size, shape, taste and after taste are important capsule attributes that can influence patient acceptability (Kozarewicz, Int. J. Pharm. 2014, vol. 469, pp 245-248). In some embodiments, the size of the capsules is kept as small as possible, and the number of capsules required per dose is kept to a minimum, e.g. not more than 1-3 capsules.

In view of the above, there is a need for a formulation of odevixibat that can be easily administered in small doses adapted to the patients' weight. In some embodiments, the formulation should be suitable for treating very young patients, should be easy to swallow, and should not be perceived as gritty.

SUMMARY

In one aspect, provided herein is a pharmaceutical formulation of odevixibat, comprising a plurality of particles, wherein each particle is between about 0.1 and 1.5 mm in size and comprises a) a core, and b) a coating layer surrounding the core, wherein the coating layer comprises odevixibat, or a pharmaceutically acceptable salt thereof, wherein the d_{90} value for the particle size distribution of odevixibat agglomerates in the coating layer is smaller than 15 µm; wherein each particle contains odevixibat, or a pharmaceutically acceptable salt thereof, in an amount of from about 0.1% w/w to 5.0% w/w based on the total weight of the particle, and wherein each particle of the formulation substantially contains the same amount of odevixibat.

In another aspect, provided herein is a use of the formulation as described herein, for the manufacture of a medicament for the treatment or prevention of a liver disease.

In another aspect, provided herein is a process for the preparation of the pharmaceutical formulation as described herein, comprising the step of preparing a homogeneous aqueous suspension of odevixibat, wherein the d_{90} value for the particle size distribution of odevixibat agglomerates in the suspension is smaller than 15 µm.

In another aspect, provided herein is a process for the preparation of the formulation as described herein, comprising the steps of a) wetting odevixibat in water using a homogenizer; and b) dispersing the wetted odevixibat in water by wet milling, thereby obtaining a homogeneous aqueous suspension of odevixibat.

In another aspect, provided herein is a formulation obtained by the process as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the X-ray powder diffractogram of dried crystal modification 1.

FIG. 2 shows the X-ray powder diffractogram of an overhydrated sample of crystal modification 1.

FIG. 3 shows the drying of crystal modification 1, with the X-ray powder diffractogram of an overhydrated sample of crystal modification 1 at the bottom and of a dried sample at the top (2θ range 5 – 13 °).

FIG. 4 shows the drying of crystal modification 1, with the X-ray powder diffractogram of an overhydrated sample of crystal modification 1 at the bottom and of a dry sample at the top (2θ range 18 – 25 °).

FIG. 5 shows the X-ray powder diffractogram of crystal modification 2A, as obtained from a mixture of ethanol and water (70:30 %v/v).

FIG. 6 shows the DSC trace of a sample of odevixibat with about 50% crystalline fraction (after pre-heating and cooling).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein is a multiparticulate formulation containing low doses of odevixibat. In some embodiments, the formulation is a paediatric formulation. In some embodiments, the formulation

CLAIMS

1. A pharmaceutical formulation of odevixibat, comprising a plurality of particles, wherein each particle is between about 0.1 and 1.5 mm in size and comprises

a) a core, and

b) a coating layer surrounding the core, wherein the coating layer comprises odevixibat, or a pharmaceutically acceptable salt thereof, wherein the d_{90} value for the particle size distribution of odevixibat agglomerates in the coating layer is smaller than 15 µm;

wherein each particle contains odevixibat, or a pharmaceutically acceptable salt thereof, in an amount of from about 0.1% w/w to 5.0% w/w based on the total weight of the particle, and wherein each particle of the formulation substantially contains the same amount of odevixibat.

2. The formulation according to claim 1, wherein each particle contains odevixibat, or a pharmaceutically acceptable salt thereof, in an amount of from about 0.5% w/w to 2.0% w/w based on the total weight of the particle.

3. The formulation according to claim 1 or 2, wherein each particle contains odevixibat, or a pharmaceutically acceptable salt thereof, in an amount of about 0.5% w/w based on the total weight of the particle.

4. The formulation according to claim 1 or 2, wherein each particle contains odevixibat, or a pharmaceutically acceptable salt thereof, in an amount of about 1.5% w/w based on the total weight of the particle.

5. The formulation according to any one of claims 1 to 4, wherein the core does not contain odevixibat.

6. The formulation according to claim 5, wherein the core comprises microcrystalline cellulose.

7. The formulation according to any one of claims 1 to 6, wherein the coating layer further comprises a film-forming polymer.

8. The formulation according to any one of claims 1 to 7, wherein the coating layer is sprayed onto the cores as a homogeneous suspension of odevixibat in water.

9. The formulation according to claim 8, wherein the homogenous suspension is prepared by dispersing odevixibat in water by wet milling.

10. The formulation according to claim 8 or 9, wherein the homogenous suspension does not contain agglomerates of odevixibat that are larger than 200 µm.

11. The formulation according to any one of claims 1 to 10, wherein the coating layer does not contain a surfactant.

12. The formulation according to any one of claims 1 to 11, wherein the particles are between about 0.1 and 1.0 mm in size.

13. The formulation according to any one of claims 1 to 12, wherein odevixibat is present as a crystalline hydrate of odevixibat.

14. The formulation according to any one of claims 1 to 13, wherein odevixibat is present as crystal modification 1 of odevixibat, having an X-ray powder diffraction (XRPD) pattern, obtained with CuKα1-radiation, with at least specific peaks at °2θ positions 5.6 ± 0.2, 6.7 ± 0.2 and/or 12.1 ± 0.2.

15. The formulation according to any one of claims 1 to 14, wherein the particles are contained within a sachet or a capsule.

16. The formulation according to any one of claims 1 to 15, wherein the d_{90} value for the particle size distribution of odevixibat agglomerates in the coating layer is smaller than 12 µm.

17. The formulation according to any one of claims 1 to 16, which is a paediatric formulation.

18. Use of the formulation according to any one of claims 1 to 17, for the manufacture of a medicament for the treatment or prevention of a liver disease.

19. The use according to claim 18, wherein the liver disease is a bile acid-dependent liver disease.

20. The use according to claim 18, wherein the liver disease is progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome (ALGS), biliary atresia or paediatric cholestatic pruritus.

21. A process for the preparation of the pharmaceutical formulation according to any one of claims 1 to 17, comprising the step of preparing a homogeneous aqueous suspension of odevixibat, wherein the d_{90} value for the particle size distribution of odevixibat agglomerates in the suspension is smaller than 15 µm.

22. The process according to claim 21, wherein the coating suspension is prepared by dispersing odevixibat in water by wet milling.

23. The process according to claim 21 or 22, wherein the coating suspension does not contain agglomerates of odevixibat that are larger than 200 µm.

24. The process according to any one of claims 21 to 23, wherein the coating suspension does not contain a surfactant.

25. A process for the preparation of the formulation according to any one of claims 1 to 17, comprising the steps of

a) wetting odevixibat in water using a homogenizer; and
b) dispersing the wetted odevixibat in water by wet milling, thereby obtaining a homogeneous aqueous suspension of odevixibat.

26. The process according to claim 25, wherein a film forming polymer is added to the suspension obtained in step (b).

27. The process according to any one of claims 21 to 26, wherein odevixibat is present as a crystalline hydrate of odevixibat.

28. The process according to claim 27, wherein odevixibat is present as crystal modification 1 of odevixibat, having an X-ray powder diffraction (XRPD) pattern, obtained with CuKα1-radiation, with at least specific peaks at °2θ positions 5.6 ± 0.2, 6.7 ± 0.2 and/or 12.1 ± 0.2.

29. A formulation obtained by the process according to any one of claims 21 to 28.