Description

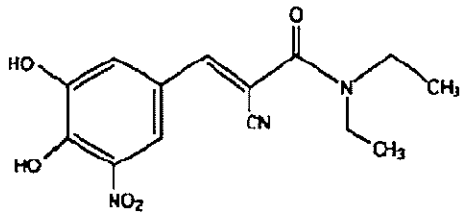
Title of Invention: AN EXTENDED RELEASE PHARMACEUTICAL COMPOSITION OF ENTACAPONE OR SALTS THEREOF

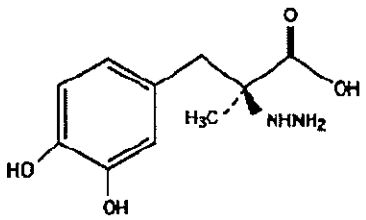
Field of the Invention

[1] There is provided an extended release pharmaceutical composition comprising from about 200mg to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients. The invention also provides an extended release pharmaceutical composition comprising triple combination of from about 30mg to about 300mg of levodopa, 10mg to about 100mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients. The invention also relates to process of preparation of such compositions.

Background of the Invention

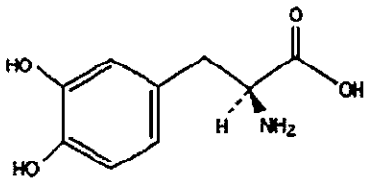
[2] Entacapone, an inhibitor of catechol-O-methyltransferase (COMT), used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy. The chemical name of entacapone is (E)-2-cyano-3-(3, 4-dihydroxy-5-nitrophenyl)-N, N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$, and its structural formula is:

[3] 

[4] 

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water. It is designated chemically as (-)-L-(α-hydrazino-(α-methyl-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_{10}H_{14}N_2O_4$ and its structural formula is:

[5] Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$, and its structural formula is:

[6] 

[7] US Patent No 6,599,530 provides oral compacted compositions of entacapone or salt thereof with pharmaceutically acceptable excipients.

[8] US Patent No 5,446,194 provides entacapone or pharmaceutically acceptable salts or esters thereof.

[9] US Patent Nos 6,500,867 and 6,797,732 provide oral solid tablet compositions comprising entacapone, levodopa and carbidopa, or pharmaceutically acceptable salts or hydrates thereof, and a pharmaceutically acceptable excipient.

[10] US Patent No 7,094,427 and US Publication No 20040166159providea composition comprising immediate release and controlled release component.

[11] US Publication No 20080051459providea method of treating Parkinson's disease comprising administering pharmaceutically effective amount of a composition comprising levodopa.

[12] US Publication No 20070275060providean extended release tablet comprising an extended release composition comprising levodopa; and an immediate or rapid release composition comprising carbidopa.

[13] US Publication No 20060173074 provides a method for treatment of restless legs syndrome in a mammal.

[14] PCT Publication No 07/073702providesa multi-layered tablet providing three different release profiles.

[15] Entacapone is available as immediate release composition under the trade name Comtan®. The marketed strength is 200mg.

[16] The triple combination of levodopa, carbidopa and entacapone is available as immediate release composition in different strengths. For example Stalevo® 50 (containing 12.5mg of carbidopa, 50mg of levodopa and 200mg of entacapone), Stalevo® 75 (containing 18.75mg of carbidopa, 75mg of levodopa and 200mg of entacapone), Stalevo®100 (containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone), Stalevo®125 (31.2575mg of carbidopa, 125mg of levodopa and 200mg of entacapone), Stalevo®150 (containing 37.5mg of carbidopa, 150mg of levodopa and 200mg of entacapone) and Stalevo®200 (containing 50 mg of carbidopa, 200 mg of levodopa and 200 mg of entacapone).

[17] Parkinson's disease is a slowly progressive disease, in which the symptoms get worse over time. Therefore, the symptoms will change and evolve. The pattern of symptoms can vary for each person. Over a number of years, however, some people may see

changes in the way their medication controls their symptoms. These changes are commonly known as motor fluctuations. Over time, symptoms begin to come back before it is time to take next dose of levodopa medication. This change in symptoms is called 'wearing-off.' As 'wearing-off' becomes more noticeable, the amount of time for a good response to levodopa (known as 'on' time) shortens and the time for poor response to levodopa (known as 'off' time) may lengthen.

[18] In the early stages of the disease, the brain is able to store enough dopamine. This permits smoother release of dopamine in the brain. It also provides a more constant control of symptoms. However, as Parkinson's disease gets worse, the brain has fewer cells that can take up levodopa and store it as dopamine for release when levels are low. Because of this reduced ability to store dopamine in the brain, symptoms may return after shorter periods of time (e.g. 'wearing-off'). If someone with a reduced ability to store dopamine is given too much levodopa, it may lead to side effects (e.g. dyskinesia).

[19] It may be possible to better control these symptoms by changing or adjusting the treatment. As these motor fluctuations emerge, other unwanted side effects may occur. These include involuntary movements, known as *dyskinesia* (e.g. twisting/turning movements) or *dystonia* (e.g. prolonged muscle cramping). The patients treated for Parkinson's disease may frequently develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia and akinesia, with levodopa therapy ('wearing off') in which the patient suffers from unpredictable swings from mobility to immobility. More than 50% of patients with Parkinson's disease develop motor response fluctuations (the 'wearing off' phenomenon) after treatment with levodopa therapy. Symptoms of wearing off include bradykinesia, dystonia, tremors, decreased manual dexterity, paresthesia, muscle pain, voice softness.

[20] It is believed that the 'wearing off' effect can be minimized in patients with a treatment regimen, which provides less rapid dissolution properties and providing a more even plasma level profile of levodopa.When administered in conjunction with levodopa, entacapone increases the bioavailability of levodopa by facilitating its passage across the blood-brain barrier.Hence, entacapone is approved as an adjunct to levodopa therapy in Parkinson's disease. However, the dosage of currently available formulation of Entacapone is eight times a day for 200 mg tablets. The frequent dosing of these formulations is associated with more fluctuating plasma entacapone concentrations. Further, this regimen is not patient compliant. Another problem with entacapone formulations is for the patients having swallowing problems. These patients cannot easily swallow the tablet.

[21] Further, it has been observed that it is very inconvenient for the patient to take a tablet of Sinemet CR and Comtan simultaneously number of times a day, which leads

to patient non-compliance especially in Parkinson's patient. Further, literature also suggests when the three ingredients are present together vis a vis entacapone, carbidopa and levodopa, it leads to decrease in bioavailability of entacapone and levodopa. Therefore, the marketed formulation Stalevo contains substantial portion of carbidopa separate from levodopa and carbidopa. Additionally, literature also reports destabilization of triple combination formulation in presence of microcrystalline cellulose.

[22] Hence, there is a need for patient compliant entacapone composition and/or triple combination comprising levodopa, carbidopa and entacapone that will dissolve slowly and provide a more even plasma level profile in patients with entacapone or levodopa/ entacapone/carbidopa treatment regimen.

Summary of the Invention

[23] In one of the aspects of the invention there is provided a pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients.

[24] In another general aspect of the invention there is provided a pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients, wherein one tablet of said composition exhibits no significant difference in rate and/or extent of absorption of entacapone as compared to 2-4 tablets of 200mg of immediate release entacapone commercially marketed as Comtan® administered at the interval of 3-4 hours.

[25] In another general aspect of the invention there is provided a method of treating Parkinson's disease in a mammal, comprising administering to a mammal in need thereof, an extended release pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts thereof in a mammal in need thereof, optionally with other pharmaceutically acceptable excipients.

[26] In another general aspect of the invention there is provided a method of treating Parkinson's disease in a mammal, comprising administering to a mammal in need thereof, an extended release pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts there of in a mammal in need thereof, optionally with other pharmaceutically acceptable excipients, wherein one tablet of the said composition exhibits no significant difference in rate and/or extent of absorption of entacapone as compared to 2-4 tablets of 200mg of immediate release entacapone commercially marketed as Comtan® administered at the interval of 3-4 hours.

[27] In another general aspect of the invention there is provided a method of reducing the 'wearing off' phenomena in Parkinson's patients, comprising administering to patient in need thereof, an extended release pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts there of in a mammal in need thereof, op-

tionally with other pharmaceutically acceptable excipients.

[28] In another general aspect of the invention there is provided a method of reducing the 'wearing off' phenomena in Parkinson's patients, comprising administering to patient in need thereof, an extended release pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts there of in a mammal in need thereof, optionally with other pharmaceutically acceptable excipients, , wherein one tablet of the said composition exhibits no significant difference in rate and/or extent of absorption of entacapone as compared to 2-4 tablets of 200mg of immediate release entacapone commercially marketed as Comtan® administered at the interval of 3-4 hours.

[29] In another general aspect of the invention there is provided a process for preparing a pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts thereof, wherein the said process comprises of coating or mixing entacapone with one or more pharmaceutically acceptable polymers, optionally with other pharmaceutical excipients and converting the mixture into suitable dosage form.

[30] In another general aspect of the invention there is provided an extended release pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts thereof, wherein the said composition exhibits a dissolution profile such that within 60 minutes at least 15% of entacapone is released, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C.

[31] In another general aspect of the invention there is provided an extended release pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts thereof, wherein the said composition exhibits a dissolution profile such that within 4 hrs at least 60% of entacapone is released, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C.

[32] In another general aspect of the invention there is provided a pharmaceutical composition comprising from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients.

[33] In another general aspect of the invention there is provided a method of treating Parkinson's disease in a mammal, comprising administering to a mammal in need thereof, an extended release pharmaceutical composition comprising from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients.

[34] In another general aspect of the invention there is provided a method of treating Parkinson's disease in a mammal, comprising administering to a mammal in need

thereof, an extended release pharmaceutical composition comprising from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients, wherein one tablet of the said composition exhibits no significant difference in rate and/or extent of absorption of entacapone, levodopa and carbidopa as compared to 2-4 tablets of immediate release entacapone, levodopa and carbidopa formulation commercially marketed as Stalevo®® administered at the interval of 3-4 hours.

[35] In another general aspect of the invention there is provided a method of reducing the 'wearing off' phenomena in Parkinson's patients, comprising administering to patient in need thereof, an extended release pharmaceutical composition comprising from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, optionally with other pharmaceutically acceptable excipients.

[36] In another general aspect of the invention there is provided an extended release pharmaceutical composition comprising from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, wherein said composition exhibits a dissolution profile such that within 60 minutes at least 15% of entacapone or at least 15% of levodopa or at least 15% of carbidopa is released, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C.

[37] In another general aspect of the invention there is provided an extended release pharmaceutical composition from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, wherein said composition exhibits a dissolution profile such that within 4hrs at least 60% of entacapone or at least 60% of levodopa or at least 60% of carbidopa is released, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C.

[38] In another general aspect of the invention there is provided a process for preparing an extended release pharmaceutical composition from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, wherein the said process comprises of coating or mixing one or more of levodopa, carbidopa and entacapone with one or more pharmaceutically acceptable polymers, optionally mixing with other pharmaceutically acceptable excipients and converting into suitable dosage form.

[39] Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutically acceptable excipients may include one or more of fillers, binders, lubricants, sweeteners, coloring and flavoring

agents, glidants, disintegrants, and the like.

[40] The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

[41] The inventors while working on the entacapone formulation have noticed that when entacapone is formulated in an extended release form, it allows for the continuous release of entacapone over a prolonged period. Extended release entacapone composition maintains controlled release of entacapone thereby leading to non-fluctuating constant plasma levels of entacapone. This further leads to reduction in the 'wearing - off' phenomena, which is observed in Parkinson's patients due to fluctuating plasma levels.

[42] The inventors have also noticed that when entacapone or levodopa or carbidopa is formulated in triple combination extended release form, it allows for the continuous release of entacapone or levodopa or carbidopa over a prolonged period. Extended release composition maintains controlled release of entacapone, levodopa and carbidopa thereby leading to non-fluctuating constant plasma levels of entacapone, levodopa and carbidopa. This further leads to reduction in the 'wearing -off' phenomena, which is observed in Parkinson's patients due to fluctuating plasma levels.

[43] The term 'extended release' as used herein refers to specific release of drug over a specified time period, which may extend from about 4hrs to about 24 hrs or more.

[44] Theextended release in the pharmaceutical composition may be achieved by one or more of coating or embedding in matrix using with hydrophilic or hydrophobic polymers or by attachment to ion-exchange resins. Further, extended release may be achieved by osmotic oral release technology also.

[45] One tablet of the composition of the invention is bioequivalent to2-4 tablets of 200mg of immediate release entacapone commercially marketed as Comtan®, when commercially available tablets are administered within at the interval of 3-4 hours.

[46] One tablet of the composition of the invention exhibits no significant difference in rate and/or extent of absorption of entacapone, levodopa and carbidopa as compared to 2-4 tablets of immediate release entacapone, levodopa and carbidopa formulation commercially marketed as Stalevo® administered at the interval of 3-4 hours.

[47] 'Bioequivalency' is established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both C_{max} and AUC under USFDA regulatory guidelines, or a 90% CI for AUC of between 0.80 to 1.25 and a 90% CI for C_{max} of between 0.70 to 1.43 under the European EMEA regulatory guidelines.

[48] The term 'confidence interval' as used herein refers to plain meaning known to ordinary skill in the art. Confidence interval refers to a statistical range with a specified

probability that a given parameter lies within the range.

[49] The term 'covariance' as used herein refers to plain meaning known to ordinary skill in the art. It is a statistical measure of the variance of two random variables that are observed or measured in the same mean time period. This measure is equal to the product of the deviations of corresponding values of the two variables from their respective means.

[50] The extended release pharmaceutical composition may include one or more of tablet, bilayered tablet, trilayered tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitablets, minitablets in capsule, pellets in capsule, sachet and the like.

[51] The amount of entacapone in thesepharmaceutical compositions varies from about 200 to about 1000 mg. The amount of levodopa in these pharmaceutical compositions varies from about 30 to about 300mg. The amount of carbidopa in these pharmaceutical compositions varies from about 10 to about 100mg.

[52] The extended release composition comprising triple combination of levodopa, carbidopa, entacapone, wherein at least one of levodopa, entacapone or carbidopa is in extended release form.

[53] Suitable hydrophilic or hydrophobic polymers comprise one or more of polyvinyl acetate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, a fatty acid, a fatty acid ester, an alkyl alcohol, a wax, shellac, rosin, zein (prolamine from corn), povidone, kollidon SR, a poly(meth)acrylate, microcrystalline cellulose or poly(ethylene oxide), polyuronic acid salts, cellulose ethers, xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum locust bean gum, alkali metal salts of alginic acid or pectic acid, sodium alginate, potassium alginate, ammonium alginate, hydroxypropyl cellulose, hydroxy ethyl cellulose, hydroxypropyl methyl cellulose, carboxyvinyl polymers, polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers like methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS) and the like. Polymer may be used from 0.1- 50% by weight of the composition.

[54] The extended release pharmaceutical composition may comprise one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include diluents, binders, disintegrants, lubricants, glidants and the like.

[55] Suitable binder may be one or more of, povidone, starch, stearic acid, gums, hydroxypropylmethyl cellulose and the like. Binder may be used from 0.1% to 40% by weight of the composition

[56] Suitable diluent may be one or more of, microcrystalline cellulose, mannitol, calcium phosphate, calcium sulfate, kaolin, dry starch, powdered sugar and the like. Diluent may be used from 1 to 50% by weight of the composition.

[57] Suitable disintegrant may be one or more of starch, croscarmellose sodium, crospovidone, sodium starch glycolate and the like. Disintegrant may be used from 2-20% by weight of the composition.

[58] Suitable lubricant may be one or more of magnesium stearate, zinc stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oil, glyceryl behenate and the like. Lubricant may be used from 0.1-5% by weight of the composition.

[59] Suitable glidant may be one or more of colloidal silicon dioxide, talc orcornstarch and the like. Glidant may be used from 0.1-5% by weight of the composition.

[60] Thepharmaceutical composition may be prepared by mixing entacapone with one or more pharmaceutically acceptable polymers, mixing with other pharmaceutically acceptable excipients and converting into suitable dosage form

[61] Thepharmaceutical composition may also be prepared by mixing entacapone, levodopa and carbidopa with one or more pharmaceutically acceptable polymers, mixing with other pharmaceutically acceptable excipients and converting into suitable dosage form.

[62] The invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

[63] Examples: The composition of batches is provided in Table 1 to 23. Following formulations are representatives of the preferred compositions of the invention. The preparation of example is detailed below.

[64] Example -I

[65] Table-1: Pharmaceutical composition of the invention

[Table 1]

[Table]

Ingredients	**%w/w**
Entacapone	60.1
Mannitol	18.0
Hydroxypropyl methyl cellulose	16.2
Povidone	0.9
Magnesium Stearate	0.9
Talc	0.2-3
Coating	
Opadry	3.8

[66] Procedure:

[67] Entacapone and mannitol were sifted and co-sifted through mesh to form a bulk.Hydroxypropyl methyl cellulosewas sifted and added to the above bulk to form a mixture. A part of magnesium stearate was sifted and mixed with the above mixture to form a bulk. The bulk was dry granulated using roller compactor to form the slugs. The slugs were size reduced to form granules. The granules were lubricated with remaining portion of magnesium stearate and talc to form a blend. The blend was compressed using suitable tooling to form tablets. The tablets were coated using Opadry.

[68] Table-2: Dissolution data of composition prepared as per example I.

[Table 2]

[Table]

Time (hrs)	**% drug released**
0.5	28
1	52
2	74
3	88
4	96

[69] Table 2 provides the dissolution data of composition prepared as per formula given in table 1. For determination of drug release rate, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium.

[70] Example -II

[71] Table-3: Pharmaceutical composition of the invention

[Table 3]

[Table]

Ingredients	**%w/w**
Entacapone	57.1
Lactose	19.3
Hydroxy ethyl cellulose	12.4
Hydroxypropyl methyl cellulose	8.6
Water	q.s.
Magnesium Stearate	1.4
Talc	1.1

[72] Procedure:Entacapone, lactose, hydroxy ethyl cellulose and hydroxypropyl methyl-cellulose were co-sifted and mixed to form a bulk. The bulk was wet granulated using water to form the granules and the granules were dried. The dried granules were size reduced. Magnesium stearate and talc were sifted and added to the size reduced granules and were compressedusing suitable tooling to form tablets.

[73] Table-4: Dissolution data of composition prepared as per example II.

[Table 4]

[Table]

Time (hrs)	**% drug released**
0.5	33
1	58
2	78
3	88
4	97

[74] Table 4 provides the dissolution data of composition prepared as per formula given in table 3. For determination of drug release rate, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium.

[75] Example -III

[76] Table-5: Pharmaceutical composition of the invention

[Table 5]

[Table]

Ingredients	%w/w
Entacapone	74.1
Microcrystalline cellulose	10.7
Kollidon SR	13.3
Magnesium Stearate	1.1
Talc	0.7

[77] Procedure: Entacapone, microcrystalline cellulose and kollidon SR were co-sifted and mixed to form a bulk. Magnesium stearate and talc were sifted to form a bulk separately. The two different bulks were mixed and compressedusing suitable tooling to form tablets.

[78] Table-6: Dissolution data of composition prepared as per example III.

[Table 6]

[Table]

Time (hrs)	% drug released
0.5	22
1	43
2	68
3	82
4	90

[79] Table 6 provides the dissolution data of composition prepared as per formula given in table 5. For determination of drug release rate, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium.

[80] Example -IV

[81] Table-7: Pharmaceutical composition of the invention

[Table 7]

[Table]

Ingredients	**%w/w**
IR Layer	
Entacapone	15.6
Mannitol	12.2
Crospovidone	3.8
Povidone	2.2
Magnesium stearate	0.6
ER Layer	
Entacapone	46.9
Mannitol	7.0
Hydroxypropyl methyl cellulose	10.2
Magnesium Stearate	0.8
Talc	0.8

[82] Procedure: IR layer granules

[83] Entacapone and mannitol were co-sifted to form a bulk. Crospovidone, povidone and a part of magnesium stearate were sifted and added to bulk and mixed to form a bulk. The bulk was dry granulated using roller compactor to form the slugs and the slugs were size reduced. The remaining portion of magnesium stearate to be added to size reduced granules and mixed.

[84] ER layer granules

[85] Entacapone and mannitol were co-sifted to form a bulk. Hydroxypropyl methyl-cellulose and a part of magnesium stearate were sifted and added to bulk and mixed to form a bulk. The above bulk was dry granulated using roller compactor to form the slugs and the slugs were size reduced. The remaining portion of magnesium stearate and talc were added to size reduced granules and mixed.

[86] Compression

[87] The IR layer and ER layer granules were compressed to form a bilayer tablet.

[88] Table-8: Dissolution data of composition prepared as per example IV.

[Table 8]

[Table]

Time (hrs)	% drug released
0.5	23
1	44
2	71
3	84
4	92

[89] Table 8 provides the dissolution data of composition prepared as per formula given in table 7. For determination of drug release rate, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium.

[90] Example -V

[91] Table-9: Pharmaceutical composition of the invention

[Table 9]

[Table]

Ingredients	%w/w
IR Layer	
Entacapone	17.1
Mannitol	9.1
Sodium starch Glycolate	4.3
Povidone	2.1
Water	q.s.
Magnesium stearate	0.5
ER Layer	
Entacapone	51.3
Mannitol	8.0
Povidone	6.0
Water	q.s.
Magnesium Stearate	0.9
Talc	0.9

[92] Procedure:IR layer granules

[93] Entacapone, sodium starch glycolate and mannitol were co-sifted to form a bulk. Povidone was dissolved in water and the bulk was wet granulated with povidone solution to form granules and the granules were dried. The granules were size reduced. The size reduced granules were lubricated with magnesium stearate.

[94] ER layer granules

[95] Entacapone and mannitol were co-sifted to form a bulk. Povidone was dissolved in water and the bulk was wet granulated with povidone solution to form granules and the granules were dried. The granules were size reduced. The size reduced granules were lubricated with magnesium stearate and talc.

[96] Compression

[97] The IR layer and ER layer granules were compressed to form a bilayer tablet.

[98] Table-10: Dissolution data of composition prepared as per example V.

[Table 10]

[Table]

Time (hrs)	**% drug released**
0.5	36
1	59
2	78
3	89
4	96

[99] Table 10 provides the dissolution data of composition prepared as per formula given in table 9. For determination of drug release rate, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium.

[100] **Example VI -**

[101] Table 11 -Pharmaceutical composition of the invention

[Table 11]

[Table]

Ingredient	**%w/w**
IR Layer	
Entacapone	4.98
Mannitol 25	1.25
Crospovidone	0.60
Povidone K30	0.45
MannitolSD 200	1.67
Magnesium stearate	0.07
Talc	0.12
Magnesium stearate	0.07
ER Layer	
Entacapone	44.83
Mannitol 25	11.21
Plasdone S630	4.48
HPMC K 100LVP	13.23
Mannitol 25	3.81
Magnesium stearate	0.45
MannitolSD 200	10.09
Magnesium stearate	1.57
Talc	0.34
Magnesium stearate	0.78

[102] Procedure: IR Layer Granules:

[103] Entacapone and Mannitol were co-sifted to form a bulk. Crospovidone, Povidone K30, & Mannitol SD 200 were also co-sifted and mixed with above bulk. This bulk was lubricated by using magnesium stearate. Dry granulated this bulk and granules were prepared. Magnesium stearate & Talc were added to these prepared granules.

[104] ER Layer Granules:

[105] Entacapone and Mannitol were co-sifted to form a bulk. Plasdone S630, HPMC K100LVP and Mannitol were co-sifted and mixed with above bulk. This bulk was lubricated by using magnesium stearate. Dry granulated this bulk and granules were

prepared. Magnesium stearate & Talc were added to these prepared granules.

[106] Compression

[107] The IR layer and ER layer granules were compressed to form a bilayer tablet.

[108] Table 12 - Dissolution data of composition prepared as per Example VI.

[Table 12]

[Table]

Time (hrs)	% drug released
0	0
0.5	27
1	34
2	45
3	57
4	72
5	91
6	93

[109] Table 12 provides the dissolution data of composition prepared as per formula given in table 11. For determination of drug release rate, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium.

[110] Table 13 - Bio Data (fed study)

[Table 13]

[Table]

PK Parameters	Ratio % (T/R)	90% C.I.	P-Value	Power (%)	MSE	Intra-CV (%)	
Lower Limit	Upper Limit						
Cmax	91.35	87.83	95.08	0.0010	97.99%	0.01851	13.58
AUCt	97.15	88.63	106.48	0.0011	98.74%	0.01852305	13.67
AUCinf	97.21	88.69	106.55	0.0011	98.74%	0.01852	13.67

[111] Table 13 provides bio profile of entacapone ER tablets prepared as per example VI under fed condition versusReference product Comtan® 200 mg. Study design include

randomized, single dose, open-label, three-treatment, three-period, three-sequence, crossover comparative bioavailability study in 15 normal, adult, human subjects under fed condition.

[112] **Example VII -**

[113] Table 14 - Pharmaceutical composition of the invention

[Table 14]

[Table]

Ingredient	**%w/w**
IR Layer	
Entacapone	10.05
Mannitol 25	2.51
Crospovidone	1.21
Povidone K30	0.90
MannitolSD 200	3.37
Magnesium stearate	0.15
Talc	0.25
Magnesium stearate	0.15
ER Layer	
Entacapone	40.20
Mannitol 25	10.05
Plasdone S630	4.02
HPMC K 100LVP	11.86
Mannitol 25	3.42
Magnesium stearate	0.40
MannitolSD 200	9.05
Magnesium stearate	0.30
Talc	0.70
Magnesium stearate	1.41

[114] Procedure: IR Layer Granules:

[115] Entacapone and Mannitol were co-sifted to form a bulk. Crospovidone, Povidone K30, & Mannitol SD 200 were also co-sifted and mixed with above bulk. This bulk was lubricated by using magnesium stearate. Dry granulated this bulk and granules

were prepared. Magnesium stearate & Talc were added to these prepared granules.

[116] ER Layer Granules:

[117] Entacapone and Mannitol were co-sifted to form a bulk. Plasdone S630, HPMC K100LVP and Mannitol were co-sifted and mixed with above bulk. This bulk was lubricated by using magnesium stearate. Dry granulated this bulk and granules were prepared. Magnesium stearate & Talc were added to these prepared granules.

[118] Compression

[119] The IR layer and ER layer granules were compressed to form a bilayer tablet.

[120] Table 15 - Dissolution data of composition prepared as per Example VII.

[Table 15]

[Table]

Time (hrs)	**% drug released**
0	0
0.5	31
1	42
2	55
3	63
4	74
5	86
6	95

[121] Table 15 provides the dissolution data of composition prepared as per formula given in table 14. For determination of drug release rate, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium.

[122] Example - VIII

[123] Table-16: Pharmaceutical composition of the invention

[Table 16]

[Table]

Ingredients	**%w/w**
Entacapone	34.8
Levodopa	34.8
Carbidopa	9.4
Starch	2.7
Lactose	6.3
Hydroxypropyl methyl cellulose	10.0
Magnesium stearate	1.0
Talc	1.0

[124] Procedure:Entacapone, carbidopa, levodopa, starch and lactose were co-sifted to form bulk. Hydroxypropyl methylcellulose was sifted and mixed with bulk. A part of magnesium stearate was sifted and mixed with bulk. The bulk was dry granulated using roller compactor to form the slugs and the slugs were size reduced. The remaining portion of magnesium stearate and talc were sifted and added to the size reduced granules to form a bulk.The bulk was compressed using suitable punches to form tablets.

[125] Table-17: Dissolution data of composition prepared as per example I.

[Table 17]

[Table]

Time (hrs)	**% Dissolved**		
	Entacapone	**Levodopa**	**Carbidopa**
0.5	26	33	35
1	48	59	62
2	74	79	79
3	86	92	94
4	93	102	101

[126] Table 17 provides the dissolution data of composition prepared as per formula given in table 16. For determination of drug release rate of entacapone, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium. Further, for determination of drug release rate of levodopa and carbidopa, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of 0.1 N

HCl at 37 °C ± 0.5°C was used as medium.

[127] Example -IX

[128] Table-18: Pharmaceutical composition of the invention

[Table 18]

[Table]

Ingredients	**%w/w**
Entacapone	35.7
Levodopa	35.7
Carbidopa	9.6
Mannitol	5.3
Microcrystalline cellulose	2.5
Poly vinyl pyrrolidone	8.5
Water	q.s.
Magnesium stearate	1.4
Talc	1.3

[129] Procedure:Entacapone, carbidopa, levodopa, starch and lactose were co-sifted and mixed to form bulk. Poly vinyl pyrrolidone was dissolved in water to form binder solution. The bulk was granulated using binder solution to from the granules and the granules were dried. The granules were size reduced. Magnesium stearate and talc were sifted and mixed with the size-reduced granules.The bulk was compressed using suitable punches to form tablets.

[130] Table-19: Dissolution data of composition prepared as per example II.

[Table 19]

[Table]

Time (hrs)	**% Dissolved**		
	Entacapone	**Levodopa**	**Carbidopa**
0.5	36	42	41
1	60	62	62
2	78	80	82
3	90	92	92
4	94	99	100

[131] Table 19 provides the dissolution data of composition prepared as per formula given in table 18. For determination of drug release rate of entacapone, USP Type 2

Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium. Further, for determination of drug release rate of levodopa and carbidopa, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of 0.1 N HCl at 37 °C ± 0.5°C was used as medium.

[132] Example -X

[133] Table-20: Pharmaceutical composition of the invention

[Table 20]

[Table]

Ingredients	**%w/w**
Entacapone ER Layer	
Entacapone	32.4
Lactose	7.7
Hydroxypropyl methyl cellulose K100LVP	5.7
Hydroxypropyl methyl cellulose E-50	4.4
Magnesium Stearate	0.6
Talc	0.6
Carbidopa- Levodopa ER Layer	
Levodopa	32.4
Carbidopa	8.7
Microcrystalline Cellulose	2.9
Hydroxypropyl methyl cellulose	3.6
Magnesium stearate	0.7
Talc	0.2

[134] Procedure: Entacapone ER layer granules

[135] Entacapone, lactose and hydroxypropyl methyl cellulose were co-sifted to form a bulk. Magnesium stearate and talc were sifted and mixed with bulk. The bulk was dry granulated using roller compactor to form the slugs and the slugs were size reduced.

[136] Levodopa-Carbidopa ER layer granules

[137] Levodopa, carbidopa, microcrystalline cellulose, hydroxypropyl methyl cellulose were co sifted to form a bulk. Magnesium stearate and talc were sifted and mixed with the bulk. The bulk was dry granulated using roller compactor to form the slugs and the slugs were size reduced.

[138] Compression

[139] The entacapone ER layer granules and levodopa-carbidopa ER layer granules were compressed to form a bilayer tablet.

[140] Table-21: Dissolution data of composition prepared as per example III.

[Table 21]

[Table]

Time (hrs)	**% Dissolved**		
	Entacapone	**Levodopa**	**Carbidopa**
0.5	25	33	34
1	44	52	54
2	72	83	83
3	85	96	95
4	93	100	102

[141] Table 21 provides the dissolution data of composition prepared as per formula given in table 20. For determination of drug release rate of entacapone, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium. Further, for determination of drug release rate of levodopa and carbidopa, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of 0.1 N HCl at 37 °C ± 0.5°C was used as medium.

[142] Example -XI

[143] Table-22: Pharmaceutical composition of the invention

[Table 22]

[Table]

Ingredients	**%w/w**
Entacapone ER Layer	
Entacapone	33.3
Microcrystalline cellulose	4.0
Lactose	4.3
Povidone	3.0
Hydroxypropyl cellulose	3.8
Water	q.s.
Magnesium Stearate	1.0
Talc	0.7
Carbidopa- Levodopa ER Layer	
Levodopa	33.3
Carbidopa	9.0
Lactose	3.0
Povidone	2.9
Water	q.s.
Magnesium stearate	1.0
Talc	0.6

[144] Procedure: Entacapone ER layer granules

[145] Entacapone, microcrystalline cellulose and lactose were co sifted.Povidone was dissolved in water and the bulk was wet granulated with povidone solution to form granules and the granules were dried. The granules were size reduced. Hydroxypropyl cellulose was sifted and added to the size reduced granules. The bulk was lubricated with magnesium stearate and talc.

[146] Levodopa-Carbidopa ER layer granules

[147] Levodopa, carbidopa and lactose were co sifted to form a bulk. Povidone was dissolved in water and the bulk was wet granulated with povidone solution to form granules and the granules were dried. The granules were size reduced. The bulk was lubricated with magnesium stearate and talc.

[148] Compression

[149] The entacapone ER layer granules and levodopa-carbidopa ER layer granules were

compressed to form a bilayer tablet.

[150] Table-23: Dissolution data of composition prepared as per example IV.

[Table 23]

[Table]

Time (hrs)	% Dissolved		
	Entacapone	**Levodopa**	**Carbidopa**
0.5	35	32	30
1	51	52	52
2	77	80	81
3	93	89	92
4	96	97	99

[151] Table 23 provides the dissolution data of composition prepared as per formula given in table 22. For determination of drug release rate of entacapone, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of pH 5.5 phosphate buffer at 37 °C ± 0.5°C was used as medium. Further, for determination of drug release rate of levodopa and carbidopa, USP Type 2 Apparatus (rpm 75) was used wherein 1000 ml of 0.1 N HCl at 37 °C ± 0.5°C was used as medium.

Claims

1. An extended release pharmaceutical composition comprising from about 200 to about 1000mg of entacapone or salts thereof, one or more rate controlling polymers, optionally with other pharmaceutically acceptable excipients.

2. The pharmaceutical composition of claim 1, wherein the composition comprises one or more of tablet, bilayered tablet, trilayered tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitablets, minitablets in capsule, pellets in capsule, sachet.

3. The pharmaceutical composition of claim 1, wherein one tablet of said composition exhibits no significant difference in rate and/or extent of absorption of entacapone as compared to 2 tablets of 200mg immediate release entacapone administered at the interval of 3-4hours.

4. Use of pharmaceutical composition of claim 1, for treating Parkinson's disease in a mammal, comprising administering the said composition to a mammal in need thereof.

5. Use of pharmaceutical composition of claim 4, wherein one tablet of the said composition exhibits no significant difference in rate and/or extent of absorption of entacapone as compared to 2-4 tablets of 200mg of immediate release administered at the interval of 3-4 hours.

6. Use of pharmaceutical composition of claim 1, for reducing the 'wearing off phenomena in Parkinson's patients, comprising administering the said composition to patient in need thereof.

7. Use of pharmaceutical composition of claim 6, wherein one tablet of the said composition exhibits no significant difference in rate and/or extent of absorption of entacapone as compared to 2-4 tablets of 200mg of immediate release entacapone administered at the interval of 3-4 hours.

8. The pharmaceutical composition of claim 1, wherein the said composition exhibits a dissolution profile such that within 60 minutes at least 15% of entacapone is released, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 ^{0}C + 0.5^{0}C.

9. The pharmaceutical composition of claim 1, wherein the said composition exhibits a dissolution profile such that within 4 hrs at least 60% of entacapone is released, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 ^{0}C + 0.5^{0}C.

10. The pharmaceutical composition of claim 1, further comprising from about 30 mg to about 300mg of levodopa and 10 mg to about 100 mg of carbidopa or salts thereof.

11. Use of pharmaceutical composition claim 10, for treating Parkinson's disease in a mammal, comprising administering the said composition to a mammal in need thereof.

12. Use of pharmaceutical composition of claim 11, wherein one tablet of the said composition exhibits no significant difference in rate and/or extent of absorption of entacapone, levodopa and carbidopa as compared to 2-4 tablets of immediate release entacapone, levodopa and carbidopa formulation administered at the interval of 3-4 hours.

13. Use of pharmaceutical composition of claim 10, for reducing the 'wearing off phenomena in Parkinson's patients, comprising administering the said composition to a patient in need thereof.

14. The pharmaceutical composition of claim 10, wherein said composition exhibits a dissolution profile such that within 60 minutes at least 15% of entacapone or at least 15% of levodopa or at least 15% of carbidopa is released, wherein the release rate is measured

in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 ^{0}C + 0.5^{0}C.

15. The pharmaceutical composition of claim 10, wherein said composition exhibits a dissolution profile such that within 4hrs at least 60% of entacapone or at least 60% of levodopa or at least 60% of carbidopa is released, wherein the release rate is measured in Apparatus 2 (USP, Dissolution, paddle, 75 rpm) using 1000 ml of pH 5.5 phosphate buffer at 37 ^{0}C + 0.5^{0}C.

16. A process for preparing an extended release pharmaceutical composition from about 30 mg to about 300mg of levodopa, 10 mg to about 100 mg of carbidopa and 200mg to about 1000mg of entacapone or salts thereof, wherein the said process comprises of coating or mixing one or more of levodopa, carbidopa and entacapone with one or more pharmaceutically acceptable polymers, optionally mixing with other pharmaceutically acceptable excipients and converting into suitable dosage form.