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, 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.

The applicant found that the preferred 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. This mass ratio of the solvent system allows for dissolving 1g of brexpiprazole in 252g of the solvent system.

The surfactant is a substance that is generally a compound which lowers the surface tension between two liquids or between a liquid and a solid. Preferably, in the disclosure, the surfactant is selected from polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, 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.

The binder is any pharmaceutically acceptable compound that has binding properties. Preferably, in the disclosure, the binder is selected from Arabic gum, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, L-hydroxypropylycellulose (low-substituted), hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, 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.

The carrier in the disclosure fills out the size of a composition, making it practical to produce and convenient for the consumer to use. The carrier is a base for active ingredients, which are physically connected to the surface of the carrier. Preferably, in the disclosure, the carrier is selected from calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, 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 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 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 aspect, 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 third aspect, 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 the fourth aspect, 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 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.

The pharmaceutical composition of the disclosure or a unit dosage form prepared using the composition or the granulate of the present disclosure may be used for any therapeutic treatment of schizophrenia, and as an adjunctive treatment for major depressive disorder (MDD).

While the present disclosure has been described in terms of its specific examples, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present disclosure.

EXAMPLES

Example 1. Preparation of the pharmaceutical compositions of the invention.

All examples were prepared in accordance with the following method. Brexpiprazole used in the study has the following characteristics D [v, 0.5] 209.3 D [v, 0.9] 313.4μm.

The proposed manufacturing process comprises the following steps:

1) Preparation of an appropriate solvent mixture and heating it up to 50°C.
2) Adding and dissolving the binder and surfactant/solubilizer, continuously stirring.
3) Adding the API and stirring until the clear, yellowish solution is obtained.
4) Spraying the API solution onto the carrier and drying the material.
5) Adding the extragranular phase ingredients.
6) Preparing the final dosage form by tablet compression or the encapsulation process.

Fluid-bed granulation was utilized as a granulation step.

The crucial step of the manufacturing process is solution preparation. This requires a mixture of organic solvents (acetone, ethanol) and water in an appropriate mass ratio 7,7:1:1. Every single gram of active compound must be dissolved in 252g of a given mixture, however solubility has not been precisely determined and an improvement of API concentration in the solution is still possible.