Thus, increasing activation of NMDA receptors via GlyT-1 inhibition may lead to agents that treat psychosis, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

Bitopertin is especially useful for the treatment of negative symptoms in schizophrenia, which are apathy, social withdrawal, emotional blunting, impaired ability to anticipate pleasure in everyday life and for the treatment of cognitive impairment such as for the treatment of difficulties with working memory, attention and planning.

It has now been found that a pharmaceutical composition comprising bitopertin in a dose of 3, 5, 10, 20, 30 or 60 mg is particularly efficient in treating negative or cognitive symptoms in schizophrenia. Furthermore, the tablet formulation in accordance with the invention may be suitable for the treatment of deficits in social communications and interactions in autism spectrum disorders (ASD), in the treatment of apathy in early Alzheimer's disease (AD), in the treatment of residual symptoms of motivation after a recent major depressive episode, in the treatment of post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia and for the treatment of apathy and cognitive deficits in Parkinson's-disease (PD).

In a first aspect, there is provided a pharmaceutical composition in form of a film-coating tablet comprising bitopertin or a salt thereof, for use in the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorders (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for use in the prophylaxis for patients at high risk of schizophrenia or for use in the treatment of apathy and cognitive deficits in Parkinson's disease, wherein bitopertin is in a micronized form and wherein the composition further comprises filler excipient with a fine mean particle size of 10 – 160 μm and a combination of corn starch and lactose, wherein the filler excipients are croscarmellose sodium, povidone, talc, magnesium stearate, and microcrystalline cellulose, and wherein the corn starch has a mean particle diameter between 10 to 25 μm.

In another aspect, there is provided a method for preparing a pharmaceutical composition as defined herein, comprising 3, 5, 10, 20, 30 or 60 mg of bitopertin or a salt thereof, by

i. Mixing bitopertin with a diluent, filler, desintegrant and binder,

ii. Granulating the mixed powder from step i using purified water,

iii. Drying and screen the granulate from step ii,

iv. Adding lubricants and compression aid to the granulate from step iii and mix,

v. Compressing the granulate into tablets,

vi. Preparing the film-coating suspension using a pre-mixture, containing a coating agent, coloring agents, plasticizer, lubricant and purified water, and

vii Film-coating the tablets with the suspension from step vi.

In another aspect, there is provided the use of a pharmaceutical composition in form of a film-coating tablet comprising bitopertin or a salt thereof for the preparation of a medicament for the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorder (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia or for the treatment of apathy and cognitive deficits in Parkinson's disease, wherein bitopertin is in a micronized form and wherein the composition further comprises filler excipient with a fine mean particle size of 10 – 160 μm and a combination of corn starch and lactose, wherein the filler excipients are croscarmellose sodium, povidone, talc, magnesium stearate, and microcrystalline cellulose, and wherein the corn starch has a mean particle diameter between 10 to 25 μm.

Bitopertin is practically insoluble in aqueous buffers and in water, but is freely soluble in polar organic solvents. Being a BCS 2 molecule (according to the Biopharmaceutics Classification System, wherein the molecule has high permeability and low solubility), the API particles size distribution has been identified as a major critical quality attribute of the drug substance. In vivo studies in both humans and cynomolgus monkeys showed a direct correlation

between the particle size distribution of the API in tablets and the resulting bioavailability of the formulation. Thus, micronized API was selected for development of a suitable formulation.

In order to optimize the bioavailability and the dissolution performance, different excipients were tested as fillers, binder, disintegrant and lubricant. It has surprisingly been found that the dissolution behavior of the resulting tablets was dependent on the particle size distribution of the selected excipients. The dissolution was better, the finer the particle of the selected excipients was (see Figure 1) and a combination of corn starch and lactose provided the finest mean particle size distribution with the best tablet dissolution, which was also able to ensure suitable granulate particle size distribution, for appropriate flow of the final blend for tablet compression It. is hypothesized that micronized bitopertin could be optimally dispersed

Claims

1. A pharmaceutical composition in form of a film-coating tablet comprising bitopertin or a salt thereof, for use in the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorders (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for use in the prophylaxis for patients at high risk of schizophrenia or for use in the treatment of apathy and cognitive deficits in Parkinson's disease, wherein bitopertin is in a micronized form and wherein the composition further comprises filler excipient with a fine mean particle size of 10 – 160 μm and a combination of corn starch and lactose, wherein the filler excipients are croscarmellose sodium, povidone, talc, magnesium stearate, and microcrystalline cellulose, and wherein the corn starch has a mean particle diameter between 10 to 25 μm.

2. A pharmaceutical composition according to claim 1 with a tablet weight of 150 mg and a film-coat weight of 5 mg.

3. A method for preparing a pharmaceutical composition as defined in claim 1 or 2, comprising 3, 5, 10, 20, 30 or 60 mg of bitopertin or a salt thereof, by

i. Mixing bitopertin with a diluent, filler, desintegrant and binder,
ii. Granulating the mixed powder from step i using purified water,
iii. Drying and screen the granulate from step ii,
iv. Adding lubricants and compression aid to the granulate from step iii and mix,
v. Compressing the granulate into tablets,
vi. Preparing the film-coating suspension using a pre-mixture, containing a coating agent, coloring agents, plasticizer, lubricant and purified water, and
vii Film-coating the tablets with the suspension from step vi.

4. A method according to claim 3, by

i. Mixing bitopertin with lactose monohydrate, maize starch, crosarmellose sodium and ovidone,
ii. Granulating the mixed powder from step i using purified water,
iii. Drying and screen the granulate from step ii,
iv. Adding talc, magnesium stearate and microcrystalline cellulose to the granulate from step iii and mix,

v. Compressing the granulate into tablets,

vi. Preparing the film-coating suspension using a pre-mixture, containing polyvinylalcohol, titanium dioxide, macrogol 3350, talc and yellow iron oxide and purified water, and

vii. Film-coating the tablets with the suspension from step vi.

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5. A pharmaceutical composition according to claim 1 or 2, comprising:

Component	**Weight (mg/tablet)**
Bitopertin	5.00
Lactose monohydrate	78.75
Maize starch	37.50
Croscarmellose sodium	3.75
Povidone 30	6.25
Microcrystalline cellulose	15.00
Talc	3.00
Magnesium stearate	0.75
Opadry II white 85F18422 (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc,	5.00

6 . A pharmaceutical composition according to claim 1 or 2, comprising:

Component	**Weight (mg/tablet)**
Bitopertin	10.00
Lactose monohydrate	73.75
Maize starch	37.50

Croscarmellose sodium	3.75
Povidone 30	6.25
Microcrystalline cellulose	15.00
Talc	3.00
Magnesium stearate	0.75
Opadry II white 85F18422 (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide yellow)	5.00

7. A pharmaceutical composition according to claim 1 or 2, comprising

Component	**Weight (mg/tablet)**
Bitopertin	20.00
Lactose monohydrate	63.75
Maize starch	37.50
Croscarmellose sodium	3.75
Povidone 30	6.25
Microcrystalline cellulose	15.00
Talc	3.00
Magnesium stearate	0.75
Opadry II white 85F18422 (polyvinyl alcohol,	5.00

titanium dioxide, macrogol 3350, talc, iron oxide yellow)	

8. The use of a pharmaceutical composition in form of a film-coating tablet comprising bitopertin or a salt thereof for the preparation of a medicament for the treatment of negative or cognitive symptoms in schizophrenia, deficits in social communications and interactions in autism spectrum disorders (ASD), apathy in early Alzheimer's disease (AD), residual symptoms of motivation after a recent major depressive episode, post traumatic stress disorder (PTSD), for the prophylaxis for patients at high risk of schizophrenia or for the treatment of apathy and cognitive deficits in Parkinson's disease, wherein bitopertin is in a micronized form and wherein the composition further comprises filler excipient with a fine mean particle size of 10 – 160 μm and a combination of corn starch and lactose, wherein the filler excipients are croscarmellose sodium, povidone, talc, magnesium stearate, and microcrystalline cellulose, and wherein the corn starch has a mean particle diameter between 10 to 25 μm.

9. A pharmaceutical composition according to any one of claims 1, 2 or 5 to 7, which is to be administered once daily.