## Field of the invention

The technical field of the present invention relates to novel pharmaceutical compositions and technology for manufacture of stable solid oral dosage forms of levodopa, carbidopa and entacapone fixed dose combinations with enhanced dissolution rate of entacapone characterized by the presence of microcrystalline cellulose and not more than 4% w/w of the total weight of the formulation of croscarmellose sodium.

## Background of the invention

Levodopa [(-)-L-α-amino-β-(3, 4-dihydroxybenzene) propanoic acid], Carbidopa [(-)-L-(α-hydrazino-(α-methyl-β-(3,4-dihydroxybenzene) propanoic acid Monohydrate] and Entacapone [(E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide] are currently being marketed as fixed dose combinations under the brand name Stalevo® for the treatment of Parkinson's disease presumably caused due to lack of dopamine in the brain. It is a synergistic combination where levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier, and presumably is converted to dopamine in the brain. Entacapone and Carbidopa decrease the metabolism of Levodopa thereby increasing its plasma levels by inhibiting the enzymes catechol-O-methyltransferase (COMT) and DOPA decarboxylase respectively.

Patents US6500867, US6797732, EP1189608B1 disclose tablet composition comprising carbidopa separated from entacapone and levodopa and composition consisting of entacapone, levodopa, and carbidopa and an excipient other than microcrystalline cellulose.

US6599530 discloses and claims a composition of entacapone containing croscarmellose sodium in an amount of atleast 6% by weight of the composition. The patent discloses that croscarmellose sodium in an amount of atleast 6% by weight of the composition is essentially required for satisfactory dissolution of entacapone.

WO 2007/069274 A2 and EP 1954256 A2 disclose dosage form comprising entacapone and alkalizing agent which is essentially free of croscarmellose sodium as a disintegrant.

EP2114374A2 and WO2008/081268A2 disclose compositions comprising entacapone having 90% of particles below 40μ and/or a wetting agent and/or cyclodextrins.

EP2104424A2 and WO2008/053297A2 disclose composition comprising entacapone separated from carbidopa & levodopa mixture and a composition comprising carbidopa separated from entacapone & levodopa mixture.

EP 2252284B1 and WO2009/098661A1 disclose composition comprising combination of entacapone, levodopa and carbidopa wherein, entacapone is comicronised with sugar alcohol.

The important challenges before the formulation scientist while formulating this fixed dose combination are:

1) Extremely low aqueous solubility of entacapone especially under acidic conditions (below pH 5.5), low dissolution rate and therefore low bioavailability and
2) Poor stability of carbidopa especially it's incompatibility with celluloses and entacapone.

The present invention addresses and overcomes these problems.

## Summary of the Invention

Accordingly the present invention discloses the pharmaceutical compositions of the fixed dose combinations of levodopa, carbidopa and entacapone which contain microcrystalline cellulose and not more than 4% w/w of the total weight of formulation of croscarmellose sodium and a method of preparation of such compositions.

The invention provides a method of preparation that involves dissolving and/or solubilizing entacapone in a pharmaceutically acceptable solvent or a mixture of pharmaceutically acceptable solvents.

The method further involves adsorbing the aforementioned entacapone solution on pharmaceutically acceptable excipients or an adsorbant premix which is a mixture of pharmaceutically acceptable excipients by spraying the entacapone solution under atomizing air pressure on to the pharmaceutically acceptable excipients or an adsorbant premix prepared therefrom while mixing or continued fluidization in a mixer or a fluid bed processor while drying off the solvents till a slightly wet mass is obtained while mixing or continued fluidization after spraying of the solution is completed followed by serially adding and mixing an adsorbant, a lubricant, levodopa and carbidopa to the above wet mass containing entacapone, while drying off the solvents, mixing while drying till the required drying end-point as ascertained from the loss on drying of the granules is attained followed by sifting the dried granules through a sieve of required aperture size, adding disintegrant and lubricating the resultant blend with a lubricant.

The lubricated blend can be optionally compressed into tablets and film coated or filled into capsules.

## Detailed description of the invention:

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.

The invention provides a method of preparation that involves dissolving and/or solubilizing entacapone in a pharmaceutically acceptable solvent or a mixture of pharmaceutically acceptable solvents.

More specifically the solvents used are methylene chloride and methanol in the volume ratio of 9 : 5.

In a preferable embodiment, entacapone is first dispersed uniformly in methylene chloride followed by the addition of methanol to this dispersion to dissolve entacapone.

The method further involves adsorbing the aforementioned entacapone solution on to an adsorbant premix which is a mixture of pharmaceutically acceptable excipients containing one or more diluents one of which is essentially microcrystalline cellulose and optionally containing other excipients like adsorbants selected from but not limited to calcium carbonate, calcium phosphate, calcium sulfate, magnesium oxide, magnesium carbonate, sodium chloride, colloidal silicon dioxide, Clays, silicates, starches, glidants, disintegrants, alkalizing agents and lubricants.

Eventhough it is preferable to prepare an adsorbant premix of the aforementioned pharmaceutically acceptable excipients for adsorption of the entacapone solution, it is not a necessity. Alternatively, the entacapone solution can also be adsorbed onto any of the aforementioned pharmaceutically acceptable excipients, either individually or mixed in any combination thereof followed by mixing or blending them together to ensure the blend and content uniformity of entacapone.

The invention further discloses the method of adsorption of entacapone solution on the adsorbant premix by spraying the entacapone solution under atomizing air pressure on to the adsorbant premix while mixing or fluidization in a mixer or a fluid bed processor while maintaining the internal or inlet temperature maintained at 60°C± 5°C and the bed temperature maintained at 50°C± 5°C and drying off the solvents till a slightly wet mass is obtained while mixing or fluidization after spraying of the solution is completed.

The atomizing air pressure may range from 0.1 $kg/cm^2$ – 5.0 $kg/cm^2$

The invention further discloses the method of adsorption of entacapone solution on the adsorbant premix by mixing the entacapone solution with the adsorbant premix in a planetary mixer or a rapid mixer granulator or any other mixer (fitted with a steam jacket) to form a wet mass or slurry and drying off the solvents till a slightly wet mass is obtained while mixing with internal or inlet temperature maintained at 60°C± 5°C.

Alternatively, entacapone and pharmaceutically acceptable excipients can be mixed together with methylene chloride and methanol and the solvents can be dried off till a slightly wet mass is obtained.

The method further involves serially adding and mixing an adsorbant in an amount not more than 10% w/w of the total weight of formulation, a lubricant in an amount not more than 10% w/w of the total weight of formulation, levodopa and carbidopa to the above wet mass containing entacapone, while maintaining the internal or inlet temperature at 40°C± 5°C., mixing till the required drying end-point as ascertained from the loss on drying of the granules is attained followed by sifting the dried granules through a sieve of required aperture size, adding croscarmellose sodium not more than 4% w/w of the total weight of formulation and lubricating the granule blend with a lubricant. The lubricated blend can be optionally compressed into tablets and film coated or filled into capsules.

The diluents may be selected from but not limited to sugars like lactose, maltodextrin, celluloses, inorganic salts like sodium chloride, starches, modified starches and starch derivatives. The disintegrants essentially include croscarmellose sodium not more than 4% w/w of the total weight of formulation and additionally may contain any selected from but not limited to sodium starch glycolate, crospovidone, starches and starch derivatives, carboxymethyl cellulose calcium, hydroxypropyl cellulose etc.,

The glidants may be purified talc and/or colloidal silicon dioxide but not limited to the aforementioned. The lubricants may be magnesium stearate, purified talc, stearic acid, hydrogenated castor oil, hydrogenated vegetable oil, calcium silicate,

sodium stearyl fumarate and the like and any combination thereof but not limited to the aforementioned.

The invention can be used to manufacture all fixed dose combinations of Entacapone, Levodopa and Carbidopa including but not limited to the following:

1) Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg
2) Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg
3) Levodopa 100mg / Carbidopa 25mg / Entacapone 200mg
4) Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg
5) Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg
6) Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg

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.

**Example 1:** Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg Tablets

| S.No | Ingredients | mg/tab |
|---|---|---|
| | **Entacapone Solution** | |
| 1 | Entacapone | 200 |
| 2 | Methylene Chloride | q.s (9 parts by volume) |
| 3 | Methanol | q.s (5 parts by volume) |
| | **Adsorbant Premix** | |
| 4 | Trisodium phosphate anhydrous | 160 |
| 5 | Microcrystalline Cellulose | 12 |
| 6 | Sodium starch glycolate | 5 |
| 7 | Lactose monohydrate | 68 |
| 8 | Colloidal Silicon Dioxide | 10 |
| | **Other Intragranular Ingredients** | |
| 9 | Purified Talc | 20 |
| 10 | Stearic Acid | 20 |
| 11 | Levodopa | 200 |
| 12 | Carbidopa monohydrate | 54 |
| | **Extragranular** | |
| 13 | Croscarmellose Sodium | 15 |
| 14 | Magnesium Stearate | 16 |
| | **Core Tablet** | **780** |
| 15 | Film Coating material | 40 |
| | **Coated Tablet** | **820** |

The processing steps involved in manufacturing the composition given in example 1 are given below:

i) The components of the adsorbant premix (In this example – Trisodium phosphate anhydrous, lactose monohydrate, microcrystalline cellulose,

sodium starch glycolate and colloidal silicon dioxide) were sifted together and mixed in a rapid mixer granulator to obtain an adsorbant premix,

ii) Solution of Entacapone was prepared by first uniformly dispersing entacapone in methylene chloride followed by the addition of methanol to this dispersion,

iii) The entacapone solution was sprayed on to the adsorbant premix of step (i) with continuous mixing in the RMG using a spray gun assembly at an atomizing air pressure of 2.5 $kg/cm^2$ while maintaining the temperature inside the mixer at 60°C ± 5°C.

iv) After completion of spraying of solution, the mixing of material inside the RMG was continued while maintaining the temperature inside the mixer at 60°C ± 5°C till a slightly wet mass is obtained.

v) To the wet mass of step (iv) in the RMG, serially added and mixed pre-sifted purified talc, stearic acid, levodopa and carbidopa monohydrate while maintaining the temperature inside the mixer at 40°C ± 5°C till the required drying end-point as ascertained from the loss on drying of the granules, not more than 1.0% w/w at 105°C (auto mode; Sartorius moisture analyzer) is attained.

vi) The dried granules of step (v) were sifted through #18 mesh ASTM sieve,

vii) The sized granules of step (vi) were blended with pre-sifted quantity of croscarmellose sodium in a double cone blender,

viii) The blend of step (vii) was lubricated with pre-sifted quantity of magnesium stearate in a double cone blender,

ix) The blend of step (viii) was compressed into tablets using capsule shaped 17.0mm x 8.0mm punch tooling.

x) The tablets of step (ix) were coated with an aqueous dispersion of a film coating material premix.

**Example 2:** Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg Tablets

| S.No | Ingredients | mg/tab |
|---|---|---|
| | **Entacapone Solution** | |
| 1 | Entacapone | 200 |
| 2 | Methylene Chloride | q.s (9 parts by volume) |
| 3 | Methanol | q.s (5 parts by volume) |
| | **Adsorbant Premix** | |
| 4 | Calcium Carbonate | 68 |
| 5 | Microcrystalline Cellulose | 8 |
| 6 | Sodium starch glycolate | 5 |
| 7 | Calcium Sulfate | 55 |
| 8 | Magnesium Carbonate | 31 |
| 9 | Dibasic calcium phosphate | 106 |
| 10 | Magnesium Oxide | 7 |
| 11 | Colloidal Silicon Dioxide | 10 |
| | **Other Intragranular Ingredients** | |
| 12 | Purified Talc | 20 |
| 13 | Stearic Acid | 20 |
| 14 | Levodopa | 200 |
| 15 | Carbidopa monohydrate | 54 |
| | **Extragranular** | |
| 16 | Croscarmellose Sodium | 10 |
| 17 | Magnesium Stearate | 16 |
| | **Core Tablet** | **810** |
| 18 | Film Coating material | 40 |
| | **Coated Tablet** | **850** |

The processing steps involved in manufacturing the composition given in example 2 is similar to that provided in example 1 with changes in the excipients constituting the adsorbant premix and is apparent to those skilled in the art.

**Example 3:** Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg Tablets

| S.No | Ingredients | mg/tab |
|---|---|---|
| | **Entacapone Solution** | |
| 1 | Entacapone | 200 |
| 2 | Methylene Chloride | q.s (9 parts by volume) |
| 3 | Methanol | q.s (5 parts by volume) |
| | **Adsorbant Premix** | |
| 4 | Sodium Chloride | 200 |
| 5 | Microcrystalline Cellulose | 10 |
| 6 | Lactose monohydrate | 50 |
| 7 | Sodium Starch glycolate | 10 |
| 8 | Colloidal Silicon Dioxide | 10 |
| | **Other Intragranular Ingredients** | |
| 9 | Purified Talc | 10 |
| 10 | Stearic Acid | 10 |
| 11 | Levodopa | 200 |
| 12 | Carbidopa monohydrate | 54 |
| | **Extragranular** | |
| 13 | Croscarmellose Sodium | 10 |
| 14 | Magnesium Stearate | 16 |
| | **Core Tablet** | **780** |
| 15 | Film Coating material | 20 |
| | **Coated Tablet** | **800** |

The processing steps involved in manufacturing the composition given in example 3 is similar to that provided in example 1 with changes in the excipients constituting the adsorbant premix and is apparent to those skilled in the art.

## Table 1: Dissolution Profile Comparison

| Entacapone | | | | |
|---|---|---|---|---|
| **Time (min.)** | **Reference (Stalevo 200)** | **Example 1** | **Example 2** | **Example 3** |
| | **900mL pH 5.5 Phosphate buffer; Basket (USP-I); 125 RPM** | | | |
| **10** | 16 | 26 | 23 | 24 |
| **20** | 69 | 70 | 71 | 74 |
| **30** | 92 | 95 | 94 | 95 |
| **45** | 96 | 98 | 99 | 101 |
| **60** | 100 | 101 | 100 | 102 |
| **Assay** | 101.2 | 102.0 | 101.3 | 101.9 |
| **Levodopa** | | | | |
| **Time (min.)** | **Reference (Stalevo 200)** | **Example 1** | **Example 2** | **Example 3** |
| | **750mL 0.1M HCl; Basket (USP-I); 50 RPM** | | | |
| **10** | 13 | 15 | 18 | 20 |
| **20** | 45 | 50 | 48 | 50 |
| **30** | 69 | 63 | 66 | 68 |
| **45** | 100 | 98 | 100 | 93 |
| **60** | 102 | 100 | 100 | 99 |
| **Assay** | 103.0 | 101.6 | 101.0 | 99.3 |
| **Carbidopa** | | | | |
| **Time (min.)** | **Reference (Stalevo 200)** | **Example 1** | **Example 2** | **Example 3** |
| | **750mL 0.1M HCl; Basket (USP-I); 50 RPM** | | | |
| **10** | 11 | 15 | 13 | 18 |
| **20** | 51 | 48 | 45 | 48 |
| **30** | 75 | 69 | 68 | 70 |
| **45** | 98 | 100 | 95 | 92 |
| **60** | 102 | 100 | 99 | 104 |
| **Assay** | 98.8 | 100.6 | 100.8 | 103.0 |

## Table 2: Stability Studies

| | **Entacapone** | | |
|---|---|---|---|
| **Study Condition** | **Example 1** | **Example 2** | **Example 3** |
| | **Assay** | | |
| **Initial** | 102.0 | 101.3 | 101.9 |
| **40°C / 75% RH – 1M** | 99.3 | 100.0 | 100.3 |
| **40°C / 75% RH – 3M** | 99.1 | 99.4 | 100.0 |
| | **Levodopa** | | |
| **Study Condition** | **Example 1** | **Example 2** | **Example 3** |
| | **Assay** | | |
| **Initial** | 101.6 | 101.0 | 99.3 |
| **40°C / 75% RH – 1M** | 99.0 | 98.9 | 98.2 |
| **40°C / 75% RH – 3M** | 96.9 | 96.2 | 95.2 |
| | **Carbidopa** | | |
| **Study Condition** | **Example 1** | **Example 2** | **Example 3** |
| | **Assay** | | |
| **Initial** | 100.6 | 100.8 | 103.0 |
| **40°C / 75% RH – 1M** | 99.1 | 98.7 | 102.0 |
| **40°C / 75% RH – 3M** | 96.0 | 96.2 | 98.1 |