Therefore, it is desirable to develop a pharmaceutical composition comprising brexpiprazole that provides good solubility and eliminates the influence of brexpiprazole particle size distribution on dissolution.

This goal is achieved by the pharmaceutical composition of the invention.

Summary

In the first ~~aspect~~example, the present disclosure refers to a pharmaceutical composition comprising a granulate comprising brexpiprazole, wherein the granulate is obtained by wet-granulation of a carrier using a granulation liquid that is a solution of brexpiprazole in a solvent system.

Such a pharmaceutical composition allows for completely eliminating an influence of brexpiprazole particle size distribution on dissolution of brexpiprazole. Furthermore, surprisingly the dissolution process can be easily controlled by the surface area of the carrier used in the pharmaceutical composition of the disclosure. The inventor observed that the higher the surface area of the carrier, the faster the dissolution of the brexpiprazole. This observation is another very important feature of the disclosure.

Brexpiprazole can be present in the pharmaceutical composition in any suitable amount. However, the applicant found that the pharmaceutical composition should comprise 0.20 wt.% – 15 wt.% brexpiprazole. Due to the relatively low dose of brexpiprazole used in the therapy, the amounts of the pharmaceutical composition in the disclosure comprising more than 15 wt.% brexpiprazole would be too small and inconvenient for daily administration. Amounts lower than 0.20 wt.% would be unsuitable due to the large final dosage form, which could cause swallowing difficulties. Preferably, the pharmaceutical composition comprises 0.25 wt.% – 5 wt.% of brexpiprazole, which fulfills patient compliance aspects.

The wet-granulation used in the granulation step can be any such process. Preferably, however, the wet-granulation is performed using a fluid-bed granulation process. More preferably, top spray fluid-bed granulation process.

Preferably, the solution comprises brexpiprazole, a solvent system, a binder, and a optional surfactant.

The solvent system is a mixture of at least two solvents that provide a complete dissolution of brexpiprazole. Selection of the proper solvent system is a crucial step.

mixture thereof, or a pellet. The pellets used, can be selected from microcrystalline cellulose pellets, sugar pellets, lactose pellets or a mixture thereof.

In the second example, the disclosure relates to a granulate comprising brexpiprazole obtained by wet-granulation of a carrier using a granulation liquid that comprises a solution of brexpiprazole in a solvent system.

In the ~~second~~ third ~~aspect~~example, the present disclosure refers to granulate comprising brexpiprazole obtained by wet-granulation of a carrier using a granulation liquid, wherein the granulation liquid comprises a solution of brexpiprazole in a solvent system.

Preferably, brexpiprazole is present in the granulate in 0.3 wt.% – 20 wt.%. Due to relatively low doses of brexpiprazole used in the therapy, amounts of the pharmaceutical composition comprising more than 20 wt.% brexpiprazole in the final dosage form would be too small for daily administration, and amounts lower than 0.3 wt.% are unsuitable due to the large final dosage form, which could cause swallowing difficulties.

Preferably, the wet-granulation is performed using a fluid-bed granulation process. More preferably, top spray fluid-bed granulation process.

Preferably, the solution of brexpiprazole comprises brexpiprazole, a solvent system, a binder, and an optional surfactant.

Preferably, the solvent system is a mixture of acetone, ethanol and water. More preferably, the acetone, ethanol and water are used in a mass ratio 7.7:1:1.

Preferably, the surfactant is selected from polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan estersn, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, potassium laureate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, benzalkonium chloride, cetyltrimethylammonium bromide, or chitosans. More preferably, the surfactant is selected from polysorbate 80, poloxamer 188, sorbitan monooleate, polysorbate 60, or polyethylene glycols.

Preferably, the binder is selected from Arabic gum, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, L-hydroxypropylycellulose (low-substituted), hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose, starch, polyvinylpyrrolidone, or polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer. More preferably, the binder is selected from polyvinyl caprolactam-polyvinyl acetate-

polyethylene glycol copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropylcellulose, or Arabic gum.

Preferably, the carrier is selected from calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin and its derivatives, dextrose, fructose, lactitol, lactose, starch and modified starches, magnesium carbonate, magnesium oxide, magnesium aluminum silicate, isomalt, mannitol, maltitol, maltodextrin, maltose, sorbitol, starch, sucrose, and xylitol, erythritol or a mixture thereof, or a sugar pellet. More preferably, the carrier is selected from lactose monohydate, magnesium aluminum silicate, microcrystalline cellulose, isomalt, mannitol, dibasic calcium phosphate, or a mixture thereof, or a sugar pellet.

In the fourth~~third aspect~~example, the present disclosure refers to unit dosage form comprising the pharmaceutical composition as disclosed herein.

The preferred unit dosage form is a tablet or a capsule. Other unit dosage forms have been discussed in previous studies.

In one aspect, the present disclosure refers to a method for manufacturing a pharmaceutical composition comprising brexpiprazole, with the following steps:

a) preparation of a solution consisting of a binder, brexpiprazole and optional surfactant in a solvent system;

b) wet-granulation of a carrier with the solution obtained in a).

In another aspect, the present disclosure refers to the use of a wet-granulation process with a solution of brexpiprazole as the granulation liquid in the preparation of the pharmaceutical composition comprising brexpiprazole.

In the ~~fourth~~ fifth ~~aspect~~example, the present disclosure refers to method for manufacturing a pharmaceutical composition comprising brexpiprazole, with the following steps:

a) Preparation of a solution of binder, brexpiprazole and optional surfactant in a solvent system.

b) Wet-granulation of a carrier with the solution obtained in a).

All preferable binders, solvent systems, carriers, optional surfactants are as described above for the pharmaceutical composition of the disclosure. Preferably, the wet-granulation method is fluid-bed granulation, and more preferably top spray fluid-bed granulation.

In the ~~fifth~~ sixth example~~aspect~~, the present disclosure refers to use of a wet-granulation process with a solution of brexpiprazole as the granulation liquid in preparation of the pharmaceutical composition comprising brexpiprazole. Such an approach allows for completely eliminating the influence of brexpiprazole particle size distribution on the dissolution profile of bexpiprazole. Control of the dissolution process of brexpiprazole can be achieved by varying the amount of carrier.

Patent claims

1. A pharmaceutical composition comprising a granulate comprising brexpiprazole, wherein the granulate is obtained by wet-granulation of a carrier using a granulation liquid that is a solution of brexpiprazole in a solvent system.

2. A pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises 0.20 wt.% – 15 wt.% brexpiprazole.

3. The pharmaceutical composition of any one of the preceding claims, wherein the granulate is obtained using fluid-bed granulation.

4. The pharmaceutical composition of any one of the preceding claims, wherein the solution of brexpiprazole comprises brexpiprazole, a solvent system, a binder, and a optional surfactant.

5. The pharmaceutical composition of claim 4, wherein the solvent system is a mixture of acetone, ethanol, and water.

6. The pharmaceutical composition of claim 5, wherein acetone, ethanol, and water are used in a mass ratio 7.7:1:1.

7. The pharmaceutical composition of claim 4, wherein the surfactant is selected from polysorbate 80, poloxamer 188, sorbitan monooleate, polysorbate 60, or polyethylene glycol.

8. The pharmaceutical composition of claim 4, wherein the binder is selected from polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropylcellulose, or Arabic gum.

9. The pharmaceutical composition of claims 1–8, wherein the carrier is selected from lactose monohydate, magnesium aluminum silicate, microcrystalline cellulose, isomalt, mannitol, dibasic calcium phosphate, or a mixture thereof, or a pellet.

10. Granulate comprising brexpiprazole obtained by wet-granulation of a carrier using a granulation liquid, wherein the granulation liquid comprises a solution of brexpiprazole in a solvent system.

~~**11.** The granulate of claim 10, wherein the carrier, solution of brexpiprazole, and solvent system are as defined in claims 1–9.~~

~~**12.** Unit dosage form comprising the pharmaceutical composition as defined in claims 1–9.~~

~~**13**1**.** A ~~M~~method for manufacturing a pharmaceutical composition comprising brexpiprazole, with the following steps:

a) ~~Preparation~~ preparation of a solution consisting of a binder, brexpiprazole and optional surfactant in a solvent system~~.~~;

b) ~~Wet~~wet-granulation of a carrier with the solution obtained in a).

~~**14**~~2**.** The ~~M~~method of claim 1~~3~~, wherein the solvent system ~~is~~ consists of a mixture of acetone, ethanol, and water.

3. The method of claim 2, wherein acetone, ethanol, and water are used in a mass ratio 7.7:1:1.

4. The method of any one of claims 1 to 3, wherein the wet-granulation is fluid-bed granulation.

~~**15.** Method of claims 13 or 14, wherein the carrier, binder and surfactant are as defined in any one of the preceding claims.~~

5. The method of any one of claims 1 to 4, wherein the carrier is selected from the group consisting of lactose monohydate, magnesium aluminum silicate, microcrystalline cellulose, isomalt, mannitol, dibasic calcium phosphate, and mixtures thereof, or is a pellet.

6. The method of any one of claims 1 to 5, wherein the binder is selected from the group consisting of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropylcellulose, and Arabic gum.

7. The method of any one of claims 1 to 6, wherein the surfactant is selected from the group consisting of polysorbate 80, poloxamer 188, sorbitan monooleate, polysorbate 60, and polyethylene glycol.

~~16. Method of claims 13–15, wherein the wet-granulation is fluid-bed granulation.~~

~~178~~**.** Use of a wet-granulation process with a solution of brexpiprazole as the granulation liquid, in the preparation of a pharmaceutical composition comprising brexpiprazole.