[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~~

[0009a] In one aspect of the present disclosure, there is provided 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 for subcutaneous, transdermal, intradermal, intravenous, intramuscularly, intratracheally, intranasally or intrathecal administration, and said COMT inhibitor is formulated as an oral composition.

[0009b] In a further aspect of the present disclosure, there is provided a use of Carbidopa, levodopa and a COMT inhibitor in the manufacture of a medicament for the treatment of Parkinson's disease, wherein the medicament comprises a sole parenteral composition and an oral composition, wherein the sole parenteral composition comprises said Carbidopa and said levodopa formulated for subcutaneous, transdermal, intradermal, intravenous, intramuscularly, intratracheally, intranasally or intrathecal administration and the oral composition comprises said COMT inhibitor.

[0010] ~~In one aspect, t~~The present ~~invention~~ disclosure also 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, or pharmaceutically acceptable salts thereof, to said individual; and orally administering a catechol-O-methyl transferase (COMT) inhibitor such as entacapone or tolcapone.

[0011] ~~In another aspect, t~~The present ~~invention~~ disclosure further 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. A method for treatment of Parkinson's disease in an individual in need thereof comprising parenterally administering a pharmaceutical composition comprising carbidopa and levopoda 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. The method of any one of claims 1 to 3, wherein said composition is substantially continuously administered.

5. The method of claim 4, wherein said composition further comprises arginine.

6. The method of claim 5, wherein said composition has a molar ratio of carbidopa and levodopa to arginine of about 1:2 to about 1:3.5.

7. The method of claim 6, wherein said 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.

8. The method of claim 7, wherein said composition is 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. The method of claim 8, wherein said composition is administered subcutaneously, transdermally, intradermally, intravenously, intramuscularly, intratracheally, intranasally or intrathecally.

~~10. The method of claim 6, wherein said 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. The method of claim 10, wherein said composition is 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. The method of claim 11, wherein said composition is administered intragastrically or intraduodenally.~~

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

~~14. The method of claim 13, wherein said 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. The method of claim 14, wherein the entacapone is administered twice a day.~~

~~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.~~

CLAIMS

1~~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 for subcutaneous, transdermal, intradermal, intravenous, intramuscularly, intratracheally, intranasally or intrathecal administration, 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.~~

220. The carbidopa, levodopa and a COMT inhibitor for use ~~of~~ according to claim ~~18~~ 1, wherein said parenteral composition is suitable for substantially continuous administration.

321. The carbidopa, levodopa and a COMT inhibitor for use ~~of any one of~~ according to claim~~s 18 to 20~~ 1 or 2, wherein said parenteral composition further comprises arginine.

422. The carbidopa, levodopa and a COMT inhibitor for use ~~of~~ according to claim ~~21~~ 3, wherein ~~the~~ said parenteral composition has a molar ratio of carbidopa and levodopa to arginine of ~~about~~ 1:2 to ~~about~~ 1:3.5.

523. The carbidopa, levodopa and a COMT inhibitor for use ~~of~~ according to claim ~~22~~ 4, wherein said 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~~; (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~~.

6. The carbidopa, levodopa and a COMT inhibitor for use according to claim 5, wherein said use comprises administering said parenteral composition at a rate of 0.1 to 1000 µl/h/site; or at a volume of 2 to 10 ml/24h/site; or at a dose of 80 to 800 mg levodopa/day and 20 to 200 mg carbidopa/day; or at a rate of 240 to 360 mg levodopa and 60 to 90 mg carbidopa/day/site.

7. The carbidopa, levodopa and a COMT inhibitor for use according to claim 6, wherein said use comprises administering said parenteral composition at a volume of 4 to 6 ml/24h/site.

8. The carbidopa, levodopa and a COMT inhibitor for use according to claim 4, wherein said parenteral composition comprises (i) 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.

9. The carbidopa, levodopa and a COMT inhibitor for use according to claim 8, wherein said use comprises administering said parenteral composition at a rate of 0.2 to 2000 ul/h/site; or at a volume of 10 to 24 ml/24h/site; or at a dose of 600 to 4000 mg

levodopa/day and 60 to 500 mg carbidopa/day; or at a rate of 800 to 1600 mg levodopa and 200 to 400 mg carbidopa/day/site.

10. The carbidopa, levodopa and a COMT inhibitor for use according to claim 9, wherein said use comprises administering said parenteral composition at a volume of 12 to 16 ml/24h/site.

11 ~~24~~. The carbidopa, levodopa and a COMT inhibitor for use ~~of~~ according to any one of claims ~~18 to 23~~ 1 to 10, wherein the COMT inhibitor is entacapone or tolcapone.

12. Use of Carbidopa, levodopa and a COMT inhibitor in the manufacture of a medicament for the treatment of Parkinson's disease, wherein the medicament comprises a sole parenteral composition and an oral composition, wherein the sole parenteral composition comprises said Carbidopa and said levodopa formulated for subcutaneous, transdermal, intradermal, intravenous, intramuscularly, intratracheally, intranasally or intrathecal administration and the oral composition comprises said COMT inhibitor.

13. The use according to claim 12, wherein said parenteral composition is suitable for substantially continuous administration.

14. The use according to claim 12 or 13, wherein said parenteral composition further comprises arginine.

15. The use according to claim 14, wherein said parenteral composition has a molar ratio of carbidopa and levodopa to arginine of 1:2 to 1:3.5.

16. The use according to claim 15, wherein said parenteral composition comprises (i) arginine, 0.1% to 2% by weight carbidopa, and 4% to 8% by weight levodopa; or (ii) arginine, 0.6% to 1.5% by weight carbidopa, and 6% by weight levodopa.

17. The use according to claim 16, wherein the parenteral composition is to be administered at a rate of 0.1 to 1000 µl/h/site; or at a volume of 2 to 10 ml/24h/site; or at a dose of 80 to 800 mg levodopa/day and 20 to 200 mg carbidopa/day; or at a rate of 240 to 360 mg levodopa and 60 to 90 mg carbidopa/day/site.

18. The use according to claim 17, wherein said parenteral composition is to be administered at a volume of 4 to 6 ml/24h/site.

19. The use according to claim 15, wherein said parenteral composition comprises (i) 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.

20. The use according to claim 19, wherein said parenteral composition is to be administered at a rate of 0.2 to 2000 µl/h/site; or at a volume of 10 to 24 ml/24h/site; or at a dose of 600 to 4000 mg levodopa/day and 60 to 500 mg carbidopa/day; or at a rate of 800 to 1600 mg levodopa and 200 to 400 mg carbidopa/day/site.

21. The use according to claim 10, wherein said parenteral composition is to be administered at a volume of 12 to 16 ml/24h/site.

22. The use according to any one of claims 11 to 21, wherein the COMT inhibitor is entacapone or tolcapone.