vulgaris, but the extent of gastrointestinal related adverse events experienced were unacceptable.

Thus, there exists a need for a pharmaceutical formulation for oral administration of a PDE inhibitor, which could maintain systemic exposure and reduce gastrointestinal adverse events.

It has been found that beneficial effects with respect to improved tolerability towards gastrointestinal adverse events and maintained systemic exposure have been achieved by formulating a PDE4 inhibitor in a modified release tablet formulation, wherein the in-vitro release is fast in comparison to a typically modified release profile but not yet as fast as for an immediate release tablet where major tolerability issues were seen. The Dissolution target area in Figure 1 illustrates the optimal area.

SUMMARY

In an aspect of the present disclosure, there is provided a modified release tablet formulation comprising:

(i) a phosphodiesterase inhibitor;

(ii) one or more of a pharmaceutically acceptable hydrophilic matrix former;

(iii) one or more pharmaceutically acceptable excipients selected from the group consisting fillers, glidants and lubricants; and

(iv) optionally a pharmaceutically acceptable coating system.

In another aspect of the present disclosure, there is provided a modified release tablet formulation comprising:

(i) a phosphodiesterase inhibitor;

(ii) a hydrophilic matrix former, wherein the hydrophilic matrix former is present in a concentration of from about 15 %w/w to about 25 %w/w hydroxypropyl methylcellulose;

(iii) from about 30 %w/w to about 78 %w/w lactose monohydrate;

(iv) optionally one or more pharmaceutically acceptable excipients selected from the group consisting of glidants and lubricants; and

(v) optionally a pharmaceutically acceptable coating system.

In a further aspect of the present disclosure, there is provided a granulated blend formulation comprising:

(i) a phosphodiesterase inhibitor;

(ii) one or more of a pharmaceutically acceptable hydrophilic matrix former;

(ii) one or more pharmaceutically acceptable excipients selected from the group consisting fillers, binders, glidants and lubricants; and
(iv) a hard capsule shell material.

In another aspect of the present disclosure, there is provided a modified release tablet formulation disclosed herein, or the granulated blend formulation disclosed herein, for use in the treatment, prevention or alleviation of a dermal disease or condition.

In a further aspect of the present disclosure, there is provided a use of the modified release tablet formulation disclosed herein, or the granulated blend formulation disclosed herein, for the manufacture of a medicament for the treatment, prevention or alleviation of a dermal disease or condition.

One object of the present disclosure is to provide modified release tablet formulations for oral administration of a PDE inhibitor, which formulations are useful in the treatment, prevention or alleviation of dermal diseases or conditions.

Another object of the present disclosure is to provide a modified release tablet formulation for oral administration of a PDE inhibitor, which shows beneficial effects with respect to maintained systemic exposure and improved tolerability towards reduced gastrointestinal adverse events.

It is hypothesised that an important driver for the gastrointestinal adverse events could be related to the local concentration of the PDE4 inhibitor in the gut and that higher local concentration of the PDE4 inhibitor could cause increased level of gastrointestinal adverse events.

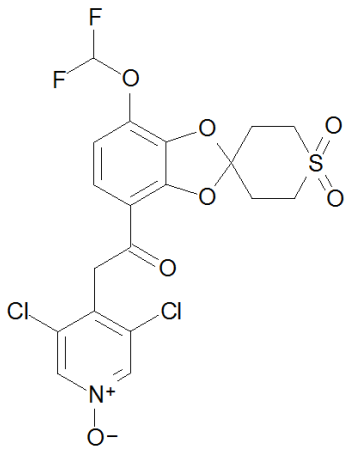
Upon entering the gastrointestinal tract, if the PDE4 inhibitor could slowly be released and dissolved, thus a high local concentration of PDE4 inhibitor could be prevented in the intestinal fluids.

It has been found that when the PDE4 inhibitor was given orally a very narrow absorption window existed in the upper part of the gastrointestinal tract. Therefore, to maintain the systemic exposure the release and dissolution of the drug substance from the modified release tablet formulation must take place in the upper part of the gastrointestinal tract.

In one example, the present disclosure relates to a modified release tablet formulation for oral administration of a PDE inhibitor, comprising:
(i) a PDE inhibitor;
(ii) one or more of a pharmaceutically acceptable hydrophilic matrix former;
(iii) one or more pharmaceutically acceptable excipients selected from the group consisting fillers, glidants and lubricants; and
(iv) optionally a pharmaceutically acceptable coating system.

In another example, the present disclosure relates to a modified release tablet formulation wherein the PDE inhibitor is a PDE4 inhibitor.

In another example, the present disclosure relates to a modified release tablet formulation for oral administration wherein the PDE4 inhibitor is a compound of formula (I)



or a pharmaceutically acceptable salt, or polymorphic forms thereof.

The compound of formula (I), 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoro-methoxy-2′,3′,5′,6′-tetrahydro-spiro[1,3-benzodioxole-2, 4′-(4H)-thiopyran-1′,1′-dioxide]-4-yl)ethanone, hereafter named Compound A, was disclosed in WO 2011/160632, relating to benzodioxole and benzodioxepene heterocyclic compounds useful as PDE4 inhibitors for use in the treatment, prevention or alleviation of a variety of diseases, such as dermal diseases or conditions, such as proliferative and inflammatory skin disorders, dermatitis, psoriasis, psoriasis vulgaris, atopic dermatitis, seborrheic dermatitis, contact dermatitis, cancer, epidermal inflammation, alopecia, alopecia areata, skin atrophy, steroid induced skin atrophy, skin ageing, photo skin ageing, acne, urticaria, pruritis, and eczema.

The compound A should be understood to include any pharmaceutically acceptable form and salts of the compound. The compound A may be present in a crystalline or amorphous form. Compound A is considered as being a poorly soluble compound. The compound A and salts thereof, and methods for synthesizing the compound, are disclosed in WO 2011/160632, WO 2015/197534, WO 2017/103058, and WO 2018/234299.

In another example, the present disclosure relates to a modified release tablet formulation for oral administration of PDE4 inhibitors in the treatment, prevention or alleviation of dermal diseases or conditions selected from the group consisting of proliferative and inflammatory skin disorders, dermatitis, psoriasis, psoriasis vulgaris (plaque-type psoriasis), atopic dermatitis, seborrheic dermatitis, contact dermatitis, cancer, epidermal inflammation, alopecia, alopecia areata, skin atrophy, steroid induced skin atrophy, skin ageing, photo skin ageing, acne, urticaria, pruritis, and eczema.
In another example, the present disclosure relates to a modified release tablet formulation for oral administration of PDE4 inhibitors in the treatment, prevention or alleviation of psoriasis vulgaris.

In another example, the present disclosure relates to a modified release tablet formulation for oral administration of PDE4 inhibitors in the treatment, prevention or alleviation of moderate to severe psoriasis vulgaris.

In another example, the present disclosure relates to a modified release tablet formulation wherein the in-vitro release is fast in comparison to a typically modified release profile but not yet as fast as for an immediate release tablet, as indicated in the background section of the present application.

The rate of dissolution will be determined by several factors e.g. the type and quantity of hydrophilic matrix former, excipients (fillers and coating) and the particle size of the drug substance.

The details of one or more examples of the present disclosure are set forth in the description below. Other features, objects and advantages of the present disclosure will be apparent from the description and claims.

CLAIMS

1. A modified release tablet formulation comprising:
(i) a phosphodiesterase inhibitor;
(ii) one or more of a pharmaceutically acceptable hydrophilic matrix former;
(iii) one or more pharmaceutically acceptable excipients selected from the group consisting fillers, glidants and lubricants; and
(iv) optionally a pharmaceutically acceptable coating system.

2. The modified release tablet formulation according to claim 1, wherein the hydrophilic matrix former comprises hydroxypropyl methylcellulose or hydroxypropylcellulose, or mixtures thereof.

3. The modified release tablet formulation according to claim 1, wherein the hydrophilic matrix former comprises one or more of hydroxypropylmethylcellulose, or mixtures thereof.

4. The modified release tablet formulation according to claim 2 or claim 3, wherein the hydroxypropylmethylcellulose is hypromellose 2910, hypromellose 2208, or mixtures thereof.

5. The modified release tablet formulation according to any one of claims 1 to 4, wherein the hydrophilic matrix former is present in a concentration from about 10 %w/w to about 30 %w/w hydroxypropylmethylcellulose.

6. The modified release tablet formulation according to any one of claims 1 to 4, wherein the hydrophilic matrix former is present in a concentration from about 15 %w/w to about 25 %w/w hydroxypropylmethylcellulose.

7. The modified release tablet formulation according to any one of claims 1 to 4, wherein the hydrophilic matrix former is present in a concentration of 17.5 %w/w hydroxypropylmethylcellulose.

8. The modified release tablet formulation according to any one of claims 1 to 7, wherein the one or more pharmaceutically acceptable excipients comprise a filler selected from lactose monohydrate and microcrystalline cellulose, and mixtures thereof.

9. The modified release tablet formulation according to claim 8, wherein the fillers are present in a concentration from about 30 % to about 78%w/w of lactose monohydrate and from 0 to about 40 %w/w of microcrystalline cellulose.

10. The modified release tablet formulation according to claim 8 or claim 9, wherein the filler is lactose monohydrate.

11. The modified release tablet formulation according to claim 10, wherein the lactose monohydrate is present in a concentration from about 30 % to about 78 %w/w.

12. The modified release tablet formulation according to claim 10 or 11, wherein the lactose monohydrate is present in a concentration of about 71 %w/w.

13. The modified release tablet formulation according to any one of claims 1 to 12, wherein one of the pharmaceutically acceptable excipients is a glidant.

14. The modified release tablet formulation according to claim 13, wherein the glidant is colloidal silicon dioxide.

15. The modified release tablet formulation according to claim 13 or claim 14, wherein the glidant is present in a concentration from about 0.1 %w/w to about 2 %w/w.

16. The modified release tablet formulation according to claim 13 or claim 14, wherein the glidant is present in a concentration of 0.5 %w/w.

17. The modified release tablet formulation according to any one of claims 1 to 16, wherein one of the pharmaceutically acceptable excipients is a lubricant.

18. The modified release tablet formulation according to claim 17, wherein the lubricant is magnesium stearate.

19. The modified release tablet formulation according to claim 17 or claim 18, wherein the lubricant is present in a concentration from about 0.1 %w/w to about 2 %w/w.

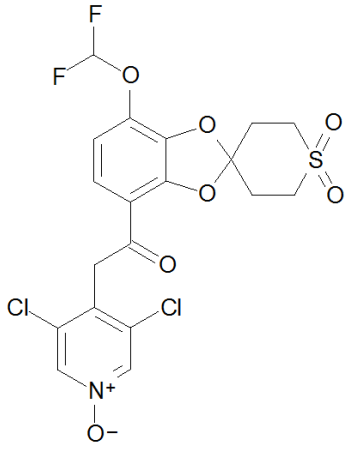
20. The modified release tablet formulation according to claim 17 or claim 18, wherein the lubricant is present in a concentration of 1.0 %w/w.

21. The modified release tablet formulation according to any one of claims 1 to 20, wherein the coating system is a PVA-based coating system.

22. A modified release tablet formulation comprising:
(i) a phosphodiesterase inhibitor;
(ii) a hydrophilic matrix former, wherein the hydrophilic matrix former is present in a concentration of from about 15 %w/w to about 25 %w/w hydroxypropyl methylcellulose;
(iii) from about 30 %w/w to about 78 %w/w lactose monohydrate;
(iv) optionally one or more pharmaceutically acceptable excipients selected from the group consisting of glidants and lubricants; and
(v) optionally a pharmaceutically acceptable coating system.

23. The modified release tablet formulation according to any one of claims 1 to 22, wherein the phosphodiesterase inhibitor is a PDE4 inhibitor.

24. The modified release tablet formulation according to claim 23, wherein the PDE4 inhibitor is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, or polymorphic forms thereof.

25. The modified release tablet formulation according to claim 24, wherein the compound of formula (I) is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2′,3′,5′,6′-tetrahydro-spiro[1,3-benzodioxole-2, 4′-(4H)-thiopyran-1′,1′-dioxide]-4-yl)ethenone, polymorphic form E.

26. The modified release tablet formulation according to any one of claims 1 to 25, wherein the phosphodiesterase inhibitor is in micronized form.

27. The modified release tablet formulation according to any one of claims 1 to 26, wherein the phosphodiesterase inhibitor has a particle size distribution with $D_{50} \leq 5$ µm.

28. The modified release tablet formulation according to any one of claims 1 to 27, wherein the phosphodiesterase inhibitor is present in an amount of from about 5 mg to about 60 mg.

29. The modified release tablet formulation according to any one of claims 1 to 28, wherein the phosphodiesterase inhibitor is present in an amount of 10 mg or 30 mg.

30. The modified release tablet formulation according to claim 1, wherein the formulation consists of about 3.3 %w/w micronized 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2′,3′,5′,6′-tetrahydro-spiro[1,3-benzodioxole-2, 4′-(4H)-thiopyran-1′,1′-dioxide]-4-yl)ethenone, about 17.5 %w/w hypromellose, about 77.7 %w/w lactose monohydrate, about 0.5 %w/w colloidal silicon dioxide, about 1.0 %w/w magnesium stearate; and optionally a PVA-based coating system.

31. The modified release tablet formulation according to claim 1, wherein the formulation consists of about 10.0 %w/w micronized 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2′,3′,5′,6′-tetrahydro-spiro[1,3-benzodioxole-2, 4′-(4H)-thiopyran-1′,1′-dioxide]-4-yl)ethenone, about 17.5 %w/w hypromellose, about 71.0 %w/w lactose monohydrate, about 0.5 %w/w colloidal silicon dioxide, about 1.0 %w/w magnesium stearate; and optionally a PVA-based coating system.

32. A granulated blend formulation comprising:
(i) a phosphodiesterase inhibitor;
(ii) one or more of a pharmaceutically acceptable hydrophilic matrix former;
(ii) one or more pharmaceutically acceptable excipients selected from the group consisting fillers, binders, glidants and lubricants; and
(iv) a hard capsule shell material.

33. The granulated blend formulation according to claim 32, wherein the hydrophilic matrix former comprises hydroxypropyl methylcellulose, or hydroxypropylcellulose, or mixtures thereof.

34. The granulated blend formulation according to claim 33, wherein the hydrophilic matrix former comprises hydroxypropylmethylcellulose.

35. The granulated blend formulation according to any one of claims 32 to 34, wherein the hydrophilic matrix former is present in a concentration from about 10 %w/w to about 30 %w/w and comprises hydroxypropylmethylcellulose.

36. The granulated blend formulation according to any one of claims 32 to 35, wherein the hydrophilic matrix former is present in a concentration of 17.5 %w/w.

37. The granulated blend formulation according to any one of claims 32 to 36, wherein the one or more pharmaceutically acceptable excipients comprise a filler selected from lactose monohydrate and microcrystalline cellulose, and mixtures thereof.

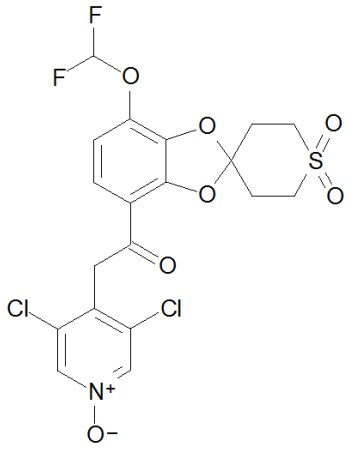
38. The granulated blend formulation according to claim 37, wherein the fillers are present in a concentration from about 30 % to about 78%w/w of lactose monohydrate and from 0 to about 40 %w/w of microcrystalline cellulose.

39. The granulated blend formulation according to claim 37 or claim 38, wherein the filler is lactose monohydrate.

40. The granulated blend formulation according to claim 39, wherein the lactose monohydrate is present in a concentration of about 71 %w/w.

41. The granulated blend formulation according to any one of claims 32 to 40, wherein the phosphodiesterase inhibitor is a PDE4 inhibitor.

42. The granulated blend formulation according to claim 41, wherein the PDE4 inhibitor is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, or polymorphic forms thereof.

43. The granulated blend formulation according to claim 42, wherein the compound of formula (I) is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoromethoxy-2′,3′,5′,6′-tetrahydro-spiro[1,3-benzodioxole-2, 4′-(4H)-thiopyran-1′,1′-dioxide]-4-yl)ethenone, polymorphic form E.

44. The granulated blend formulation according to any one of claims 32 to 43, wherein the phosphodiesterase inhibitor is in micronised form and has a particle size distribution with $D_{50} \leq 5$ µm.

45. The granulated blend formulation according to any one of claims 32 to 44, wherein the phosphodiesterase inhibitor is present in an amount of from about 5 mg to about 60 mg.

46. The modified release tablet formulation according to any one of claims 1 to 31, or the granulated blend formulation according to any one of claims 32 to 45, for use in the treatment, prevention or alleviation of a dermal disease or condition.

47. Use of the modified release tablet formulation according to any one of claims 1 to 31, or the granulated blend formulation according to any one of claims 32 to 45, for the manufacture of a medicament for the treatment, prevention or alleviation of a dermal disease or condition.

48. The modified release tablet formulation for use of claim 46, or the use of claim 47, wherein the dermal disease or condition is selected from the group consisting of proliferative and inflammatory skin disorders, dermatitis, psoriasis, psoriasis vulgaris (plaque-type psoriasis), atopic dermatitis, seborrheic dermatitis, contact dermatitis,

cancer, epidermal inflammation, alopecia, alopecia areata, skin atrophy, steroid induced skin atrophy, skin ageing, photo skin ageing, acne, urticaria, pruritis, and eczema.

49. The modified release tablet formulation for use of claim 46, or the use of claim 47, wherein the dermal disease or condition is psoriasis vulgaris or atopic dermatitis.