[0008] Nyholm *et al.* (European Journal of Neurology, 2012, 19, 820-826) shows that oral administration of 200 mg entacapone and concomitant intraintestinal infusion of levodopa and carbidopa at a dosage equal to 80% of the optimized dose of a patient, allows maintaining a blood level of levodopa that is substantially the same as that achieved by administration of the optimized dose of levodopa and carbidopa, without entacapone. In other words, Nyholm *et al.* shows that oral administration of entacapone allows reducing the initial dose of levodopa and carbidopa administered by 20% and still maintain the desired blood level of levodopa.

[0009] Yet, the various formulations disclosed do not provide the optimal treatment of Parkinson's disease due to still relatively high level of side effects and levodopa blood level fluctuations. There is thus an ongoing and urgent need for methods for treatment of movement disorders such as Parkinson's, that will provide patients with a constant blood levodopa level that will lead to constant dopaminergic stimulation in the brain, and at the same time limit the side effects caused by high peripheral levodopa concentration resulting from high dose levodopa administration.

SUMMARY ~~OF INVENTION~~

[0010] In one ~~aspect~~example, the present ~~invention~~disclosure provides a method for treatment of Parkinson's disease in an individual in need thereof comprising parenterally administering a pharmaceutical composition comprising carbidopa and ~~levopoda~~levodopa, or pharmaceutically acceptable salts thereof, to said individual; and orally administering a catechol-O-methyl transferase (COMT) inhibitor such as entacapone or tolcapone.

[0010a] In one aspect of the present disclosure, there is provided a use of a sole parenteral composition comprising carbidopa and levodopa in the manufacture of a medicament for the treatment of Parkinson's disease, wherein the medicament is to be administered subcutaneously and in combination with an oral composition comprising a catechol-O-methyl transferase (COMT) inhibitor.

[0011] In another ~~aspect~~example, the present ~~invention~~disclosure relates to carbidopa or a pharmaceutically acceptable salt thereof, levodopa or a pharmaceutically acceptable salt thereof, and a COMT inhibitor for use as a combination in treatment of Parkinson's disease, wherein the carbidopa and the levodopa (or salts thereof) are formulated as a sole parenteral composition, and said COMT inhibitor is formulated as an oral composition.

BRIEF DESCRIPTION OF THE FIGURES

[0012] Figs. 1A-1B show the effect of carbidopa on the stability of levodopa *in vitro* and *ex vivo:* **1A**. 6% by weight levodopa and arginine solution with various concentrations (2, 1.5, 1, 0.5%) of carbidopa or no carbidopa were tested for physical stability *in vitro.* The results show that carbidopa prevented dark yellow color formation in the presence of air, in

CLAIMS

1. Use of a sole parenteral compositionA method for treatment of Parkinson's disease in an individual in need thereof comprising parenterally administering a pharmaceutical composition comprising carbidopa and levopodalevodopa in the manufacture of a medicament for the treatment of Parkinson's disease, wherein the medicament is to be administered subcutaneously and in combination with an oral composition comprising to said individual; and orally administering a catechol-O-methyl transferase (COMT) inhibitor.

2. The method of claim 1, wherein said composition is administered subcutaneously, transdermally, intradermally, intravenously, intramuscularly, intratracheally, intranasally, intrathecally, intragastrically or intraduodenally.

3. The method of claim 1, wherein said composition is administered in one or more sites on the individual's body.

4.2. The methoduse according to of any one of claims 1 to 3, wherein said sole parenteral composition is suitable for substantially continuously administeredadministration.

5.3. The methoduse according to of claim 41 or 2, wherein said sole parenteral composition further comprises arginine.

6.4. The methoduse according to of claim 53, wherein said sole parenteral composition has a molar ratio of carbidopa and levodopa to arginine of about 1:2 to about 1:3.5.

7.5. The methoduse according to of claim 64, wherein said sole parenteral composition comprises (i) arginine, about 0.1% to about 2% by weight carbidopa, and about 4% to about 8% by weight levodopa; or (ii) arginine, about 0.6% to about 1.5% by weight carbidopa, and about 6% by weight levodopa.

6. The use according to claim 4, wherein said sole parenteral composition comprises arginine, 0.1% to 2% by weight carbidopa, and 4% to 8% by weight levodopa.

8.7. The methoduse according to of claim 75 or 6, wherein saidthe sole parenteral composition is to be administered at a rate of about 0.1 to about 1000 µl/h/site; or at a volume of about 2 to about 10, preferably about 4 to about 6, ml/24h/site; or at a dose of about 80 to about 800 mg levodopa/day and about 20 to about 200 mg carbidopa/day; or at a rate of about 240 to about 360 mg levodopa and about 60 to about 90 mg carbidopa/day/site.

~~9.~~8. The ~~method~~use according to ~~of~~ claim ~~8~~5 or 6, wherein said sole parenteral composition is to be administered at a volume of 4 to 6 ml/24h/site~~subcutaneously, transdermally, intradermally, intravenously, intramuscularly, intratracheally, intranasally or intrathecally~~.

~~10.~~9. The ~~method~~use according to ~~of~~ claim ~~6~~4, wherein said sole parenteral composition comprises (i) arginine, about 1% to about 4% by weight carbidopa, and about 6% to about 16% by weight levodopa; or (ii) arginine, about 1.5% to about 2.5% by weight carbidopa, and about 12% by weight levodopa.

~~11.~~10. The ~~method~~use according to ~~of~~ claim ~~10~~9, wherein said sole parenteral composition is to be administered at a rate of ~~about~~ 0.2 to ~~about~~ 2000 µl/h/site; or at a volume of ~~about~~ 10 to ~~about~~ 24~~, preferably about 12 to about 16~~ ml/24h/site; or at a dose of ~~about~~ 600 to ~~about~~ 4000 mg levodopa/day and ~~about~~ 60 to ~~about~~ 500 mg carbidopa/day; or at a rate of ~~about~~ 800 to ~~about~~ 1600 mg levodopa and ~~about~~ 200 to ~~about~~ 400 mg carbidopa/day/site.

~~12.~~11. The ~~method~~use according to ~~of~~ claim ~~11~~10, wherein said sole parenteral composition is to be administered at a volume of 12 to 16 ml/24h/site~~intragastrically or intraduodenally~~.

~~13.~~12. The ~~method~~use according to ~~of~~ any one of claims 1 to ~~12~~11, wherein ~~said~~the COMT inhibitor is entacapone or tolcapone~~, and is administered 1, 2, 3, 4 or 5 times a day~~.

~~14.~~13. The ~~method~~use according to ~~of~~ claim ~~13~~12, wherein ~~said~~the COMT inhibitor is entacapone~~, and is administered at a dose of about 200 mg to about 600 mg, preferably about 400 mg, twice or three times a day~~.

~~15.~~14. The ~~method~~use according to ~~of~~ claim ~~14~~13, wherein the entacapone is to be administered ~~twice~~two times ~~a~~per day at a dose of 400 mg.

15. The use according to any one of claims 1-14, wherein the sole parenteral composition is a liquid composition.

~~16. The method of claim 13, wherein said COMT inhibitor is tolcapone, and is administered at a dose of about 50 mg to about 200 mg, preferably about 100 mg, once or twice or three times a day.~~

~~17. The method of claim 16, wherein the tolcapone is administered twice a day.~~

~~18. Carbidopa, levodopa and a COMT inhibitor for use as a combination in treatment of Parkinson's disease, wherein the carbidopa and the levodopa are formulated as a sole parenteral composition, and said COMT inhibitor is formulated as an oral composition.~~

~~19. The use of claim 18, wherein the carbidopa and the levodopa are formulated as a subcutaneous, transdermal, intradermal, intravenous, intramuscularly, intratracheally, intranasally, intrathecal, intragastrical or intraduodenal composition.~~

~~20. The use of claim 18, wherein said parenteral composition is suitable for substantially continuous administration.~~

~~21. The use of any one of claims 18 to 20, wherein said parenteral composition further comprises arginine.~~

~~22. The use of claim 21, wherein the composition has a molar ratio of carbidopa and levodopa to arginine of about 1:2 to about 1:3.5.~~

~~23. The use of claim 22, wherein said composition comprises (i) arginine, about 0.1% to about 2% by weight carbidopa, and about 4% to about 8% by weight levodopa; (ii) arginine, about 0.6% to about 1.5% by weight carbidopa, and about 6% by weight levodopa; (iii) arginine, about 1% to about 4% by weight carbidopa, and about 6% to about 16% by weight levodopa; or (iv) arginine, about 1.5% to about 2.5% by weight carbidopa, and about 12% by weight levodopa.~~

~~24. The use of any one of claims 18 to 23, wherein the COMT inhibitor is entacapone or tolcapone.~~