2 , in order to maintain the stability of the multiple unit oral dosage forms.

In particular, in the examples herein disclosed, the inventors have surprisingly found that the multiple unit oral dosage forms of the present invention are physicochemically stable and photostable in different conditions, and that they have a similar behaviour to the dosage forms with TiO_2 of the prior art, even though they are free of TiO_2 and they do not contain any alternative opacifier.

More in details, the inventors have observed the above-mentioned surprising effects by monitoring the visual appearance of the dosage form and of the small particles, the dissolution profile of doxylamine and pyridoxine, and the content of doxylamine and pyridoxine in the dosage form through accelerated and long-term stability studies. By doing so, the inventors have surprisingly found that the multiple unit oral

dosage forms of the present invention, although using a capsule shell free of TiO_2 , and free of an alternative opacifier as well, have the same stability of the same dosage forms comprising a capsule shell with TiO_2 .

Furthermore, the absence of TiO_2 in the multiple unit oral dosage forms of the present invention provide with an improved safety profile. This is advantageous for the oral dosage form of the present invention, because they will be aligned with the most updated safety regulations of the food legislation and the possibly future restrictions of the Health Authorities, which in the future will probably require obtaining pharmaceutical forms free of TiO_2 , for safety reasons.

The first aspect of the present invention therefore relates to a multiple unit oral dosage form comprising a capsule shell, a first plurality of modified release units of doxylamine or a pharmaceutically acceptable salt thereof and a second plurality of modified release units of pyridoxine or a pharmaceutically acceptable salt thereof, characterized in that said capsule shell does not contain TiO_2 .

According to a preferred embodiment said capsule shell is a hard capsule shell and comprises at least one capsule shell material.

In an embodiment, said capsule shell comprises at least one pharmaceutically acceptable capsule shell material and at least one pharmaceutically acceptable organic colourant.

In a further preferred embodiment, in the oral dosage form of the present invention the capsule shell consists of at least one pharmaceutically acceptable capsule shell material, at least one pharmaceutically acceptable organic colourant, water and, optionally, at least a pharmaceutically acceptable gelling agent, at least one pharmaceutically acceptable co-gelling agent (also known as gelling promoter), at least one pharmaceutically acceptable plasticizer and/or at least one

pharmaceutically acceptable inorganic colourant other than TiO_2 .

Preferably, said capsule shell material is selected from gelatine, hydroxypropylmethylcellulose (also known as hypromellose or HPMC), pullulan, alginate, carrageenan, cellulose and/or starch.

According to a preferred embodiment, said capsule shell consists of gelatine, water, at least one pharmaceutically acceptable organic colourant and, optionally, at least one pharmaceutically acceptable plasticizer and/or at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .

According to a further preferred embodiment, said capsule shell consists of gelatine, water, at least one pharmaceutically acceptable organic colourant and, optionally, at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .

According to a preferred embodiment, said capsule shell consists of HPMC, water, at least one pharmaceutically acceptable gelling agent, at least one pharmaceutically acceptable co-gelling agent, at least one pharmaceutically acceptable organic colourant and, optionally, at least one pharmaceutically acceptable plasticizer and/or at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .

According to a further preferred embodiment, said capsule shell consists of HPMC, water, at least one pharmaceutically acceptable gelling agent, at least one pharmaceutically acceptable co-gelling agent, at least one pharmaceutically acceptable organic colourant and optionally at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .

According to a preferred embodiment, said capsule shell consists of HPMC, water, at least one pharmaceutically acceptable organic colourant and optionally at least one pharmaceutically acceptable plasticizer and/or at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .

According to a preferred embodiment, said pharmaceutically acceptable organic colourant can be any organic colourant approved by the pertinent authorities for use in medicines and/or food. Preferably, it is selected from the group consisting of Curcumin (E100), Riboflavin (E101), Riboflavin-5'-phosphate (E101a), Tartrazine (E102 or FD&C Yellow 5), Quinoline yellow (E104), Sunset Yellow FCF (E110 or Orange Yellow S, FD&C Yellow 6), Carminic acid/Carmine (E120 or Natural Red 4), Carmoisine (E122 or Azorubine), Amaranth (E123 or FD&C Red 2), Ponceau 4R (E124 or Brilliant Scarlet 4R), Erythrosine (E127 or FD&C Red 3), Allura Red AC (E129 or FD&C 40), Patent Blue V (E131), Indigo carmine (E132 or FD&C Blue 2), Brilliant blue FCF (E133 or FD&C Blue 1), Chlorophylls and Chlorophyllins (E140), copper complexes of Chlorophylls and Chlorophyllins (E141), Green S (E142), Fast Green FCF (E143 or FD&C Green 3), Plain caramel (E150a), Caustic sulfite caramel (E150b), Ammonia caramel (E150c), Sulfite ammonia caramel (E150d), Black PN (E151 or Brilliant Black BN), Brown HT (E155), Alpha-carotene, Beta-carotene, Gamma-carotene (E160a), Annatto, Bixin, Norbixin (E160b), Paprika oleoresin: capsanthin, capsorubin (E160c), Lycopene (E160d), Beta-apo-8'-carotenal (E160e), Lutein (E161b), Canthaxanthin (E161g), Beetroot Red, Betanin (E162), Anthocyanins (E163), Saffron (E164) and mixtures thereof.

In a preferred embodiment, said organic colourant is selected from Indigo carmine, Patent Blue V, Brilliant blue, Erythrosine, Allura Red AC, Quinoline yellow and mixtures thereof. Even more preferably, it is Indigo carmine and/or Patent Blue V.

According to a preferred embodiment of the present invention the multiple units of doxylamine or a pharmaceutically acceptable salt thereof and the multiple units of pyridoxine or a pharmaceutically acceptable salt thereof are contained within the capsule shell, preferably within a hard capsule shell constituted by a body and a cap.

In a preferred embodiment, in the oral dosage form of the present invention the modified release units of doxylamine or a pharmaceutically acceptable salt thereof are small particles, preferably pellets, and the modified release units of pyridoxine or a pharmaceutically acceptable salt thereof are small particles, preferably pellets, and neither of them contain TiO₂.

In a preferred embodiment, each modified released unit of doxylamine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;
- an inner active coating layer comprising a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, one or more coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients;
- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, one or more anticaking agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients; and/or

each modified released unit of pyridoxine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;
- an inner active coating layer comprising a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, one or more coating agents,

and optionally one or more pharmaceutically acceptable excipients;

- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and

- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients; wherein the nucleus and any of the pharmaceutically acceptable excipients, preferably any of the coating agents, are free of TiO_2 .

In a further preferred embodiment in the oral dosage form of the present invention each modified released unit of doxylamine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;
- an inner active coating layer comprising a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, one or more coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients;
- an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, one or more anticaking agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients; and/or

each modified released unit of pyridoxine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;
 - an inner active coating layer comprising a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, one or more coating agents, and optionally one or more pharmaceutically acceptable excipients; and
 - an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients;
- wherein said nucleus and any of the pharmaceutically acceptable excipients, preferably any of the coating agents, are free of TiO_2 .

In a further preferred embodiment, in the oral dosage form of the present invention each modified released units of doxylamine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable active nucleus comprising a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipients;
- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, one or more anticaking agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients; and

each modified released units of pyridoxine or a pharmaceutically acceptable salt thereof comprising:

- a pharmaceutically acceptable active nucleus comprising a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipients; and
- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients, wherein said nucleus and any of the pharmaceutically acceptable excipients, preferably any of the coating agents, are free of TiO_2 .

According to a preferred embodiment the oral dosage form of the present invention comprises a pharmaceutically acceptable salt of doxylamine and a pharmaceutically acceptable salt of pyridoxine; preferably, it comprises doxylamine succinate and pyridoxine hydrochloride.

According to a further preferred embodiment, the oral dosage form according to the present invention comprises from 5 mg to 50 mg per oral dosage form of doxylamine or a pharmaceutically acceptable salt thereof; and from 5 mg to 50 mg per oral dosage form of pyridoxine or a pharmaceutically acceptable salt thereof.

The second aspect of the present invention relates to the use in therapy as medicament of the multiple unit oral dosage form of the present invention.

According to a preferred embodiment, the multiple unit oral dosage forms of the

present invention are for use in the symptomatic treatment of nausea and vomiting. Preferably, the multiple unit oral dosage forms of the invention are for use in the symptomatic treatment of nausea and vomiting associated with pregnant women (NVP).

In preferred embodiment, the multiple unit oral dosage forms of the invention are for use in the symptomatic treatment of nausea and vomiting associated with oncologic treatments, for instance chemotherapy or radiotherapy. This aspect could be also formulated as the use of multiple unit oral dosage form of the invention as defined above for the preparation of a medicament for the symptomatic treatment of nausea and vomiting. It also relates to a method for the prophylaxis and/or treatment of a mammal suffering, or susceptible to suffer, from nausea and vomiting, wherein the method comprises administering to said mammal the multiple unit oral dosage form of the invention as defined above. Preferably, the nausea and vomiting are associated with pregnant women (NVP) or with oncologic treatments, for instance chemotherapy or radiotherapy.

All the embodiments disclosed above for the multiple unit oral dosage form of the invention also apply for the multiple unit oral dosage form of the invention limited by its use.

The third aspect of the present invention refers to the manufacturing process for the preparation of the multiple unit dosage form of the present invention.

According to a preferred embodiment, the manufacturing process of the multiple unit oral dosage forms of the present invention comprises:

a) preparing, separately, a first plurality of modified release units of doxylamine or a pharmaceutically acceptable salt thereof and a second plurality of modified release units of pyridoxine or a pharmaceutically acceptable salt thereof,

- b) optionally, mixing one or both pluralities of said units prepared in step a) with additional excipients, or
- c) alternatively, mixing the first and second plurality of modified release units prepared in step a) together and then, optionally, mixing such mixture with additional excipients,
- d) filling a TiO₂-free capsule shell with:
 - individually and separately, the first plurality of modified release units of doxylamine or a pharmaceutically acceptable salt thereof obtained in step a), optionally mixed with additional excipients, and the second plurality of modified release units of pyridoxine or a pharmaceutically acceptable salt thereof obtained in step a), optionally mixed with additional excipients, or
 - alternatively, the mixture of the first and the second plurality of modified release units of doxylamine or a pharmaceutically acceptable salt and pyridoxine or a pharmaceutically acceptable salt thereof obtained in step c), optionally further mixed with additional excipients; and
- e) optionally, packaging the capsules obtained in step d) in blisters or bottles.

According to a preferred embodiment, said modified release units of doxylamine or a pharmaceutically acceptable salt thereof are small particles, preferably pellets, and said modified release units of pyridoxine or a pharmaceutically acceptable salt thereof are small particles, preferably pellets.

Detailed disclosure of the invention

All terms as used herein in this application, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions for certain terms as used in the present application are as set forth below and are intended to apply uniformly through-out the specification and claims unless

an otherwise expressly set out definition provides a broader definition.

For the purposes of the present invention, any ranges given include both the lower and the upper end-points of the range. Ranges and values given, such as temperatures, times, and the like, should be considered approximate, unless specifically stated.

The terms "percentage (%) by weight" or "percentage (%) w/w" have the same meaning and are used interchangeable. This term refers to the percentage of a component in relation to the total weight.

The terms "approximately" and "about" or "around" herein refer to the range of the experimental error, which may occur in a measurement. Preferably, the term "about" or "around" as used herein refers to a range of values $\pm 10\%$ of a specified value. For example, the expression "about 10" or "around 10" includes $\pm 10\%$ of 10, i.e. from 9 to 11.

The terms "comprising", "having", "including" and "containing" are to be construed open-ended terms (i.e. meaning "including, but not limited to") and are to be considered as providing support also for terms as "consist essentially of", "consisting essentially of", "consist of" or "consisting of".

The terms "consist essentially of", "consisting essentially of" are to be construed as semi-closed terms, meaning that no other ingredients which materially affects the basic and novel characteristics of the invention are included (optional excipients may thus be included). The terms "consists of", "consisting of" are to be construed as closed terms.

As it is known in the state of the art, the term "administration" refers to a method of delivering a formulation to a desired site. The terms "oral" and "oral administration" have the same meaning and they are used interchangeable. Specifically, they refer

to ingesting a drug by swallowing or chewing. Preferably, by swallowing.

The term “oral dosage form” refers to a dosage form to be ingested by oral route and usually intended for systemic effects resulting from drug absorption from the gastrointestinal tract. Preferably, the oral dosage form of the present invention is ingested by swallowing.

The term “multiple unit dosage form” defines a dosage form which consists of more than one unit which contains the effective amount of doxylamine or a pharmaceutically acceptable salt thereof and pyridoxine or a pharmaceutically acceptable salt thereof. Usually, the multiple unit dosage forms are based on subunits such as small particles, for instance granules or pellets, or minitabets and delivered in hard capsules or transformed into tablets. Preferably, the units of the present invention are small particles, such as granules or pellets, delivered in hard capsules.

In a preferred embodiment, the multiple unit dosage form of the present invention comprises a TiO₂-free hard capsule shell containing modified release units, preferably small particles, more preferably pellets, that comprise an effective amount of doxylamine or a pharmaceutically acceptable salt thereof and pyridoxine or a pharmaceutically acceptable salt thereof.

In the context of the present invention, the terms “TiO₂-free”, “free of TiO₂”, “does not contain TiO₂” or “devoid of TiO₂” means substantially free of titanium dioxide or only containing trace amounts of titanium dioxide or containing amounts of TiO₂ lower than the ones that could lead to a daily intake higher than 1.5 µg/day (threshold of genotoxic impurities that are expected to pose negligible carcinogenic risk according to the guideline ICH M7: *Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk* issued by the

European Medicines Agency), when used as excipient, particularly as colourant and/or opacifying agent, in coating formulations or dosage forms.

The term “opacifying agent” or “opacifier” refers to a substance added to a dosage form in order to make it opaque, not allowing light to pass through.

The term “colouring agent” or “colourant” refers to a substance added to a dosage form in order to give or change its colour.

In the context of the present invention, the colourants, both organic and inorganic, are used for the sole purpose of imparting a distinctive appearance to the capsule shell and they do not have opacifying properties.

The oral dosage form of the present invention does not contain any opacifier. Particularly, the capsule shell does not contain titanium dioxide, a calcium salt, a barium salt, zinc oxide and/or magnesium oxide.

As it is mentioned above, the multiple unit dosage form of the present invention comprises a capsule shell free of TiO_2 . Preferably, said TiO_2 -free capsule shell is a hard capsule shell and comprises at least one capsule shell material.

The hard capsules, unlike the soft capsules, are generally made of two halves, the body and the cap. The hard capsule shell of the present invention may be any of those approved by the pertinent authorities for pharmaceutical and/or food use on condition that it is free of TiO_2 .

In an embodiment, the capsule shell of the multiple unit dosage form of the present invention comprises at least one capsule shell material selected from the group consisting of gelatine, hydroxypropyl methylcellulose (also known as Hypromellose or HPMC), pullulan, alginate, carrageenan, cellulose, starch and mixtures thereof. Preferably, the capsule shell material is gelatine and/or HPMC.

The gelatine suitable for making the gelatine capsule shell of the present invention is

any of those approved by the pertinent authorities for pharmaceutical and/or food use. These gelatines are mainly obtained from bovine or porcine raw materials. Depending on the capsule content and on the target market group, manufacturers have flexibility in the raw material type and sometimes they opt to combine both types. In a particular embodiment, the gelatine capsule shell of the invention comprises gelatine of bovine origin.

The HPMC suitable for making the capsule shell of the present invention is any of those approved by the pertinent authorities for pharmaceutical and/or food use. HPMC is produced by synthetic modification of cellulose obtained from wood pulp and consists of partly methylated and hydroxypropylated cellulose units.

In an embodiment, the capsule shell comprises at least one capsule shell material and at least one organic colourant.

In a preferred embodiment, in the oral dosage form of the present invention the capsule shell consists of at least one capsule shell material, at least one organic colourant, water and, optionally, at least one gelling agent, at least one co-gelling agent, at least one inorganic colourant and/or at least one plasticizer.

In an embodiment, said organic colourant is selected from the group consisting of Curcumin (E100), Riboflavin (E101), Riboflavin-5'-phosphate (E101a), Tartrazine (E102 or FD&C Yellow 5), Quinoline yellow (E104), Sunset Yellow FCF (E110 or Orange Yellow S, FD&C Yellow 6), Carminic acid/Carmine (E120 or Natural Red 4), Carmoisine (E122 or Azorubine), Amaranth (E123 or FD&C Red 2), Ponceau 4R (E124 or Brilliant Scarlet 4R), Erythrosine (E127 or FD&C Red 3), Allura Red AC (E129 or FD&C 40), Patent Blue V (E131), Indigo carmine (E132 or FD&C Blue 2), Brilliant blue FCF (E133 or FD&C Blue 1), Chlorophylls and Chlorophyllins (E140), copper complexes of Chlorophylls and Chlorophyllins (E141), Green S (E142), Fast

Green FCF (E143 or FD&C Green 3), Plain caramel (E150a), Caustic sulfite caramel (E150b), Ammonia caramel (E150c), Sulfite ammonia caramel (E150d), Black PN (E151 or Brilliant Black BN), Brown HT (E155), Alpha-carotene, Beta-carotene, Gamma-carotene (E160a), Annatto, Bixin, Norbixin (E160b), Paprika oleoresin: capsanthin, capsorubin (E160c), Lycopene (E160d), Beta-apo-8'carotenal (E160e), Lutein (E161b), Canthaxanthin (E161g), Beetroot Red, Betanin (E162), Anthocyanins (E163), Saffron (E164) and a mixture thereof.

In a preferred embodiment, said organic colourant is selected from Indigo carmine, Patent Blue V, Brilliant blue, Erythrosine, Allura Red AC, Quinoline yellow and mixtures thereof, preferably it is selected from Indigo carmine; Patent Blue V; Brilliant blue; Patent Blue V and erythrosine; Indigo carmine and quinoline yellow; Indigo carmine and Allura Red AC. Even more preferably, the organic colourant is Indigo carmine and/or Patent Blue V.

For the purpose of the present invention Indigo carmine (also known as FD&C Blue 2 or indigotine or E132) refers to CAS Number 860-22-0. Patent Blue V (also known as E 131) refers to CAS Number 3536-49-0. Brilliant blue 1 (also known as FD&C Blue 1 or E133) refers to CAS Number 3844-45-9.

Erythrosine (also known as FD&C Red 3 or E127) refers to CAS Number 16423-68-0. Allura Red AC (also known as FD&C Red 40 or E12)) refers to CAS Number 25956-17-6. Quinoline yellow (also known as E104) refers to CAS Number 8004-92-0.

In a preferred embodiment, the inorganic colourant other than TiO_2 is selected from black, red and/or yellow iron oxides (E172), preferably it is yellow iron oxide.

In a preferred embodiment, any of the organic colourant is optionally used together with an inorganic colourant other than TiO_2 .

In a further preferred embodiment, any organic colourant selected from Indigo carmine, Patent Blue V, Brilliant blue, Erythrosine, Allura Red AC, Quinoline yellow and their mixtures, is used together with the inorganic colourant other than TiO_2 , preferably with yellow iron oxide.

In a preferred embodiment, the colourant is selected from Brilliant blue; Patent Blue V; Indigo carmine; Brilliant blue and yellow iron oxide, Patent Blue V and erythrosine; Indigo carmine and quinoline yellow; Indigo carmine and Allura Red AC.

The CAS Registry Numbers (also referred to as CAS RN or CAS Number) are well known by the skilled person in the art. Each CAS Number is a unique identification number assigned by the Chemical Abstracts Service (CAS) to every chemical substance described in the open scientific literature. E numbers are codes for substances used as food additives, for use within the European Union (EU) and European Free Trade Association (EFTA). The numbering scheme follows that of the International Numbering System (INS) as determined by the Codex Alimentarius committee. Particularly, the E100- E199 number range refers to colourants.

In a preferred embodiment, the gelling agent is selected from carrageenan, pectin, curdlan, gelatine and agar, preferably is carrageenan.

In a preferred embodiment, the co-gelling agent is a water-soluble compound containing one or more of potassium, ammonium and/or calcium ions, preferably is a potassium salt, more preferably is a potassium salt selected from chloride, acetate, sulphate, nitrate, bromide, citrate, phosphate and oxalate salt, even more preferably is potassium chloride.

In a preferred embodiment, the plasticizer is selected from glycerine, sorbitol and propylene glycol.

According to a preferred embodiment, said capsule shell is a hard capsule shell that

consists of gelatine, water, at least one organic colourant and, optionally, at least one plasticizer and/or at least one inorganic colourant other than TiO_2 .

According to a preferred embodiment, said capsule shell is a hard capsule shell that consists of gelatine, water and at least one organic colourant.

According to a preferred embodiment, said capsule shell is a hard capsule shell that consists of gelatine, water, at least one organic colourant and at least one inorganic colourant other than TiO_2 .

In a preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the TiO_2 -free capsule shell comprises gelatine in an amount from 80% w/w to 90% w/w, preferably from 81% w/w to 89% w/w, more preferably from 82% w/w to 86% w/w of the total weight of the capsule shell (cap and body).

In a further preferred embodiment, the multiple unit dosage form of the invention is one wherein the TiO_2 -free capsule shell comprises at least one organic colourant in an amount from 0,005% w/w to 5% w/w, preferably from 0,01% w/w to 3% w/w of the total weight of the capsule shell (cap and body).

In a further preferred embodiment, the multiple unit dosage form of the invention is one wherein the TiO_2 -free capsule shell comprises water in an amount from 12% w/w to 16% w/w, preferably from 13% w/w to 15% w/w, more preferably around 14,5% w/w of the total weight of the capsule shell (cap and body).

In a further preferred embodiment, the amounts of gelatine, organic colourant and water are such that their addition gives a result of 100% w/w.

In a further embodiment, the multiple unit dosage form of the invention is one wherein the TiO_2 -free capsule shell comprises at least one inorganic colourant other than TiO_2 in an amount from 0,5% w/w to 5% w/w, preferably from 1% w/w to 3% w/w of the total weight of the capsule shell (cap and body).

In a further embodiment, when the capsule shell comprises at least one inorganic colourant other than TiO_2 , the amounts of gelatine, organic colourant, water and inorganic colourant are such that their addition gives a result of 100% w/w.

In a preferred embodiment, the TiO_2 -free hard capsule shell of the invention consists of:

- gelatine in an amount from 81% to 89% w/w of the total weight of the capsule shell,
- at least one organic colourant in an amount from 0.01% to 3% w/w of the total weight of the capsule shell,
- water in an amount from 13% to 15% w/w of the total weight of the capsule shell.

According to a further preferred embodiment, said capsule shell is a hard capsule shell that consists of HPMC, at least one gelling agent, at least one co-gelling agent, at least one organic colourant, water and optionally at least one plasticizer and/or at least one inorganic colourant other than TiO_2 .

According to a further preferred embodiment, said capsule shell is a hard capsule shell that consists of HPMC, at least one organic colourant, water and optionally at least one plasticizer and/or at least one inorganic colourant other than TiO_2 .

According to a further preferred embodiment, said capsule shell is a hard capsule shell that consists of HPMC, at least one gelling agent, at least one co-gelling agent, at least one organic colourant and water.

According to a further preferred embodiment, said capsule shell is a hard capsule gel shell that consists of HPMC, at least one organic colourant and water.

In further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the TiO_2 -free capsule shell comprises HPMC in an amount from 90%

w/w to 99% w/w, preferably from 91% w/w to 97% w/w, more preferably from 93 to 94% w/w of the total weight of the capsule shell (cap and body).

In a further preferred embodiment, the multiple unit dosage form of the invention is one wherein the TiO₂-free capsule shell comprises at least one organic colourant in an amount from 0,01% to 5% w/w, preferably from 0,05% to 3% w/w, more preferably from 0.1% w/w and 1.5% w/w of the total weight of the capsule shell (cap and body).

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the TiO₂-free capsule shell comprises a gelling agent, preferably carrageenan, in an amount from 0.05% w/w to 5% w/w, preferably from 0.1% w/w to 1% w/w, more preferably from 0.2% w/w to 0.6% w/w of the total weight of the capsule shell (cap and body).

In a further preferred embodiment, the multiple unit dosage form of the invention is one wherein the TiO₂-free capsule shell comprises a co-gelling agent in an amount from 0.1% w/w to 1% w/w, preferably from 0.3% w/w to 0.7% w/w, more preferably from 0.4% w/w to 0.6% w/w of the total weight of the capsule shell (cap and body).

In a further preferred embodiment, the multiple unit dosage form of the invention is one wherein the TiO₂-free capsule shell comprises water in an amount from 2% w/w to 8% w/w, preferably from 3% w/w to 7% w/w, more preferably around 5% w/w of the total weight of the capsule shell (cap and body).

In a preferred embodiment, the amounts of HPMC, organic colourant, gelling agent, co-gelling agent and water are such that their addition gives a result of 100% w/w.

In a further preferred embodiment, when the capsule shell does not comprise either a gelling agent or a co-gelling agent, the amounts of HPMC, organic colourant and water are such that their addition gives a result of 100% w/w.

In a preferred embodiment, the TiO₂-free hard capsule shell of the invention consists

of:

- HPMC in an amount from 91% to 97% w/w of the total weight of the capsule shell,
- at least one organic colourant in an amount from 0.01% to 3% w/w of the total weight of the capsule shell,
- at least one gelling agent in an amount from 0.1% to 1% w/w of the total weight of the capsule shell,
- at least one co-gelling agent in an amount from 0.3% to 0.7% w/w of the total weight of the capsule shell,
- water in an amount from 3% to 7% w/w of the total weight of the capsule shell.

As it is disclosed above, the multiple unit dosage form of the present invention comprises two plurality of modified release units, preferably small particles. A "small particle" refers to a particle of which diameter, length, height, width, or the like is from 100 μm to 3000 μm , particularly from 300 μm to 1700. Small particles have approximately uniform sizes if the diameter, length, height, width, or the like of the smallest particle is at least about one half of the average diameter, length, height, width, or the like of the particles and if the diameter, length, height, width, or the like of the largest particle is at most about twice the average diameter, length, height, width, or the like of the particles. The term "pellet" refers to small particles with approximately uniform shapes and sizes produced by an extrusion process or by coating of pharmaceutically acceptable inert nucleus. Then, the term "pellet", "spherical pellet", "beads", "beadlets", "spherical particles", "spheroids" and "microspheres" have the same meaning and are used interchangeable. The term "granule" refers to small particles without approximately uniform shapes and sizes obtained by a granulation process. Generally, granules are less uniform in size or

shape than pellets. Thus, granules have a lower uniformity due to their irregular surfaces and afford unacceptable dose uniformity and an inappropriate dissolution profile. Therefore, for the purpose of the invention the term “pellet” and “granule” are not the same and they are not interchangeable.

The terms “modified release” dosage form small particle and “modified delivery” dosage form small particle have the same meaning and are interchangeable. Both terms are to be understood as a dosage form or small particle that exhibits a slower release of the active ingredients than that of a conventional immediate release pharmaceutical composition administered by the same route. In general, the term “modified release” means that the active ingredient is released from the pharmaceutical dosage form in a controlled, sustained, prolonged or extended release.

In the context of the present invention, the term “modified release” refers to a multiple unit oral dosage form that exhibits a dissolution profile according to which the content of doxylamine and pyridoxine is not fully released immediately after the start of the dissolution test. Particularly, it refers to a multiple unit oral dosage form in which $\leq 85\%$ by weight of the content of doxylamine or a pharmaceutically acceptable salt thereof and $\leq 85\%$ by weight of the content of pyridoxine or a pharmaceutically acceptable salt thereof dissolve within 30 min after the start of the dissolution test.

In the context of the present invention, the term “modified release” refers as well to a multiple unit oral dosage form that exhibits a dissolution profile according to which the content of doxylamine and pyridoxine fully released at least within the 8 hours after the start of the dissolution test. Particularly, it refers to a multiple unit oral dosage form in which $\geq 75\%$ by weight of the content of doxylamine or a pharmaceutically acceptable salt thereof and the content of pyridoxine or a

pharmaceutically acceptable salt dissolve within 7 hours after the start of the dissolution test.

Particularly, the term “modified release” refers to a multiple unit oral dosage form that exhibits a dissolution profile according to which: from 5% to 35% by weight of doxylamine content is dissolved at 1st hour in 0.1 N HCl medium (pH = 1); then, the medium is replaced by a pH = 4.5 medium (0.05 M acetate buffer) and at 4th hour from an accumulated more than 35% to 75% by weight of doxylamine initial content is dissolved; then, the medium is replaced by a pH = 6.8 medium (0.05 M phosphate buffer) and at 7th hour at least an accumulated more than 75% by weight of doxylamine initial content is dissolved; and from 5% to 35% by weight of pyridoxine content is dissolved at 1st hour in 0.1 N HCl medium (pH = 1); then, the medium is replaced by a pH = 4.5 medium (0.05 M acetate buffer) and at 4th hour from an accumulated more than 35% to 75% by weight of pyridoxine initial content is dissolved; then, the medium is replaced by a pH = 6.8 medium (0.05 M phosphate buffer) and at 7th hour at least an accumulated more than 75% by weight of pyridoxine initial content is dissolved; wherein the dissolution profile is measured using an appropriate method.

Commonly an appropriate method is a USP method such as for example by using a USP type 2 apparatus (basket), placing the composition in 900mL of the corresponding media / buffered 37°C ± 0.5 °C and 100 rpm (revolution per minute) or using a USP type 3 apparatus (reciprocating cylinder), placing the composition in 250mL of the corresponding media / buffered at 37°C ± 0.5 °C and 15 dpm (dipping per minute). In the present invention, the measurement of the dissolution profile of the multiple unit oral dosage form is performed by USP type 2 apparatus (basket), placing the composition in 900mL of the corresponding media / buffered 37°C ± 0.5

°C and 100 rpm (revolution per minute).

In an embodiment, the multiple unit oral dosage form that exhibits a dissolution profile according to which: from 10% to 35% by weight of doxylamine content is dissolved at 1st h in 0.1 N HCl medium (pH = 1); then, the medium is replaced by a pH = 4.5 medium (0.05 M acetate buffer) and at 4th h from an accumulated 45% to 70% by weight of doxylamine initial content is dissolved; then, the medium is replaced by a pH = 6.8 medium (0.05 M phosphate buffer) and at 7th h at least an accumulated 80% by weight of doxylamine initial content is dissolved; and from 10% to 35% by weight of pyridoxine content is dissolved at 1st h in 0.1 N HCl medium (pH = 1); then, the medium is replaced by a pH = 4.5 medium (0.05 M acetate buffer) and at 4th h from an accumulated 40% to 65% by weight of pyridoxine initial content is dissolved; then, the medium is replaced by a pH = 6.8 medium (0.05 M phosphate buffer) and at 7th h at least an accumulated 80% by weight of pyridoxine initial content is dissolved; wherein the dissolution profile is measured using an appropriate method.

In the context of the invention, the term “coating agents” and “film-forming coating agents” have the same meaning and are used interchangeable. Both terms are to be understood as an agent capable of forming a thin coat to a solid dosage form or dosage form intermediate such as tablet and pellets. Examples of each one of the types of coating agents are disclosed below.

In the context of the invention, the term “inner active coating layer” refers to a film comprising a coating agent and an active ingredient. Examples of the coating agent of the inner active coating layer of the first and the second plurality of modified release units, preferably small particles, include without limitation polyvinylpyrrolidone, hydroxypropyl cellulose, microcrystalline cellulose, amino methacrylate

copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, carboxymethyl-cellulose calcium, carboxymethylcellulose sodium, carboxymethylcellulose sodium enzymatically-hydrolyzed, cellaburate, cellacefate, cellulose acetate, cetyl alcohol, chitosan, coconut oil, coconut oil, hydrogenated, copovidone, corn syrup solids, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylcellulose aqueous dispersion, ethylcellulose dispersion type b, ethylene glycol and vinyl alcohol graft copolymer, gelatin, glaze pharmaceutical, glucose liquid, glyceryl behenate, glyceryl dibehenate, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, hypromellose phthalate, isomalt, alpha-lactalbumin, maltitol, maltodextrin, methacrylic acid and ethyl acrylate copolymer, methacrylic acid and ethyl acrylate copolymer dispersion, methacrylic acid and ethyl acrylate copolymer partially-neutralized, methacrylic acid and methyl methacrylate copolymer, methylcellulose, palm kernel oil, palm oil, palm oil hydrogenated, polydextrose, polydextrose hydrogenated, polyethylene glycol, polyethylene glycol 3350, polyethylene oxide, polyvinyl acetate, polyvinyl acetate dispersion, polyvinyl acetate phthalate, polyvinyl alcohol, pullulan, rapeseed oil fully hydrogenated, rapeseed oil superglycerinated fully hydrogenated, shellac, starch pregelatinized modified, sucrose, sugar confectioner's, sunflower oil, wax carnauba, wax microcrystalline, xylitol, zein and alginic acid, amino methacrylate copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, carboxymethylcellulose calcium, carboxymethylcellulose sodium, carboxymethylcellulose sodium enzymatically-hydrolyzed, cellaburate, cellacefate, cellulose acetate, chitosan, copovidone, dibutyl phthalate, diethyl phthalate, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylcellulose aqueous dispersion, ethylcellulose

dispersion type b, ethylene glycol and vinyl alcohol grafted copolymer, gelatin, glaze pharmaceutical, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, hypromellose phthalate, methacrylic acid and ethyl acrylate copolymer, methacrylic acid and ethyl acrylate copolymer dispersion, methacrylic acid and ethyl acrylate copolymer partially-neutralized, methacrylic acid and methyl methacrylate copolymer, methylcellulose, polyethylene glycol 3350, polyvinyl acetate, polyvinyl acetate dispersion, polyvinyl acetate phthalate, polyvinyl alcohol, pullulan, pyroxylin, shellac, sodium alginate, and a mixture thereof.

In an embodiment, the multiple unit oral dosage form of the present invention is one wherein the coating agent of the inner active coating layer of the first and the second plurality of modified release units, preferably small particles, more preferably pellets, are independently selected from the group consisting of polyvinylpyrrolidone, shellac, hypromellose, hydroxypropyl cellulose, microcrystalline cellulose and a mixture thereof.

In the context of the invention, the term “modified release coating agent” refers to an agent capable of forming films which allow the delivery of the drug at a predetermined rate and/or location according to the needs of the body and disease states for a definite time of period. Illustrative but non-limitative examples of “modified release polymers” and “modified delivery polymers” are polymers which provide a controlled release, a sustained release, a prolonged release or an extended release. Examples of modified release coating agent include without limitation acrylic polymers, celluloses and their derivatives, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and their mixtures. Examples of suitable acrylic polymers include, but not limited to are methacrylic acid-alkyl methacrylate copolymer, methacrylic acid-methyl methacrylate copolymer, acrylic acid and methacrylic acid

copolymers, methyl methacrylate copolymers, poly ethoxy ethyl methacrylate, poly cyanoethyl methacrylate, poly amino alkyl methacrylate copolymer, poly (acrylic acid), poly (methacrylic acid), methacrylic acid alkyl amide copolymer, poly (methyl methacrylate), poly (methacrylic acid anhydride), poly alkyl methacrylate, poly alkyl acrylates, polymethacrylate, poly (methyl methacrylate) copolymer, polyacrylamide, amino alkyl methacrylate copolymer, glycidyl methacrylate copolymers, and their mixtures. Preferably, the modified release coating agent is selected from the group consisting of methacrylic acid-methyl methacrylate copolymer and shellac.

Further examples of modified release coating agent include without limitation alginic acid, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, carrageenan, cellaburate, ethylcellulose, ethylcellulose aqueous dispersion, ethylcellulose dispersion type b, glyceryl monooleate, glyceryl monostearate, guar gum, hydroxypropyl betadex, hydroxypropyl cellulose, hypromellose, polyethylene oxide, polyvinyl acetate dispersion, shellac, sodium alginate, starch, pregelatinized starch, pregelatinized modified or xanthan gum. Preferably, the modified release coating agent is shellac, particularly dewaxed shellac.

The modified release polymers can be accompanied by plasticizers such as triethyl citrate (TEC), polyethylene glycol (PEG), cetyl and stearyl alcohol, acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, castor oil, chlorobutanol, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, mannitol, polyethylene glycol, polyethylene glycol 3350, polyethylene glycol monomethyl ether, propylene glycol, pullulan, sorbitol, sorbitol sorbitan solution, sucrose diacetate hexaisobutyrate, triacetin, tributyl citrate, triethyl citrate and vitamin E; surface-active agents such as sodium lauryl sulphate, polysorbate and poloxamer; pigments such as iron

sesquioxide; lubricants such as talc, magnesium stearate, glyceryl monostearate, behenoyl polyoxyglycerides, calcium stearate, castor oil hydrogenated, coconut oil hydrogenated, glyceryl behenate, glyceryl dibehenate, glyceryl mono and dicaprylate, glyceryl mono and dicaprylocaprate, glyceryl monocaprylate, glyceryl monocaprylocaprate, glyceryl monostearate, glyceryl tricaprylate, glyceryl tristearate, lauric acid, magnesium stearate, mineral oil light, myristic acid, palm oil hydrogenated, palmitic acid, poloxamer, polyethylene glycol, polyethylene glycol 3350, polyoxyl 10 oleyl ether, polyoxyl 15 hydroxystearate, polyoxyl 20 cetostearyl ether, polyoxyl 35 castor oil, polyoxyl 40 castor oil hydrogenated, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, potassium benzoate, sodium benzoate, sodium lauryl sulfate, sodium stearate, sodium stearyl fumarate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate, stearic acid, stearic acid purified, sucrose stearate, talc, vegetable oil hydrogenated, type I, zinc stearate and mixtures thereof.

In an embodiment, the multiple unit oral dosage form of the present invention is one wherein the modified release coating agents are independently selected from the group consisting of methacrylic acid-methyl methacrylate copolymer and shellac, particularly methacrylic acid-methyl methacrylate copolymer and dewaxed shellac and a mixture thereof.

In the context of the invention, the term "enteric release" refers to a composition or layer of a dosage form that is formulated to release the active ingredient(s) upon exposure to a characteristic aspect of the gastrointestinal tract. In an embodiment, the enteric material is pH-sensitive and is affected by changes in pH encountered within the gastrointestinal tract (pH-sensitive release). The enteric material typically

remains insoluble at gastric pH, then allows for release of the active ingredient in the higher pH environment of the downstream gastrointestinal tract (e.g. often the duodenum, or sometimes the colon). In another embodiment, the enteric material comprises enzymatically degradable polymers that are degraded by bacterial enzymes present in the lower gastrointestinal tract, particularly in the colon. Optionally, the unit dosage form is formulated with a pH-sensitive enteric material designed to result in a release within about appropriate hours when at or above a specific pH. In various embodiments, the specific pH can for example be from about 4 to about 7, such as about 4.5, 5, 5.5, 6, 6.5, 6.8 or 7.

In the context of the invention, the term “enteric release coating agent” refers to an agent capable of forming films which allow the delivery of doxylamine and/or pyridoxine upon exposure to a characteristic aspect of the gastrointestinal tract as defined above.

Materials used for enteric release formulations, for example as coatings, are well known in the art and include, but are not limited to, cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, methylcellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, and other methacrylic resins that are commercially available under the trade-name Acryl-EZE® (Colorcon, USA), Eudragit® (Rohm Pharma; Westerstadt, Germany), including Eudragit® L30D-55 and L100-55 (soluble at pH 5.5 and above), Eudragit® L100 and L12.5 (soluble at pH 6.0

and above), Eudragit® S, S12.5 and FS 30D (soluble at pH 7.0 and above, as a result of a higher degree of esterification), and Eudragit® NE, NM, RL and RS (water-insoluble polymers having different degrees of permeability and expandability); vinyl polymers and copolymers such as polyvinyl pyrrolidone, or other vinyl polymers and copolymers formed from vinyl acetate, vinyl acetate phthalate, vinyl acetate crotonic acid copolymer, and ethylene-vinyl acetate copolymer; enzymatically degradable polymers such as azo polymers, pectin, chitosan, amylose and guar gum; zein and shellac. Combinations of different enteric materials may also be used. Multi-layer coatings using different polymers may also be applied. The properties, manufacture and design of enteric delivery systems are well known to those of ordinary skill in the art.

In a particular embodiment, the enteric coating agent is selected from the group consisting of copolymer of methacrylic acid and methyl methacrylate, copolymer of methacrylic acid and methyl acrylate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate sodium alginate, cellulose acetate trimellitate and a mixture thereof. More particularly, Eudragit L® such as for example Eudragit L100 (sold by Evonik). In an embodiment, the multiple unit oral dosage form of the present invention is one wherein the enteric coating agents are independently selected from the group consisting of methacrylic acid-methyl methacrylate copolymer, methacrylic acid-methyl acrylate copolymer, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate sodium alginate, cellulose acetate trimellitate and a mixture thereof. In an embodiment, the multiple unit oral dosage form of the present invention is one wherein the enteric coating agents is a methacrylic acid-methyl methacrylate copolymer, particularly Eudragit L100.

As it is disclosed above, the multiple unit oral dosage form of the present invention comprises a first plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof and a second plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof.

The term "therapeutically effective amount" as used herein, refers to the amount of an active ingredient per multiple unit dosage form that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease which is addressed. The particular dose of compound administered according to this invention will be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and the similar considerations.

In a preferred embodiment, the oral dosage form according to the present invention comprises from 5 mg to 50 mg per oral dosage form of doxylamine or a pharmaceutically acceptable salt thereof; and from 5 mg to 50 mg per oral dosage form of pyridoxine or a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable salt(s)" used herein encompasses any salt formed from pharmaceutically acceptable non-toxic acids including inorganic or organic acids. There is no limitation regarding the salts, except that if used for therapeutic purposes, they must be pharmaceutically acceptable. As doxylamine and pyridoxine are basic compounds, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include

among others acetic, benzene sulfonic, benzoic, camphor sulfonic, citric, ethansulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, lactic, maleic, malic, mandelic, methanesulfonic, phosphoric, succinic, sulphuric, tartaric or p-toluensulfonic acid. The preparation of pharmaceutically acceptable salts of doxylamine and pyridoxine can be carried out by methods known in the art. For instance, they can be prepared from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate pharmaceutically acceptable base or acid in water or in an organic solvent or in a mixture of them.

In an embodiment, the multiple unit oral dosage form of the present invention is one which comprises a pharmaceutically acceptable salt of doxylamine and a pharmaceutically acceptable salt of pyridoxine, preferably, comprises doxylamine succinate and pyridoxine hydrochloride.

In an embodiment, the multiple unit oral dosage form comprises a first plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of a pharmaceutically acceptable salt of doxylamine, particularly doxylamine succinate.

In an embodiment, the multiple unit oral dosage form comprises the first plurality of modified release units, preferably small particles, more preferably pellets, which comprises from 5 mg to 50 mg of doxylamine or a pharmaceutically acceptable salt thereof, preferably doxylamine succinate, per dosage form, particularly from 6 mg to 40 mg, more preferably from 7 mg to 30 mg, even more preferably from 8 mg to 22 mg of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate, per dosage form.

In an embodiment, the multiple unit oral dosage form comprises the first plurality of small particles, preferably pellets, having much more particularly from 9 mg to 11 mg or from 19 mg to 21 mg of doxylamine or a pharmaceutically acceptable salt thereof, preferably doxylamine succinate, per dosage form.

In a more preferred embodiment, the multiple unit oral dosage form comprises the first plurality of small particles, preferably pellets, having 10 mg of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate, per multiple unit dosage form. In another more particular embodiment, the multiple unit oral dosage form comprises the first plurality of small particles, preferably pellets, having 20 mg of doxylamine or a pharmaceutically acceptable salt thereof, preferably doxylamine succinate, per multiple unit dosage form.

In an embodiment, the multiple unit oral dosage form comprises a second plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of a pharmaceutically acceptable salt of pyridoxine, preferably pyridoxine hydrochloride.

In an embodiment, the multiple unit oral dosage form comprises the second plurality of modified release units, preferably small particles, more preferably pellets, which comprises from 5 mg to 50 mg of pyridoxine or a pharmaceutically acceptable salt thereof, preferably pyridoxine hydrochloride, per dosage form, particularly from 6 mg to 40 mg, more preferably from 7 mg to 30 mg, even more preferably from 8 mg to 22 mg of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride, per dosage form.

In an embodiment, the multiple unit oral dosage form comprises the second plurality of small particles, preferably pellets, having much more particularly from 9 mg to 11 mg or from 19 mg to 21 mg of pyridoxine or a pharmaceutically acceptable salt

thereof, preferably pyridoxine hydrochloride, per dosage form.

In a more preferred embodiment, the multiple unit oral dosage form comprises the second plurality of small particles, preferably pellets, having 10 mg of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride per multiple unit dosage form. In another more preferred embodiment, the multiple unit oral dosage form comprises the second plurality of small particles, preferably pellets, having 20 mg of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride, per multiple unit dosage form.

In an embodiment, the multiple unit oral dosage form comprises the first plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, preferably doxylamine succinate; and the second plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, preferably the pyridoxine hydrochloride.

In an embodiment, the multiple unit oral dosage form comprises the first plurality of small particles, preferably pellets, which comprises from 5 mg to 50 mg of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate, per multiple unit dosage form, particularly 10 mg or 20mg of doxylamine or a pharmaceutically acceptable salt thereof; particularly doxylamine succinate per multiple unit dosage form; and the second plurality of small particles, preferably pellets, which comprises from 5 mg to 50 mg of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride, per multiple unit dosage form, particularly 10 mg or 20mg of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride, per multiple unit dosage form.

In a particular embodiment, the multiple unit oral dosage form comprises the first plurality of small particles, preferably pellets, which comprises 10 mg of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate, per multiple unit dosage form; and the second plurality of small particles, preferably pellets, which comprises 10 mg of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride, per multiple unit dosage form. In another particular embodiment, the multiple unit oral dosage form comprises the first plurality of small particles, preferably pellets, which comprises 20 mg of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate, per multiple unit dosage form; and the second plurality of small particles, preferably pellets, which comprises 20 mg of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride, per multiple unit dosage form.

In an embodiment, the multiple unit dosage form comprises from 20 mg to 220 mg, preferably from 40 mg to 140 mg, of the first plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate.

In an embodiment, the multiple unit dosage form comprises about 60 mg or about 120 mg of the first plurality of small particles, preferably pellets, which comprises a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate.

In preferred embodiment, the multiple unit dosage form comprises from 20 mg to 220 mg, preferably from 40 mg to 140 mg, of the second plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt

thereof, preferably pyridoxine hydrochloride.

In a preferred embodiment, the multiple unit dosage form comprises about 60 mg or about 120 mg, of the second plurality of small particles, preferably pellets which comprises a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable thereof, particularly pyridoxine hydrochloride.

In an embodiment, the multiple unit dosage form comprises from 20 mg to 220 mg of the first plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, particularly doxylamine succinate; and from 20 mg to 220 mg of the second plurality of modified release units, preferably small particles, more preferably pellets, which comprises a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, particularly pyridoxine hydrochloride.

In an embodiment, the multiple unit dosage form comprises from 40 mg to 140 mg, more particularly about 60 mg or about 120 mg, of the first plurality of small particles, preferably pellets, which comprises from 5 mg to 50 mg of doxylamine succinate, particularly 10 mg or 20 mg of doxylamine succinate; and from 40 mg to 140 mg, more particularly about 60mg or about 120 mg, of the second plurality of small particles, preferably pellets, which comprises from 5 mg to 50 mg of pyridoxine hydrochloride, particularly 10 mg or 20 mg of pyridoxine hydrochloride.

As it is mentioned above, the multiple unit oral dosage form of the present invention comprises pharmaceutically acceptable nucleus (active or inert) having a particle size such that at least 90% of the inert nucleus have a particle size from 300 μm to 1700 μm measured by analytical sieving, and at least the 90% of the pharmaceutically acceptable inert nucleus have a particle size variability of 200 μm measured by

analytical sieving or optical microscopy; particularly a particle size variability of 150 μm , particularly a particle size variability of 100 μm , particularly a particle size variability of 75 μm and more particularly a particle size variability of 50 μm .

In an embodiment, the multiple unit oral dosage form of the present invention comprises pharmaceutically acceptable nucleus (inert or active) having a particle size such that at least 90% of the inert nucleus have a particle size from 300 μm to 1400 μm , preferably from 600 μm to 1180 μm , more preferably from 710 μm to 1000 μm , measured by analytical sieving. In an embodiment, at least the 90% of any of these pharmaceutically acceptable inert nuclei have a particle size variability of 150 μm , particularly a particle size variability of 100 μm , more particularly a particle size variability of 75 μm and even more particularly a particle size variability of 50 μm , measured by analytical sieving or optical microscopy.

In an embodiment, the multiple unit oral dosage form of the present invention comprises pharmaceutically acceptable nucleus (inert or active) having a particle size such that at least 90% of the inert nucleus have a particle size from 710 μm to 850 μm measured by analytical sieving and at least the 90% of the pharmaceutically acceptable inert nucleus have a particle size variability of 70 μm ; and particularly a particle size variability of 50 μm measured by analytical sieving or optical microscopy.

In an embodiment, the multiple unit oral dosage form of the present invention comprises pharmaceutically acceptable nucleus (inert or active) having a particle size such that at least 90% of the inert nucleus have a particle size from 850 μm to 1000 μm measured by analytical sieving and at least the 90% of the pharmaceutically acceptable inert nucleus have a particle size variability of 70 μm ; and particularly a particle size variability of 50 μm measured by analytical sieving or optical microscopy.

As it is mentioned above, in a preferred embodiment the multiple unit oral dosage

form of the present invention comprises a pharmaceutically acceptable active nucleus. The term "active nucleus" refers to small particles which comprises doxylamine or a salt thereof, or pyridoxine or a salt thereof and optionally a pharmaceutically acceptable substance selected from sorbitol, mannitol, sucrose, saccharose, starch, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, lactose, glucose, trehalose, maltitol, fructose, colloidal silicon dioxide, polyvinylpyrrolidone, magnesium stearate, silica (colloidal silicon dioxide; particularly Aerosil), talc.

In a further preferred embodiment, the multiple unit oral dosage form of the present invention comprises pharmaceutically acceptable inert nucleus. The term "inert nucleus" refers to neutral microspheres which comprises in their composition at least one of the following substances: sorbitol, mannitol, sucrose, saccharose, starch, microcrystalline cellulose, lactose, glucose, trehalose, maltitol, fructose, colloidal silicon dioxide. In an embodiment, the pharmaceutically acceptable inert nucleus are neutral microspheres of a mixture of sucrose and starch.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form is one wherein the particle size of the first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the modified release units, preferably small particles, more preferably pellets, have a particle size from 400 μm to 1900 μm , preferably from 600 μm to 1400 μm , more preferably from 710 μm to 1320 μm , even more preferably from 800 μm to 1250, measured by analytical sieving.

In a preferred embodiment, at least the 90% of any of these pharmaceutically acceptable small particles, preferably pellets, have a particle size variability of 150

µm, particularly a particle size variability of 100 µm, more particularly a particle size variability of 75 µm and even more particularly a particle size variability of 50 µm, measured by analytical sieving or optical microscopy.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form is one wherein the particle size of the first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the modified release units, preferably small particles, more preferably pellets, have a particle size from 800 µm to 1100 µm measured by analytical sieving and at least the 90% of the modified release units, preferably small particles, more preferably pellets, have a particle size variability of 100 µm, particularly a particle size variability of 75 µm, and more particularly a particle size variability of 50 µm, measured by analytical sieving or optical microscopy.

In a preferred embodiment, the multiple unit oral dosage form is one wherein the particle size of the first plurality of modified release modified release units, preferably small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles, preferably pellets, have a particle size from 900 µm to 1250 µm measured by analytical sieving and at least the 90% of the small particles, preferably pellets, have a particle size variability of 100 µm, particularly a particle size variability of 75 µm, and more particularly a particle size variability of 50 µm, measured by analytical sieving or optical microscopy.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form is one wherein the particle size of the second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a

pharmaceutically acceptable salt thereof is such that at least 90% of the modified release units, preferably small particles, preferably pellets, have a particle size from 400 μm to 1900 μm , preferably from 600 μm to 1400 μm , more preferably from 710 μm to 1320 μm , even more preferably from 800 μm to 1250 μm , measured by analytical sieving.

In an embodiment, at least the 90% of any of these pharmaceutically acceptable small particles, preferably pellets, have a particle size variability of 150 μm , particularly a particle size variability of 100 μm , more particularly a particle size variability of 75 μm and even more particularly a particle size variability of 50 μm , measured by analytical sieving or optical microscopy.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form is one wherein the particle size of the second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof is such that at least 90% of the modified release units, preferably small particles, more preferably pellets have a particle size from 800 μm to 1100 μm measured by analytical sieving and at least the 90% of the modified release units, preferably small particles, more preferably pellets have a particle size variability of 100 μm ; particularly a particle size variability of 75 μm ; and more particularly a particle size variability of 50 μm measured by analytical sieving or optical microscopy.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form is one wherein the particle size of the second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles, preferably pellets have a particle size from 900 μm to 1250 μm measured

by analytical sieving and at least the 90% of the small particles, preferably pellets have a particle size variability of 100 μm ; particularly a particle size variability of 75 μm ; and more particularly a particle size variability of 50 μm measured by analytical sieving or optical microscopy.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form of the present invention is one wherein the particle size of the first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles, preferably pellets, have a particle size from 400 μm to 1900 μm measured by analytical sieving; and the particle size of the second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles, preferably pellets, have a particle size from 400 μm to 1900 μm measured by analytical sieving.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form of the present invention is one wherein:

the particle size of the pharmaceutically acceptable nucleus (active or inert) is such that at least 90% of the nucleus have a particle size from 300 μm to 1700 μm measured by analytical sieving, and at least the 90% of the pharmaceutically acceptable inert nucleus have a particle size variability of 200 μm ; particularly of 150 μm , particularly of 100 μm , more particularly of 75 μm and even more particularly of 50 μm , measured by analytical sieving or optical microscopy;

the particle size of the first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle

size from 400 μm to 1900 μm measured by analytical sieving and at least the 90% of the small particles have a particle size variability of 200 μm ; particularly of 150 μm ; particularly of 100 μm ; more particularly of 75 μm ; and even more particularly of 50 μm measured by analytical sieving or optical microscopy; and the particle size of the second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle size from 400 μm to 1900 μm measured by analytical sieving and at least the 90% of the small particles have a particle size variability of 200 μm ; particularly of 150 μm ; particularly of 100 μm ; more particularly of 75 μm ; and even more particularly of 50 μm measured by analytical sieving or optical microscopy.

In an embodiment, the capsule content of the multiple unit oral dosage form of the present invention is one wherein:

the particle size of the pharmaceutically acceptable nucleus (active or inert) is such that at least 90% of the nucleus have a particle size from 710 μm to 1000 μm measured by analytical sieving and at least the 90% of the pharmaceutically acceptable inert nucleus have a particle size variability of 100 μm , particularly of 75 μm and more particularly of 50 μm measured by analytical sieving or optical microscopy;

the particle size of the first plurality of modified release units, preferably modified release small particles, preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle size from 800 μm to 1250 μm measured by analytical sieving and at least the 90% of the small particles have a particle size variability of 150 μm ; particularly of 100 μm ; particularly of 75 μm ; and more particularly of 50 μm measured by analytical sieving

or optical microscopy; and

the particle size of the second plurality of modified release units, preferably modified release small particles, preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle size from 800 μm to 1250 μm measured by analytical sieving and at least the 90% of the small particles have a particle size variability of 150 μm ; particularly of 100 μm ; particularly of 75 μm ; and more particularly of 50 μm measured by analytical sieving or optical microscopy.

In a further preferred embodiment, the capsule content of the multiple unit oral dosage form of the present invention is one wherein:

the particle size of the pharmaceutically acceptable nucleus (active or inert) is such that at least 90% of the nucleus have a particle size from 710 μm to 850 μm measured by analytical sieving and at least the 90% of the pharmaceutically acceptable nucleus have a particle size variability of 70 μm ; particularly of 50 μm measured by analytical sieving or optical microscopy;

the particle size of the first plurality of modified release units, preferably modified release small particles, preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle size from 800 μm to 1100 μm measured by analytical sieving and at least the 90% of the small particles have a particle size variability of 100 μm ; particularly of 75 μm ; more particularly of 50 μm measured by analytical sieving or optical microscopy; and the particle size of the second plurality of modified release units, preferably modified release small particles, preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle size from 800 μm to 1100 μm measured by analytical sieving and at least the 90% of

the small particles have a particle size variability of 100 μm ; particularly of 75 μm ; more particularly of 50 μm measured by analytical sieving or optical microscopy.

In a preferred embodiment, the capsule content of the multiple unit oral dosage form of the present invention is one wherein:

the particle size of the pharmaceutically acceptable nucleus (active or inert) is such that at least 90% of the nucleus have a particle size from 850 μm to 1000 μm measured by analytical sieving and at least the 90% of the pharmaceutically acceptable nucleus have a particle size variability of 70 μm ; particularly of 50 μm measured by analytical sieving or optical microscopy;

the particle size of the first plurality of modified release units, preferably modified release small particles, preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle size from 900 μm to 1250 μm measured by analytical sieving and at least the 90% of the small particles have a particle size variability of 100 μm ; particularly of 75 μm ; more particularly of 50 μm measured by analytical sieving or optical microscopy; and the particle size of the second plurality of modified release units, preferably modified release small particles, preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof is such that at least 90% of the small particles have a particle size from 900 μm to 1250 μm measured by analytical sieving and at least the 90% of the small particles have a particle size variability of 100 μm ; particularly of 75 μm ; more particularly of 50 μm measured by analytical sieving or optical microscopy .

In a preferred embodiment, the multiple unit oral dosage form is one wherein the particle size of doxylamine or a pharmaceutically acceptable salt is characterized for having a D90 equal to or below than 250 μm . In an embodiment, the multiple unit oral dosage form is one wherein the particle size of pyridoxine or a pharmaceutically

acceptable salt thereof is characterized for having a D90 equal to or below than 250 μm .

In an embodiment, the multiple unit oral dosage form is one wherein: the particle size of doxylamine or a pharmaceutically acceptable salt is characterized for having a D90 equal to or below than 250 μm ; and the particle size of pyridoxine or a pharmaceutically acceptable salt thereof is characterized for having a D90 equal to or below than 250 μm .

In a preferred embodiment, the multiple unit oral dosage form is one wherein the particle size of the one or more anticaking agent is characterized for having a D90 equal to or below than 250 μm . In an embodiment, the multiple unit oral dosage form is one wherein the particle size of the one or more optionally present pore-forming agents is characterized for having a D90 equal to or below than 250 μm .

In a preferred embodiment, the multiple unit oral dosage form is one wherein the particle size of doxylamine or a pharmaceutically acceptable salt is characterized for having a D90 equal to or below than 250 μm ; the particle size of pyridoxine or a pharmaceutically acceptable salt thereof is characterized for having a D90 equal to or below than 250 μm ; the particle size of the one or more anticaking agent is characterized for having a D90 equal to or below than 250 μm ; and optionally, the particle size of the one or more pore-forming agent is characterized for having a D90 equal to or below than 250 μm .

The particle size of the pharmaceutically acceptable nucleus (inert or active), the modified release units, preferably small particles, the active ingredients and the excipients can be measured by any method disclosed in the state of the art. Examples of methods commonly used for measuring the particle size is Dynamic light scattering (DLS) reporting the number average diameter value, Atomic force

microscopy (AFM) or transmission electron microscopy (TEM) to measure dried particles; laser diffraction (Laser Mastersizer, Mie Theory; ISO 13320-1) and by sedimentation analysis (Sedigraph-Stoke's Law; ISO 13317-3) and by analytical sieving. For the purpose of the present invention, the particle size of the pharmaceutically acceptable inert nucleus and of the pellets of the first and the second plurality as defined herein is preferably measured by analytical sieving, particularly as directed by European Pharmacopoeia (cf. European Pharmacopoeia chapter 2.9.38).

The terms "variability" and "dispersion" have the same meaning and are used interchangeable. They refer to how spread out a set of data is. Variability gives you a way to describe how much data sets vary. In particular, the term "particle size variability" refers to how spread out the particle size of a given value is.

The expression "at least the 90% [...] have a particle size from X to Y μm " means that the 90% of the totality of the population of particles has a particle size comprised between X and X μm . For the purpose of the invention, the expression "at least the 90% of the pharmaceutically acceptable inert nucleus or pellets have a particle size variability of 200 μm " means that for a given value, the 90% of the population of pharmaceutically acceptable inert nucleus or pellets have a particle size comprised from $\pm 200 \mu\text{m}$. For instance, for the given value 500 μm , at least the 90% of the population of pharmaceutically acceptable inert nucleus have a particle size from 300 μm to 700 μm (i.e. $\pm 200 \mu\text{m}$). The particle size variability of the pharmaceutically acceptable inert nucleus or the pellets can be measured by any method disclosed in the state of the art. Examples of methods commonly used for measuring the particle size variability is Dynamic light scattering (DLS) reporting the number average diameter value, Atomic force microscopy (AFM) or transmission electron microscopy

(TEM) to measure dried particles; laser diffraction (Laser Mastersizer, Mie Theory; ISO 13320-1), by sedimentation analysis (Sedigraph-Stoke's Law; ISO 13317-3), by analytical sieving and optical microscopy. For the purpose of the present invention, the particle size variability is preferably measured by analytical sieving or optical microscopy.

The DX value indicates that a certain percentage X of the particles has a size equal to or below a certain limit. A D90 indicates that the 90% of the particles has a size equal to or below a certain limit. For instance, a D90 value equal to or below than 250 μm means that 90 % by volume of the particles have a diameter equal to or below than 250 μm . The DX (and particularly the D90) can be measured using any appropriate method disclosed above for the measurement of the particle size of the pharmaceutically acceptable inert nucleus, the pellets, the active ingredients and the excipients of the present invention, such as for example analytical sieving.

For the purpose of the invention, the TiO_2 -free hard capsule is understood as a hard capsule suitable to be used in fully automatic capsule filling machine. Commonly, these capsules are made up of two cylindrical halves, wherein one of them is large in diameter but shorter in length called cap and other is shorter in diameter but longer in length called body.

In an embodiment, the multiple unit oral dosage form is a hard capsule having a capsule size from size 0 to size 5. In an embodiment, the multiple unit oral dosage form is a hard capsule having a capsule size from size 1 to size 5. In an embodiment, the multiple unit oral dosage form is a hard capsule having a capsule size from size 1 to size 4. In an embodiment, the multiple unit oral dosage form is a hard capsule having a capsule size of 3. In an embodiment, the multiple unit oral dosage form is a hard capsule having a capsule size of 2. In an embodiment, the multiple unit oral

dosage form is a hard capsule having a capsule size of 1.

According to a preferred embodiment, the multiple unit dosage form of the present invention comprises a TiO₂-free hard capsule shell and from 20 mg to 220 mg, preferably from 40 mg to 140 mg, of the first plurality of modified release units, preferably modified release small particles, preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof; and from 20 mg to 220 mg, preferably from 40 mg to 140 mg, of the second plurality of modified release units, preferably modified release small particles, preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof.

In an embodiment, the multiple unit dosage form of the present invention comprises a TiO₂-free hard capsule shell and about 60 mg of the first plurality of modified release units, preferably modified release small particles, preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof; and about 60 mg of the second plurality of modified release units, preferably modified release small particles, preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof. Particularly, the TiO₂-free hard capsule shell has a size selected from size 2 or size 3 or size 4, more particularly has a size 3.

In a preferred embodiment, the multiple unit dosage form of the present invention comprises a TiO₂-free hard capsule shell and about 120 mg of the first plurality of modified release units, preferably modified release small particles, preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof; and about 120 mg of the second plurality of modified release units, preferably modified release small particles, preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof. Particularly, the hard capsule shell has a size selected from size 1, size 2 and size 3, more particularly has a size 1.

In a preferred embodiment, the multiple unit dosage form of the present invention comprises a TiO₂-free hard capsule shell and about 10 mg per capsule of doxylamine succinate and about 10 mg per capsule of pyridoxine hydrochloride; and, particularly, the hard capsule shell has a size 3.

In an embodiment, the multiple unit dosage form of the present invention comprises a TiO₂-free hard capsule shell and about 20 mg per capsule of doxylamine succinate and about 20 mg per capsule of pyridoxine hydrochloride; and, particularly, the hard capsule shell has a size 1.

For the purpose of the present invention, the multiple unit dosage form of the present invention, particularly the TiO₂-free hard capsules, can be conditioned in appropriate package. The type of package can readily be determined by those skilled in the art according to the type of formulation being prepared.

In an embodiment, the modified release multiple unit dosage form of the present invention is packaged in blisters. In an embodiment, the modified release multiple unit dosage form of the present invention is packaged in bottles with or without desiccant placed inside the bottle or integrated in the closure system of the bottle).

For the purpose of the invention, the multiple unit dosage form of the present invention, particularly the TiO₂-free hard capsules, is primary packaged in blisters or bottles as defined above and secondary packaged in an outer carton.

Materials commonly used for assembling the blisters in which the multiple unit dosage form of the present invention, particularly TiO₂-free hard capsules, are primary packaged are PVC (polyvinylchloride), PVdC (polyvinylidene chloride), PE (polyethylene comprising HDPE or high-density polyethylene and LDPE or low-density polyethylene), PET (polyethylene terephthalate), PETG (poly-ethylene terephthalate glycol), PCTFE (polychlorotrifluoroethylene, commercially available as

polyAclar®), PVC/PE/PVdC (commercially available as AquaBa®), PVC/PVdC/PVC, PVC+PVdC, COC (Cyclic olefin copolymer), Aluminium or a combination thereof.

Materials commonly used for making bottles and the relevant closures or caps, in which the multiple unit dosage form of the present invention, particularly TiO₂-free hard capsules, are primary packaged are glass, aluminium and plastic materials. Examples of plastic material are PE (comprising HDPE and LDPE), PET, PP (polypropylene), PVC, PETG, PS (polystyrene), COC, and/or a mixture of more than one plastic material thereof and/or a mixture of one or more plastic material with further additives. Examples of plastic material additives are binders, desiccants, plasticizers, flame retardants, antioxidants, acid scavengers, light and heat stabilizers, lubricants, colourants, pigments, antistatic agents, slip compounds and thermal stabilizers. Examples of desiccants are moisture barrier materials, molecular sieve such as for example zeolites, calcium oxide, activated charcoal, calcium sulphate, calcium chloride and silica. The desiccant can be either mixed/incorporated with a suitable binder in the plastic material used to make the bottle or placed inside the bottle or integrated in the closure system of the bottle.

In a preferred embodiment, the TiO₂-free hard gelatine or HPMC capsules of the present invention are packaged in a primary packaging selected from the group consisting of blisters made with any of the materials mentioned above and plastic bottles made with any plastic material mentioned above without desiccant. They allow long-term storage of the multiple unit dosage forms of the present invention at or below 25°C and 60% Relative Humidity (climatic zones I and II countries).

In a preferred embodiment TiO₂-free hard gelatine or HPMC capsules of the present invention are primary packaged in blisters made of PVC/PVdC or PVC/PVdC/PVC (on one side of the blister) and aluminium (on the other side of the blister), that allow

storage at or below 25°C and 60% Relative Humidity for at least one year.

In a preferred embodiment, the TiO₂-free hard gelatine or HPMC capsules are packaged in a primary packaging selected from the group consisting of blisters made with any of the materials as define above or plastic bottles made with any plastic materials mentioned above with desiccant. They allow long-term storage also at or below 30°C and 75% Relative Humidity (climatic zone III and IV countries) (hot dry and hot humid / tropical zone countries) without particular restrictions (for example without the need to store in a refrigerator).

In a preferred embodiment, the TiO₂-free hard HPMC capsules of the present invention are primary packaged in blisters particularly made in PVC/PE/PVdC (AquaBa®), PVC/PVdC/PVC or Alu/Alu (Aluminium in both sides of the blister), that allow storage at or below 30°C and 75% Relative Humidity for at least one year.

In the context of the present invention, the term “anticaking agent” or “anticaking agents” refers to any pharmaceutically acceptable agent capable to reduce surface tackiness and the incidence of nuclei or small particles sticking together during coating and consequently improve process efficiency, coating uniformity, and appearance, preventing the formation of lumps (aggregates) and allows easing packaging, transport, flowability, filling into final dosage form and consumption. Examples of anticaking agents include, but are not limited to, calcium stearate, magnesium stearate, silica, silicates, talc, flour, starch calcium phosphate tribasic, calcium silicate, cellulose powdered, magnesium silicate, magnesium trisilicate, silica dental-type, silica hydrophobic colloidal, silicon dioxide colloidal, sodium stearate and a mixture thereof. In an embodiment, the multiple unit dosage form comprises one or more anticaking agents selected from the group consisting of talc and silica (colloidal silicone dioxide; particularly Aerosil) and a mixture thereof. In an embodiment, the

multiple unit dosage form comprises talc as anticaking agent.

In a preferred embodiment, the multiple unit dosage form comprises one or more anticaking agents having a particle size distribution characterized for having a D90 equal to or below than 250 μm ; particularly lower than 150 μm ; more particularly lower than 100 μm . In an embodiment, the multiple unit dosage form comprises one or more anticaking agents having a particle size distribution characterized for having a D90 equal to or below than 75 μm . In an embodiment, the multiple unit dosage form comprises talc as anticaking agent having a D90 particle diameter lower than 250 μm ; particularly lower than 150 μm ; more particularly lower than 100 μm . In an embodiment, the multiple unit dosage form comprises talc as anticaking agent having a D90 particle diameter lower than 75 μm .

The term "pore-forming agent" refers to any pharmaceutically acceptable agent capable of forming one or more pores in the shell/coating to allow modified the release of the active ingredients. The pore-forming agent can be organic or inorganic, or any combination thereof. Examples of pore-forming agent include, but are not limited to, polyethylene glycol (PEG), propylene glycol, isopropyl alcohol, glycerol, lactose, glucose, sucrose, mannitol, sorbitol, sodium chloride, potassium chloride, talc, hydroxypropyl cellulose, micronized sugar, hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohols, methacrylic acid copolymers, or a mixture therefore. In an embodiment, the pore-forming agent is selected from the group consisting of talc, micronized sugar, sodium or potassium chloride and a mixture thereof.

As it is mentioned above, the modified release multiple unit oral dosage form of the present invention optionally comprises one or more pore-forming agents. In an embodiment, the one or more pore-forming agents as defined above are present in the multiple unit oral dosage form. In an embodiment, the one or more pore-forming

agents as defined above are absent in the multiple unit oral dosage form.

In the context of the present invention, the term “pharmaceutically acceptable” refers to any composition, compound or material suitable for use in the pharmaceutical technology. For the purpose of the present invention, the term “pharmaceutically acceptable excipients or carriers” refers to that excipients or carriers for preparing compositions with medical use. The appropriate excipients and/or carriers, and their amounts, can readily be determined by those skilled in the art according to the type of formulation being prepared.

In an embodiment, the modified release multiple unit dosage form of the present invention further comprises one or more binders, glidants, fillers, lubricants, wicking agents and mixtures thereof. In an embodiment, the process comprises preparing a multiple unit dosage form which can comprise one or more pharmaceutically acceptable excipients or carriers.

As it is mentioned above, the modified release multiple unit oral dosage form of the present invention optionally comprises one or more pharmaceutically acceptable excipients or carriers. In an embodiment, the modified release multiple unit oral dosage form comprises one or more pharmaceutically acceptable excipients or carriers.

In an embodiment, the multiple unit oral dosage form comprises: one or more pore-forming agents as defined above; and one or more pharmaceutically acceptable excipients or carriers.

The term “binder” refers to any pharmaceutically acceptable compound having binding properties. Materials commonly used as binders include microcrystalline cellulose, polyvinylpyrrolidone (also called povidone or PVP), methylcellulose polymers, hydroxyethyl cellulose, hydroxypropyl cellulose, L-hydroxypropyl cellulose

(low substituted), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose, carboxymethylene, carboxymethyl hydroxyethyl cellulose and other cellulose derivatives, starches or modified starches, polyethylene glycol (PEG) 6000, guar gum, starch or shellac and mixture thereof.

Examples of binders include acacia, agar, alginic acid, amino methacrylate copolymer, ammonium methacrylate copolymer, ammonium methacrylate copolymer dispersion, , calcium lactate, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, cellulose, microcrystalline, cellulose, silicified microcrystalline, coconut oil, hydrogenated, copovidone, corn syrup, corn syrup solids, dextrates, dextrin, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylene glycol and vinyl alcohol graft copolymer, gelatin, glucose liquid, glyceryl behenate, glyceryl dibehenate, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl cellulose low-substituted, hypromellose, hypromellose acetate succinate, inulin, invert sugar, alpha-lactalbumin, lactose monohydrate, maltodextrin, maltose, methacrylic acid and ethyl acrylate copolymer, methacrylic acid and ethyl acrylate copolymer dispersion, methacrylic acid and methyl methacrylate copolymer, methylcellulose, palm oil hydrogenated, polycarbophil, polydextrose hydrogenated, polyethylene oxide, polyvinyl acetate, povidone, pullulan, sodium alginate, starch pregelatinized, starch pregelatinized modified, starch corn, starch hydroxypropyl corn, starch pregelatinized hydroxypropyl corn, starch pea, starch hydroxypropyl pea, starch pregelatinized hydroxypropyl pea, starch potato, starch hydroxypropyl potato, starch pregelatinized hydroxypropyl potato, starch tapioca, starch wheat, starch hydrolysate hydrogenated, sucrose, sucrose diacetate hexaisobutyrate, sunflower oil, syrup, trehalose, vegetable oil hydrogenated, vitamin E polyethylene glycol succinate or zein.

In a preferred embodiment, the multiple unit oral dosage form is one wherein the pharmaceutically acceptable excipients or carriers comprises one or more binder; preferably comprises shellac and polyvinylpyrrolidone (PVP), and more particular embodiment are dewaxed shellac and PVP-K30.

The term "glidant" refers to a pharmaceutically acceptable substance which improves the flow characteristics of powder mixtures in the dry state. Materials commonly used as a glidant include magnesium stearate, silica (colloidal silicon dioxide; particularly Aerosil) or talc. In an embodiment, the multiple unit oral dosage form is one wherein the pharmaceutically acceptable excipients or carriers comprises one or more glidant; preferably comprises colloidal silicon dioxide, and more preferably Aerosil 200 Pharma.

The term "lubricant" refers to a pharmaceutically acceptable substance that prevents composition ingredients from clumping together and from sticking to the tablet punches or capsule filling machine and improves flowability of the composition mixture. Materials commonly used as a lubricant include sodium oleate, sodium stearate, sodium benzoate, sodium stearate, sodium chloride, stearic acid, sodium stearyl fumarate, calcium stearate, magnesium stearate, magnesium lauryl sulfate, sodium stearyl fumarate, sucrose esters or fatty acid, zinc, polyethylene glycol, talc and mixtures thereof.

Examples of lubricants include behenoyl polyoxylglycerides, calcium stearate, castor oil hydrogenated, coconut oil hydrogenated, glyceryl behenate, glyceryl dibehenate, glyceryl mono and dicaprylate, glyceryl mono and dicaprylocaprate, glyceryl monocaprylate, glyceryl monocaprylocaprate, glyceryl monostearate, glyceryl tricaprylate, glyceryl tristearate, lauric acid, magnesium stearate, mineral oil light, myristic acid, palm oil hydrogenated, palmitic acid, poloxamer, polyethylene glycol,

polyethylene glycol 3350, polyoxyl 10 oleyl ether, polyoxyl 15 hydroxystearate, polyoxyl 20 cetostearyl ether, polyoxyl 35 castor oil, polyoxyl 40 castor oil hydrogenated, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, potassium benzoate, sodium benzoate, sodium lauryl sulfate, sodium stearate, sodium stearyl fumarate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate, stearic acid, stearic acid purified, sucrose stearate, talc, vegetable oil hydrogenated type I and zinc stearate.

The terms "filler" and "diluent" have the same meaning and are used interchangeably. They refer to any pharmaceutically acceptable excipient or carrier (material) that fill out the size of a composition, making it practical to produce and convenient for the consumer to use. Materials commonly used as filler include, calcium carboxymethyl cellulose, cellulose, cellulose products such as microcrystalline cellulose and its salts, dextrin derivatives, dextrin, dextrose, fructose, lactitol, lactose, starches or modified starches, magnesium carbonate, , maltitol, maltodextrins, maltose, mannitol, sorbitol, starch, sucrose, sugar, xylitol, erythritol and mixtures thereof. In an embodiment, the multiple unit oral dosage form is one wherein the pharmaceutically acceptable excipients or carriers comprises one or more fillers; preferably comprises sucrose, starch or microcrystalline cellulose.

Examples of fillers include amino methacrylate copolymer; ammonium methacrylate copolymer; ammonium methacrylate copolymer dispersion; cellaburate; cellulose, microcrystalline; cellulose, silicified microcrystalline; cellulose, powdered; cellulose acetate; corn syrup; corn syrup solids; dextrates; dextrin; dextrose; dextrose excipient; erythritol; ethyl acrylate and methyl methacrylate copolymer dispersion; fructose; invert sugar; isomalt; kaolin; alpha-lactalbumin; lactitol; lactose, anhydrous;

lactose, monohydrate; magnesium carbonate;; maltitol; maltodextrin; maltose; mannitol; methacrylic acid and ethyl acrylate copolymer; methacrylic acid and ethyl acrylate copolymer dispersion; methacrylic acid and methyl methacrylate copolymer; polydextrose; polyethylene glycol; polyethylene glycol 3350; propylene glycol monocaprylate; pullulan; simethicone; sodium chloride; sorbitol; starch, pregelatinized; starch, pregelatinized modified; starch, corn; starch, hydroxypropyl corn; starch, pregelatinized hydroxypropyl corn; starch, pea; starch, hydroxypropyl pea; starch, pregelatinized hydroxypropyl pea; starch, potato; starch, hydroxypropyl potato; starch, pregelatinized hydroxypropyl potato; starch, tapioca; starch, wheat; starch hydrolysate, hydrogenated; sucrose; sugar, compressible; sugar, confectioner's; sugar spheres; sunflower oil; talc; trehalose; and xylitol.

The term "wicking agents" refers to the pharmaceutically acceptable material that has the ability to draw water into the porous network of a delivery device. It has the ability to undergo physisorption with water. It acts like a carrier and facilitate the entry of water to the inner surfaces of the core. Materials commonly used as wicking agent include sodium lauryl sulfate, kaolinalumina, bentonite, magnesium aluminium silicate, povidone and colloidal silicon dioxide (Aerosil).

In a preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the pharmaceutically acceptable excipients or carriers comprises one or more wicking agents; preferably kaolin, alumina, bentonite, magnesium aluminium silicate, povidone and colloidal silicon dioxide (Aerosil). In an embodiment, the multiple unit oral dosage form of the invention is one wherein the pharmaceutically acceptable excipients or carriers comprises one or more wicking agents; preferably comprises povidone or colloidal silicon dioxide (Aerosil) or a mixture thereof.

In a preferred embodiment, the multiple unit oral dosage form of the invention is one

wherein the modified release multiple unit oral dosage form comprises: a first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof not comprising an inner active coating layer but comprising an active nucleus comprising a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients selected from the group consisting of sorbitol, mannitol, sucrose, saccharose, starch, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropyl methyl cellulose, lactose, glucose, trehalose, maltitol, fructose, colloidal silicon dioxide, cellulose, polyvinylpyrrolidone, magnesium stearate, silica (colloidal silicon dioxide; particularly Aerosil), talc.

In a preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises: a first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof comprising an inert nucleus and an inner active coating layer comprising: from 6 to 20 % by weight of one or more coating agents in relation to the total weight of the inner active coating layer; from 15 to 30 % by weight of one or more anticaking agent in relation to the total weight of the inner active coating layer; optionally one or more pore forming agent, and optionally one or more additional pharmaceutically acceptable excipient, being the sum of the components up to 100% by weight in relation to the weight of the inner active coating layer.

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof

comprising an intermediate enteric release coating layer comprising: from 45 to 65 % by weight of one or more enteric coating agents in relation to the total weight of the intermediate enteric release coating layer; from 35 to 55 % by weight of one or more anticaking agent in relation to the total weight of the intermediate enteric release coating layer; optionally one or more pore forming agent; and optionally one or more additional pharmaceutically acceptable excipients being the sum of the components up to 100% by weight in relation to the weight of the intermediate enteric release coating layer.

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof comprising an external modified release coating layer comprising: from 7 to 14 % by weight of one or more enteric coating agents; from 38 to 46 % by weight of one or more modified release coating agents in relation to the total weight of the external modified release coating layer; from 42 to 52 % by weight of one or more anticaking agent in relation to the total weight of the external modified release coating layer; optionally one or more pore forming agent; and optionally one or more additional pharmaceutically acceptable excipients, being the sum of the components up to 100% by weight in relation to the weight of the external modified release coating layer.

In a preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof comprising:

- optionally, an inner active coating layer comprising:
 - a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof; and
 - from 6 to 20 % by weight of one or more coating agents in relation to the total weight of the inner active coating layer; and
 - from 15 to 30 % by weight of one or more anticaking agent in relation to the total weight of the inner active coating layer; and
 - optionally one or more pore forming agents; and optionally one or more additional pharmaceutically acceptable excipients; and
 - being the sum of the components up to 100% by weight in relation to the weight of the inner active coating layer;
- optionally, an intermediate enteric release coating layer comprising:
 - from 45 to 65 % by weight of one or more enteric coating agents in relation to the total weight of the intermediate enteric release coating layer; and
 - from 35 to 55 % by weight of one or more anticaking agents in relation to the total weight of the intermediate enteric release coating layer; and
 - optionally, one or more pore forming agents; and
 - optionally one or more additional pharmaceutically acceptable excipients; and
 - being the sum of the components up to 100% by weight in relation to the weight of the intermediate enteric release coating layer;
- an external modified release coating layer comprising:
 - from 7 to 14 % by weight of one or more enteric coating agents in relation to the total weight of the external modified release coating layer; and
 - from 38 to 46 % by weight of one or more modified release coating agents in relation to the total weight of the external modified release coating layer; and

from 42 to 52 % by weight of one or more anticaking agent in relation to the total weight of the external modified release coating layer; and optionally, one or more pore-forming agent; and optionally, one or more additional pharmaceutically acceptable excipients; and being the sum of the components up to 100% by weight in relation to the weight of the external modified release coating layer, wherein any of the pharmaceutically acceptable excipients, particularly any of the coating agents, are free of titanium dioxide.

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof comprising not an inner active coating layer but an active nucleus comprising a therapeutically effective amount of pyridoxine or a pharmaceutically salt thereof and one or more pharmaceutically acceptable excipients selected from the group consisting of nucleus is formed with at least one acceptable excipient of the active nucleus is selected from the group consisting of sorbitol, mannitol, sucrose, saccharose, starch, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, glucose, trehalose, maltitol, fructose, colloidal silicon dioxide, cellulose, polyvinylpyrrolidone, magnesium stearate, silica (colloidal silicon dioxide; particularly Aerosil), talc.

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof

comprising an inert nucleus and an inner active coating layer comprising from 13 to 25 % by weight of one or more coating agents in relation to the total weight of the inner active coating layer; and optionally one or more pharmaceutically acceptable excipients; being the sum of the components up to 100% by weight in relation to the weight of the inner active coating layer.

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a first plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof comprising an intermediate enteric release coating layer comprising: from 45 to 65 % by weight of one or more enteric coating agents in relation to the total weight of the intermediate enteric release coating layer; from 35 to 55 % by weight of one or more anticaking agent in relation to the total weight of the intermediate enteric release coating layer; optionally one or more pore forming agent; and optionally one or more additional pharmaceutically acceptable excipients being the sum of the components up to 100% by weight in relation to the weight of the intermediate enteric release coating layer.

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof comprising an external modified release coating layer comprising: from 2 to 8 % by weight of one or more enteric coating agents in relation to the total weight of the external modified release coating layer; from 30 to 49 % by weight of one or more modified release coating agents in relation to the total weight of the external modified

release coating layer; from 46 to 65 % by weight of one or more anticaking agents in relation to the total weight of the external modified release coating layer and optionally one or more pore forming agents; optionally one or more pharmaceutically acceptable excipients being the sum of the components up to 100% by weight in relation to the weight of the external modified release coating layer.

In a further preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises a second plurality of modified release units, preferably modified release particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof comprising:

- optionally, an inner active coating layer comprising:

a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof; and

from 13 to 25 % by weight of one or more coating agents in relation to the total weight of the inner active coating layer; and

optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the inner active coating layer;

- optionally, an intermediate enteric release coating layer comprising:

from 45 to 65 % by weight of one or more enteric coating agents in relation to the total weight of the intermediate enteric release coating layer; and

from 35 to 55 % by weight of one or more anticaking agents in relation to the total weight of the intermediate enteric release coating layer; and

optionally, one or more pore forming agents; and optionally one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight of the intermediate enteric release coating layer;

- an external modified release coating layer comprising:

from 2 to 8 % by weight of one or more enteric coating agents in relation to the total weight of the external modified release coating layer; and

from 30 to 49 % by weight of one or more modified release coating agents in relation to the total weight of the external modified release coating layer; and

from 46 to 65 % by weight of one or more anticaking agents in relation to the total weight of the external modified release coating layer; and

optionally, one or more pore forming agents; and optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the external modified release coating layer;

wherein any of the pharmaceutically acceptable excipients, particularly any of the coating agents, are free of titanium dioxide.

In a preferred embodiment, the multiple unit oral dosage form of the invention is one wherein the modified release multiple unit oral dosage form comprises:

a first plurality of modified release units, preferably modified release small particles, more preferably pellets, of doxylamine or a pharmaceutically acceptable salt thereof comprising:

- a pharmaceutically acceptable inert nucleus;

- an inner active coating layer comprising:

a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof; and

from 6 to 20 % by weight of one or more coating agents in relation to the total weight

of the inner active coating layer; and

from 15 to 30 % by weight of one or more anticaking agent in relation to the total weight of the inner active coating layer; and

optionally, one or more pore forming agents; and, optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the inner active coating layer;

- optionally, an intermediate enteric release coating layer comprising:

from 45 to 65 % by weight of one or more enteric coating agents in relation to the total weight of the intermediate enteric release coating layer; and

from 35 to 55 % by weight of one or more anticaking agents in relation to the total weight of the intermediate enteric release coating layer; and

optionally, one or more pore forming agents; and optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the intermediate enteric release coating layer;

- an external modified release coating layer comprising:

from 7 to 14 % by weight of one or more enteric coating agents in relation to the total weight of the external modified release coating layer; and

from 38 to 46 % by weight of one or more modified release coating agents in relation to the total weight of the external modified release coating layer; and

from 42 to 52 % by weight of one or more anticaking agent in relation to the total weight of the external modified release coating layer; and

optionally, one or more pore-forming agent; and optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the external modified release coating layer; and

a second plurality of modified release units, preferably modified release small particles, more preferably pellets, of pyridoxine or a pharmaceutically acceptable salt thereof comprising:

- a pharmaceutically acceptable inert nucleus;

- an inner active coating layer comprising:

a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof; and

from 13 to 25 % by weight of one or more coating agents in relation to the total weight of the inner active coating layer; and

optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the inner active coating layer;

- optionally, an intermediate enteric release coating layer comprising:

from 45 to 65 % by weight of one or more enteric coating agents in relation to the total weight of the intermediate enteric release coating layer; and

from 35 to 55 % by weight of one or more anticaking agents in relation to the total weight of the intermediate enteric release coating layer; and

optionally, one or more pore forming agents; and optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the intermediate enteric release coating layer;

- an external modified release coating layer comprising:

from 2 to 8 % by weight of one or more enteric coating agents in relation to the total

weight of the external modified release coating layer; and

from 30 to 49 % by weight of one or more modified release coating agents in relation to the total weight of the external modified release coating layer; and

from 46 to 65 % by weight of one or more anticaking agents in relation to the total weight of the external modified release coating layer; and

optionally, one or more pore forming agents; and optionally, one or more additional pharmaceutically acceptable excipients; and

being the sum of the components up to 100% by weight in relation to the weight the external modified release coating layer;

wherein said nucleus and any of the pharmaceutically acceptable excipients, particularly any of the coating agents, are free of titanium dioxide.

Examples

Example 1. Capsule shells

The qualitative composition of empty capsules with and without TiO₂, used on examples 2.1.1, 2.1.2, 2.1.3 and 2.1.4, is disclosed in Table 1 below.

Table 1

Capsule code	Colourant	Titanium dioxide	Shell material	Example
<u>ITF RES-1</u>	FDC Blue 1	<u>NO</u>	<u>Gelatine</u>	<u>Example 2.1.1.</u>
<u>ITF RES-2</u>	Patent Blue V	<u>NO</u>	<u>Gelatine</u>	<u>Example 2.1.1.</u>
<u>ITF RES-3</u>	FDC Blue 1 & yellow iron oxide	<u>NO</u>	<u>Gelatine</u>	<u>Example 2.1.1.</u>
<u>ITF RES-4</u>	FDC Blue 2	<u>NO</u>	<u>Gelatine</u>	<u>Examples 2.1.1 and 2.1.2</u>
<u>ITF RES-5</u>	Patent Blue V & erythrosine	<u>NO</u>	<u>Gelatine</u>	<u>Examples 2.1.1 and 2.1.2</u>
<u>ITF RES-6</u>	FDC Blue 2 & quinoline yellow	<u>YES</u>	<u>Gelatine</u>	<u>Example 2.1.1</u>

ITF RES-7	FDC Blue 2	YES	Gelatine	Example 2.1.2
ITF RES-8	FDC Blue 2	NO	HPMC	Examples 2.1.3 and 2.1.4
ITF RES-9	FDC Blue 2 & FDC Red 40	NO	HPMC	Example 2.1.3
ITF RES-10	FDC Blue 2	YES	HPMC	Example 2.1.3

Example 2. Capsule shells filled with pellets of doxylamine succinate and pyridoxine hydrochloride

2.1 Composition per hard capsule

The qualitative and quantitative composition of the different hard capsule formulations are described below.

2.1.1 Hard gelatine capsules with Doxylamine succinate 10 mg and Pyridoxine hydrochloride 10 mg.

Table 2

Ingredient	Quantity per capsule (mg)	Function
Active ingredients		
Doxylamine succinate	10.0	Active ingredient
Pyridoxine hydrochloride	10.0	Active ingredient
Excipients		
Sugar spheres of sucrose and starch ⁽¹⁾	79.5	Pharmaceutically acceptable inert nucleus
(dewaxed) Shellac	7.6	Coating agent/ binder solution
Polyvinylpyrrolidone (Povidone K-30)	0.2	Coating agent/ binder solution
Talc (D90 equal to or below 250 µm)	9.5	Anticaking agent
Methacrylic acid - methyl methacrylate copolymer (1:1) (Eudragit L)	1.1	Enteric coating agent
Silica colloidal anhydrous (Aerosil)	0.7	Anticaking, gliding agent

Hard gelatine capsule, size 3(ITF RES-1, ITF RES-2, ITF RES-3, ITF RES-4, ITF RES-5 or ITF RES-6, as reported in Table 1)	about 46 ⁽³⁾	Container of dose units (pellets)
Each capsule is filled with about 60 mg ⁽²⁾ of pellets of doxylamine succinate and about 60 mg ⁽²⁾ of pellets of pyridoxine hydrochloride.		

(1) at least 90% of the nucleus have a particle size from 710 µm to 1000 µm and at least the 90% of the pharmaceutically acceptable nucleus have a particle size variability of 100 µm

(2) 60 mg +/- 10%, practical target filling weight_is calculated based upon actual potency of the pellets in doxylamine succinate or pyridoxine hydrochloride so as to assure the theoretical content of 10.0 mg of doxylamine succinate and 10.0 mg of pyridoxine hydrochloride per capsule

(3) 46 mg +/- 8%, based upon capsule supplier specifications

2.1.2. Hard gelatine capsules with Doxylamine succinate 20 mg and Pyridoxine hydrochloride 20 mg.

Table 3

Ingredient	Quantity per capsule (mg)	Function
Active ingredients		
Doxylamine succinate	20.0	Active ingredient
Pyridoxine hydrochloride	20.0	Active ingredient
Excipients		
Sugar spheres of sucrose and starch ⁽¹⁾	159.0	Pharmaceutically acceptable inert nucleus
(dewaxed) Shellac	15.2	Coating agent/ binder solution
Polyvinylpyrrolidone (Povidone K-30)	0.4	Coating agent/ binder solution
Talc (D90 equal to or below 250 µm)	19.0	Anticaking agent
Methacrylic acid - methyl methacrylate copolymer (1:1) (Eudragit L)	2.2	Enteric coating agent

Silica colloidal anhydrous (Aerosil)	1.4	Anticaking, gliding agent
Hard gelatine capsule, size 1 (ITF RES-4, ITF RES-5 or ITF RES-7 as reported in Table 1)	about 76 (3)	Container of dose units (pellets)
Each capsule is filled with about 120 mg ⁽²⁾ of pellets of doxylamine succinate and about 120 mg ⁽²⁾ of pellets of pyridoxine hydrochloride		

(1) at least 90% of the nucleus have a particle size from 710 µm to 1000 µm and at least the 90% of the pharmaceutically acceptable nucleus have a particle size variability of 100 µm

(2) 120 mg +/- 10%, practical target filling weight is calculated based upon actual potency of the pellets in doxylamine succinate or pyridoxine hydrochloride so as to assure the theoretical content of 20.0 mg of doxylamine succinate and 20.0 mg of pyridoxine hydrochloride per capsule

(3) 76 mg +/- 7.5%, based upon capsule supplier specifications.

2.1.3. HPMC capsules with Doxylamine succinate 10 mg and Pyridoxine hydrochloride 10 mg:

Table 4

Ingredient	Quantity per capsule (mg)	Function
Active ingredients		
Doxylamine succinate	10.0	Active ingredient
Pyridoxine hydrochloride	10.0	Active ingredient
Excipients		
Sugar spheres of sucrose and starch ⁽¹⁾	79.5	Pharmaceutically acceptable inert nucleus
(dewaxed) Shellac	7.6	Coating agent/ binder solution
Polyvinylpyrrolidone (Povidone K-30)	0.2	Coating agent/ binder solution
Talc (D90 equal to or below 250 µm)	9.5	Anticaking agent
Methacrylic acid - methyl methacrylate copolymer (1:1) (Eudragit L)	1.1	Enteric coating agent
Silica colloidal anhydrous (Aerosil)	0.7	Anticaking, gliding agent

Hard HPMC capsule, size 3 (ITF RES-8, ITF RES-9 or ITF RES-10, as reported in Table 1)	about 46 ⁽³⁾	Container of dose units (pellets)
Each capsule is filled with about 60 mg ⁽²⁾ of pellets of doxylamine succinate and about 60 mg ⁽²⁾ of pellets of pyridoxine hydrochloride		

(1) at least 90% of the nucleus have a particle size from 710 µm to 1000 µm and at least the 90% of the pharmaceutically acceptable nucleus have a particle size variability of 100 µm

(2) 60 mg +/- 10%, practical target filling weight_is calculated based upon actual potency of the pellets in doxylamine succinate or pyridoxine hydrochloride so as to assure the theoretical content of 10.0 mg of doxylamine succinate and 10.0 mg of pyridoxine hydrochloride per capsule

(3) 46 mg +/- 8%, based upon capsule supplier specifications.

2.1.4. HPMC capsules with Doxylamine succinate 20 mg and Pyridoxine hydrochloride 20 mg.

Table 5

Ingredient	Quantity per capsule (mg)	Function
Active ingredients		
Doxylamine succinate	20.0	Active ingredient
Pyridoxine hydrochloride	20.0	Active ingredient
Excipients		
Sugar spheres of sucrose and starch ⁽¹⁾	159.0	Pharmaceutically acceptable inert nucleus
(dewaxed) Shellac	15.2	Coating agent/ binder solution
Polyvinylpyrrolidone (Povidone K-30)	0.4	Coating agent/ binder solution
Talc (D90 equal to or below 250 µm)	19.0	Anticaking agent
Methacrylic acid - methyl methacrylate copolymer (1:1) (Eudragit L)	2.2	Enteric coating agent
Silica colloidal anhydrous (Aerosil)	1.4	Anticaking, gliding agent
Hard HPMC capsule, size 1 (ITF RES-8, as reported in Table 1)	about 76 ⁽³⁾	Container of dose units (pellets)

Each capsule is filled with about 120 mg⁽²⁾ of pellets of doxylamine succinate and about 120 mg⁽²⁾ of pellets of pyridoxine hydrochloride

(1) at least 90% of the nucleus have a particle size from 710 µm to 1000 µm and at least the 90% of the pharmaceutically acceptable nucleus have a particle size variability of 100 µm.

(2) 120 mg +/- 10%, practical target filling weight_is calculated based upon actual potency of the pellets in doxylamine succinate or pyridoxine hydrochloride so as to assure the theoretical content of 20.0 mg of doxylamine succinate and 20.0 mg of pyridoxine hydrochloride per capsule

(3) 76 mg +/- 7.5%, based upon capsule supplier specifications.

Example 3: Pre-stability study

Samples of empty capsules ITF RES 1, ITF RES 2, ITF RES 3, ITF RES 4, ITF RES 5 and ITF RES 6, disclosed in Example 1, were manually filled with TiO₂ free small particles of doxylamine succinate and pyridoxine hydrochloride detailed in the Example 2.1.1., blistered in a material equivalent to the commercial one and subjected during 30 days to a stability stress test (based on high temperature and humidity), in which aspect (colour of capsule shell, colour and absence of agglomeration of pellets) was monitored at 24 and 30 days. The capsule ITF RES 6 was used as positive control containing TiO₂.

Samples were considered compliant (C) if showing absence of agglomerated pellets, homogenous white/yellowish colour of the pellets and homogenous colour of the capsules according to their specifications after 30 days of storage at the conditions detailed in the table below.

The results obtained are summarized in Table 6 below:

Table 6

	25°C / 60%RH		50°C / --%HR		RT/light	
	24 days	30 days	24 days	30 days	24 days	30 days
ITF RES-1	C	C	C	C	C	C
ITF RES-2	ND	ND	C	C	C	C

ITF RES-3	ND	ND	C	C	C	C
ITF RES-4	C	C	C	C	C	C
ITF RES-5	ND	ND	C	C	C	C
ITF RES-6 (with TiO ₂)	C	C	C	C	C	C

(C: Complies / ND: Not Determined)

Conclusions:

As inferred from the study, the TiO₂-free small particles included in TiO₂-free capsules of the present invention are surprisingly found as stable as the ones contained in capsules containing TiO₂ since no alterations in the appearance of the capsules and the pellets were detected in all conditions.

Example 4: Stability study performed with hard Gelatin capsules.

Samples of empty capsules ITF RES 4, ITF RES 5 and ITF RES 7, disclosed in Example 1, were filled with TiO₂ free pellets of doxylamine succinate and pyridoxine hydrochloride detailed in the Example 2.1.2 and subjected to the stability test disclosed below. The capsule shell ITF RES 7 was used as positive control containing TiO₂.

The samples of filled capsules were placed in stability chambers in the following climatic conditions:

- 25° C/60 % RH,
- 30° C/65 % RH
- 30° C/75 % RH

At each time point, the parameters appearance, doxylamine and pyridoxine content and doxylamine and pyridoxine dissolution profile were analyzed according to the methods described below. The specifications for each test are also described.

Specifications and methods used:

Appearance (Visual test) (AP): Samples are visually analysed and are considered compliant if showing absence of agglomerated pellets, homogenous white/yellowish colour of the pellets and homogenous colour of the capsules without defects in structure, according to their own specifications.

Dissolution test (DT): Samples are analysed by HPLC following the method described in table 7, with one capsule per vase of the dissolution equipment.

Samples are considered compliant when the dissolution profile of doxylamine shows the following results:

- from 5% to 35% by weight of doxylamine theoretical content is dissolved at the end of the 1st hour
- from 35% to 75% by weight of doxylamine theoretical content is dissolved at the end of the 4th hour more than 75% by weight of doxylamine theoretical content is dissolved at the end of the 7th hour.

Samples are considered compliant when the dissolution profile of pyridoxine shows the following results:

- from 5% to 35% by weight of pyridoxine theoretical content is dissolved at the end of the 1st hour
- from 35% to 75% by weight of pyridoxine theoretical content is dissolved at the end of the 4th hour
- more than 75% by weight of pyridoxine theoretical content is dissolved at the end of the 7th hour.

Table 7.

Dissolution media	HCl 0.1N (1hour), buffer pH 4.5 (hours 2-4), buffer pH 6.8 (hours 4-7)
Medium temperature	37 ± 0.5°C
Volume	900 ml

Equipment	Agilent 708-DS
Apparatus	Paddles (USP type II)
Rotation speed	100 rpm
Sampling volume	5 ml
Sample measure technique	RP-HPLC/DAD (Reverse Phase High-Performance Liquid Chromatography-Photodiode Array Detector)

Assay test (AS): Samples of the pellets contained in the capsules of Example 2.1.2 are analysed using the HPLC method described in table 8.

Samples are considered compliant when the content of doxylamine succinate is between 19 and 21 mg per capsule and the content of pyridoxine hydrochloride is 19 and 21 mg per capsule.

Table 8

Column:	Kromasil 100-5C18, 150x4 mm or equivalent
Pre-column:	Phenomenex SecurityGuard C18 4,0 x 3,0 mm or equivalent
Flux (ml/min):	1.0 ml/min
Column temperature (°C)	25°C
Wavelength (nm)	220 nm
Mobile phase:	Methanol/Acetate buffer pH 5.0
Gradient	Yes
Runtime	25 min

As mentioned above, the TiO₂-free pellets of doxylamine succinate and pyridoxine hydrochloride of the Example 2.1.2. contained in capsules ITF RES 4, ITF RES 5 and ITF RES 7 of the Example 1 were stored up to 3 months under the conditions:

- 25°C/60%HR,
- 30°C/65%HR
- 30°C/75%HR

The results of this stability study are summarized in the table 9 below.

Table 9. Stability Data up to 3 months

	25°C/60%HR			30°C/65%HR			30°C/75%HR		
	AP	DT	AS	AP	DT	AS	AP	DT	AS
ITF RES-4	C	C	C	C	C	C	C	C	C
ITF RES-5	C	C	C	C	C	C	C	C	C
(C: ITF RES-7 (withTiO ₂))	C	C	C	C	C	C	C	C	C

complies)

The TiO₂-free pellets contained in capsules ITF RES 4 and ITF RES 7 were maintained in the chamber at 25°C/60%HR up to 11 months.

The results of this extended stability study are summarized in the table 10 below.

Table 10: Stability data up to 11 months

Gelatine	25°C/60%HR		
	AP	DT	AS
ITF RES-4	C	C	C
ITF RES-7 (with TiO ₂)	C	C	C

(C: Complies)

Conclusion:

As inferred from the study, the TiO₂-free small particles contained in the TiO₂-free hard gelatine capsules of the present invention are as stable as the small particles in hard gelatine capsules containing TiO₂.

According to the results, despite lacking the protective effect of TiO₂, the multiple units dosage forms of the present invention show no alterations in their appearance, dissolution test and active ingredients content for at least 3 months under all the studied conditions and at least 11 months at 25°C/60% RH condition.

Example 5: Stability study performed with HPMC capsules

Samples of empty capsules ITF RES 8, ITF RES 9 and ITF RES 10, disclosed in

Example 1, were filled with TiO₂-free pellets of doxylamine succinate and pyridoxine hydrochloride detailed in Example 2.1.3. and subjected to the stability test disclosed below. The capsule shell ITF RES 10 was used as positive control containing TiO₂. The samples of filled capsules were placed in stability chambers in the following climatic conditions:

- 25° C/60 % RH,
- 30° C/65 % RH

At each time point, the parameters appearance, assay and dissolution profile were analysed by visual test or HPLC according to the methods described below. The specifications for each test are also described.

Specifications and methods used:

Appearance (Visual test) (AP): Samples are to be considered compliant if showing absence of agglomerated pellets, homogenous white/yellowish colour of the pellets and homogenous colour of the capsules without defects in structure, according to their specifications.

Dissolution test (DT): Samples are analysed by HPLC following the method described in Table 11, with one capsule per vase of the dissolution equipment. The dissolution is performed during 7 hours at different pH. Samples are dissolved during the 1st hour in a 0.1 N HCl medium (pH = 1.2); then the medium is replaced by a 0.05 M acetate buffer medium (pH = 4.5) where the samples are dissolved for 3 additional hours. Finally the medium is replaced by a 0.05 M phosphate buffer medium (pH = 6.8) where samples are dissolved from the last three hours.

Samples are to be considered compliant when dissolution profile complies with the following in terms of doxylamine release:

- from 5% to 35% by weight of doxylamine theoretical content is dissolved at the

end of the 1st hour

- from 35% to 75% by weight of doxylamine theoretical content is dissolved at the end of the 4th hour
- more than 75% by weight of doxylamine theoretical content is dissolved at the end of the 7th hour.

Samples are to be considered compliant when dissolution profile complies with the following in terms of Pyridoxine release:

- from 5% to 35% by weight of pyridoxine theoretical content is dissolved at the end of the 1st hour
- from 35% to 75% by weight of pyridoxine theoretical content is dissolved at the end of the 4th hour
- more than 75% by weight of pyridoxine theoretical content is dissolved at the end of the 7th hour.

Table 11

Dissolution media	HCl 0.1N (1hour), buffer pH 4.5 (hours 2-4), buffer pH 6.8 (hours 4-7)
Medium temperature	37 ± 0.5°C
Volume	900 ml
Equipment	Agilent 708-DS
Apparatus	Paddles (USP type II)
Rotation speed	100 rpm
Sampling volume	5 ml
Sample measure technique	RP-HPLC/DAD (Reverse Phase High-Performance Liquid Chromatography-Photodiode Array Detector)

Assay test (AS): Samples of pellets contained in the capsules of Example 2.1.3 are analysed, by duplicate, using the HPLC method described in Table 12.

Samples are to be considered compliant when the content of doxylamine succinate is between 9.5 and 10.5 mg per capsule and the content of pyridoxine hydrochloride is

9.5 and 10.5 mg per capsule.

Table 12

Column:	Kromasil 100-5C18, 150x4 mm or equivalent
Pre-column:	Phenomenex SecurityGuard C18 4,0 x 3,0 mm or equivalent
Flux (ml/min):	1.0 ml/min
Column temperature (°C)	25°C
Wavelength (nm)	220 nm
Mobile phase:	Methanol/Acetate buffer pH 5.0
Gradient	Yes
Runtime	25 min

Table 13. Stability Data at 3 months :

HPMC	25°C/60%HR			30°C/65%HR		
	AP	DT	AS	AP	DT	AS
ITF RES-8	C	C	C	C	C	C
ITF RES-9	C	C	C	C	C	C
ITF RES-10 (with TiO ₂)	C	C	C	C	C	C

(C: complies)

Table 14. Data at 12 months

HPMC	25°C/60%HR		
	AP	DT	AS
ITF RES-8	C	C	C
ITF RES-9	C	C	C
ITF RES-10 (with TiO ₂)	C	C	C

(C: Complies)

Conclusion:

As inferred from the study, the TiO₂-free small particles contained in the TiO₂-free HPMC capsules of the present invention are as stable as the small particles in

capsules containing TiO₂ in all conditions.

According to the results, despite lacking the protective effect of TiO₂, the multiple unit dosage forms of the present invention show no significative alterations in their appearance, dissolution test and active ingredients content for at least 12 months under all the studied conditions.

Citation List

1. WO2013123569
2. WO2016029290
3. European Pharmacopoeia chapter 2.9.38
4. European Pharmacopoeia Doxylamine hydrogen succinate monograph
5. European Pharmacopoeia Pyridoxine hydrochloride monograph
6. Cariban Patient Leaflet
7. Xonvea Patient Leaflet
8. Commission Regulation (EU) 2022/63 on TiO₂
9. ICH M7 guideline
10. Handbook of Pharmaceutical Excipients, 2020
11. EMA/504010/2021

Claims

1. A multiple unit oral dosage form comprising a capsule shell, a first plurality of modified release units of doxylamine or a pharmaceutically acceptable salt thereof and a second plurality of modified release units of pyridoxine or a pharmaceutically acceptable salt thereof, characterized in that said capsule shell does not contain TiO_2 .
2. The oral dosage form according to claim 1, characterized in that said capsule shell comprises at least one pharmaceutically acceptable capsule shell material.
3. The oral dosage form according to anyone of claims 1 or 2, characterized in that said capsule shell comprises at least one pharmaceutically acceptable capsule shell material and at least one pharmaceutically acceptable organic colourant.
4. The oral dosage form according to anyone of the preceding claims, characterized in that said capsule shell consists of at least one pharmaceutically acceptable capsule shell material, at least one pharmaceutically acceptable organic colourant, water and, optionally, at least a pharmaceutically acceptable gelling agent, at least one pharmaceutically acceptable co-gelling agent, at least one pharmaceutically acceptable plasticizer and/or at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .
5. The oral dosage form according to anyone of claims 2 to 4, characterized in that said capsule shell material is selected from gelatine, hydroxypropylmethylcellulose, pullulan, alginate, carrageenan, cellulose and/or starch.
6. The oral dosage form according to anyone of the preceding claims, characterized in that said capsule shell consists of gelatine, water, at least one pharmaceutically acceptable organic colourant and, optionally, at least one plasticizer and/or at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .

7. The oral dosage form according to anyone of the preceding claims, characterized in that said capsule shell consists of HPMC, water, at least one pharmaceutically acceptable gelling agent, at least one pharmaceutically acceptable co-gelling agent, at least one pharmaceutically acceptable organic colourant and, optionally, at least one pharmaceutically acceptable plasticizer and/or at least one pharmaceutically acceptable inorganic colourant other than TiO_2 .

8. The oral dosage form according to anyone of claims 3 to 7, characterized in that said at least one pharmaceutically acceptable organic colourant is selected from the group consisting of Curcumin (E100), Riboflavin (E101), Riboflavin-5'-phosphate (E101a), Tartrazine (E102 or FD&C Yellow 5), Quinoline yellow (E104), Sunset Yellow FCF (E110 or Orange Yellow S, FD&C Yellow 6), Carminic acid/Carmines (E120 or Natural Red 4), Carmoisine (E122 or Azorubine), Amaranth (E123 or FD&C Red 2), Ponceau 4R (E124 or Brilliant Scarlet 4R), Erythrosine (E127 or FD&C Red 3), Allura Red AC (E129 or FD&C 40), Patent Blue V (E131), Indigo carmine (E132 or FD&C Blue 2), Brilliant blue FCF (E133 or FD&C Blue 1), Chlorophylls and Chlorophyllins (E140), copper complexes of Chlorophylls and Chlorophyllins (E141), Green S (E142), Fast Green FCF (E143 or FD&C Green 3), Plain caramel (E150a), Caustic sulfite caramel (E150b), Ammonia caramel (E150c), Sulfite ammonia caramel (E150d), Black PN (E151 or Brilliant Black BN), Vegetable carbon (E153), Brown HT (E155), Alpha-carotene, Beta-carotene, Gamma-carotene (E160a), Annatto, Bixin, Norbixin (E160b), Paprika oleoresin: capsanthin, capsorubin (E160c), Lycopene (E160d), Beta-apo-8'-carotenal (E160e), Lutein (E161b), Canthaxanthin (E161g), Beetroot Red, Betanin (E162), Anthocyanins (E163), Saffron (E164) and mixtures thereof, preferably said organic colourant is selected from the group consisting of Indigo carmine, Patent Blue V, Brilliant blue, Erythrosine, Allura Red

AC, Quinoline yellow and mixtures thereof.

9. The oral dosage form according to anyone of claims 3 to 8, characterized in that said at least one pharmaceutically acceptable organic colourant is selected from the group consisting of Brilliant blue; Patent Blue V; Indigo carmine; Patent Blue V and erythrosine; Indigo carmine and quinoline yellow; Indigo carmine and Allura Red AC.

10. The oral dosage form according to claim 9, further containing an inorganic colourant other than TiO_2 , preferably yellow iron oxide.

11. The oral dosage form according to anyone of the preceding claims, characterized in that the modified released units of doxylamine or a pharmaceutically acceptable salt thereof and the modified released units of pyridoxine or a pharmaceutically acceptable salt thereof are contained within the capsule shell, preferably within a hard capsule shell constituted by a body and a cap.

12. The oral dosage form according to any of the preceding claims, characterized in that the modified release units of doxylamine or a pharmaceutically acceptable salt thereof are small particles, preferably pellets, and the modified release units of pyridoxine or a pharmaceutically acceptable salt thereof are small particles, preferably pellets and in that neither of them contain TiO_2 .

13. The oral dosage form according to anyone of the preceding claims, characterized in that each modified release unit of doxylamine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;
- an inner active coating layer comprising a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, one or more coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients;

- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and

- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, one or more anticaking agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients; and/or

each modified release unit of pyridoxine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;

- an inner active coating layer comprising a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, one or more coating agents, and optionally one or more pharmaceutically acceptable excipients;

- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and

- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients;

wherein the nucleus and any of the pharmaceutically acceptable excipient, preferably any of the coating agents, are free of TiO_2 .

14. The oral dosage form according to anyone of the preceding claims, characterized in that each modified release unit of doxylamine or a pharmaceutically acceptable

salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;
- an inner active coating layer comprising a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, one or more coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients;
- an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, one or more anticaking agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients; and/or

each modified release unit of pyridoxine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable inert nucleus;
- an inner active coating layer comprising a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, one or more coating agents, and optionally one or more pharmaceutically acceptable excipients; and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients;

wherein said nucleus and any of the pharmaceutically acceptable excipients, preferably any of the coating agents, are free of titanium dioxide.

15. The oral dosage form according to anyone of the preceding claims, characterized

in that each modified release unit of doxylamine or a pharmaceutically acceptable salt thereof comprises:

- a pharmaceutically acceptable active nucleus comprising a therapeutically effective amount of doxylamine or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipients;
- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, one or more anticaking agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients; and

each modified release unit of pyridoxine or a pharmaceutically acceptable salt thereof comprising:

- a pharmaceutically acceptable active nucleus comprising a therapeutically effective amount of pyridoxine or a pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable excipients; and
- optionally an intermediate enteric release coating layer comprising one or more enteric coating agents, one or more anticaking agents, optionally one or more pore-forming agent; and optionally one or more pharmaceutically acceptable excipients, and
- an external modified release coating layer comprising one or more enteric coating agents, one or more modified release coating agents, optionally one or more pore-forming agents, and optionally one or more pharmaceutically acceptable excipients,

wherein said nucleus and any of the pharmaceutically acceptable excipients, preferably any of the coating agents, are free of titanium dioxide.

16. The oral dosage form according to anyone of the preceding claims, comprising a pharmaceutically acceptable salt of doxylamine and a pharmaceutically acceptable salt of pyridoxine; preferably, it comprises doxylamine succinate and pyridoxine hydrochloride.

17. The oral dosage form according to anyone of the preceding claims, comprising from 5 mg to 50 mg per oral dosage form of doxylamine or a pharmaceutically acceptable salt thereof; and from 5 mg to 50 mg per oral dosage form of pyridoxine or a pharmaceutically acceptable salt thereof.

18. The oral dosage form according to anyone of the preceding claims characterized by not containing any opacifier.

19. A manufacturing process for the preparation of the oral dosage form according to anyone of the preceding claims, comprising:

a) preparing, separately, a first plurality of modified release modified release units of doxylamine or a pharmaceutically acceptable salt thereof and a second plurality of modified release units of pyridoxine or a pharmaceutically acceptable salt thereof,

b) optionally, mixing one or both pluralities of the modified release units prepared in step a) with additional excipients, or

c) alternatively, mixing the first and second plurality of modified release units prepared in step a) together and, optionally, mixing such mixture with additional excipients,

d) filling a capsule shell with:

- individually and separately, the first plurality of modified release units of doxylamine or a pharmaceutically acceptable salt thereof obtained in step a), optionally mixed

with additional excipients, and the second plurality of modified release units of pyridoxine or a pharmaceutically acceptable salt thereof obtained in step a), optionally mixed with additional excipients, or

- alternatively, the mixture of the first and the second plurality of modified release units of doxylamine or a pharmaceutically acceptable salt and pyridoxine or a pharmaceutically acceptable salt thereof obtained in step c), optionally further mixed with additional excipients; and

e) optionally, packaging the capsules obtained in step d) in blisters or bottles.

20. The oral dosage form according to anyone of claims 1 to 18 for use as a medicament.