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

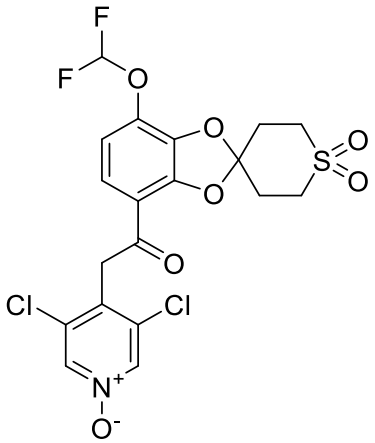
In a first aspect of the present disclosure, there is provided a modified release tablet formulation comprising:

(i) a phosphodiesterase (PDE) inhibitor;

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

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

wherein the PDE inhibitor is a compound of the formula (I):



(I);

and wherein the modified release tablet formulation provides a modified release of the compound of the formula (I) of:

from 12 to 69% at 30 minutes,

from 24 to 83% at 60 minutes,
from 36 to 88% at 90 minutes,
from 48 to 93% at 120 minutes,
from 60 to 96% at 150 minutes, or
from 72 to 97% at 180 minutes,

when measured *in-vitro* using a standard USP/Ph.Eur. app.II (paddles) apparatus at 75 rpm, in 900 mL 0.1N HCl and 0.5% SDS at 37°C.

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

(i) a PDE inhibitor;

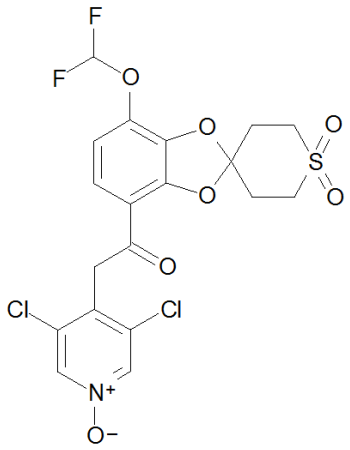
(ii) one or more of a pharmaceutically acceptable hydrophilic matrix former; and

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

wherein:

the hydrophilic matrix former is present in a concentration from 10 %w/w to 30 %w/w hydroxypropyl methylcellulose;

the PDE inhibitor is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, or polymorphic forms thereof.

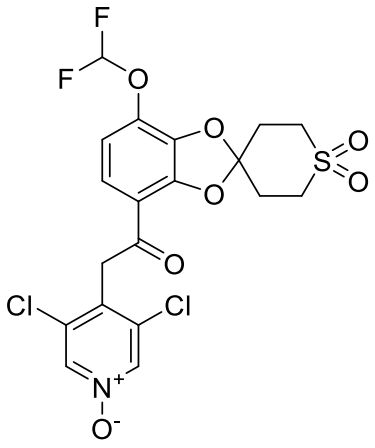
In yet another aspect of the present disclosure, there is provided a modified release tablet formulation comprising:

(i) a PDE inhibitor;

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

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

wherein the PDE inhibitor is a compound of the formula (I):



(I).

In another aspect of the present disclosure, there is provided a modified release tablet 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, 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.

CLAIMS

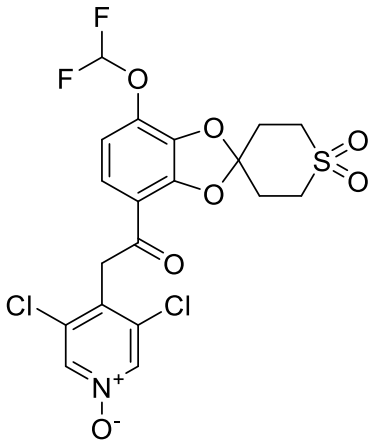
1. A modified release tablet formulation comprising:

(i) a phosphodiesterase (PDE) inhibitor;

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

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

wherein the PDE inhibitor is a compound of the formula (I):



(I);

and wherein the modified release tablet formulation provides a modified release of the compound of the formula (I) of:

from 12 to 69% at 30 minutes,

from 24 to 83% at 60 minutes,

from 36 to 88% at 90 minutes,

from 48 to 93% at 120 minutes,

from 60 to 96% at 150 minutes, or

from 72 to 97% at 180 minutes,

when measured *in-vitro* using a standard USP/Ph.Eur. app.II (paddles) apparatus at 75 rpm, in 900 mL 0.1N HCl and 0.5% SDS at 37°C.

2. The modified release tablet formulation according to claim 1, wherein the modified release tablet formulation provides a modified release of the compound of the formula (I) of:

from 12 to 69% at 30 minutes,

from 24 to 83% at 60 minutes,

from 36 to 88% at 90 minutes,

from 48 to 93% at 120 minutes,

from 60 to 96% at 150 minutes, and

from 72 to 97% at 180 minutes,

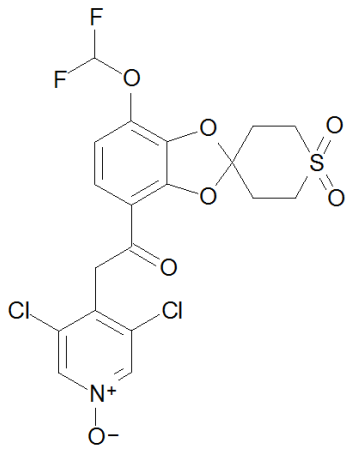
when measured *in-vitro* using a standard USP/Ph.Eur. app.II (paddles) apparatus at 75 rpm, in 900 mL 0.1N HCl and 0.5% SDS at 37°C.

3. The modified release tablet formulation according to claim 1, wherein the modified release tablet formulation provides a modified release of the compound of the formula (I) substantially in accordance with the dissolution target area of Figure 1 when measured *in-vitro* using a standard USP/Ph.Eur. app.II (paddles) apparatus at 75 rpm, in 900 mL 0.1N HCl and 0.5% SDS at 37°C.

4. The modified release tablet formulation according to any one of claims 1 to 3, wherein the hydrophilic matrix former comprises hydroxypropyl methylcellulose or hydroxypropylcellulose, 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 10 %w/w to 30 %w/w hydroxypropyl methylcellulose.

6. A modified release tablet formulation comprising:
(i) a PDE inhibitor;
(ii) one or more of a pharmaceutically acceptable hydrophilic matrix former; and
(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of fillers, glidants and lubricants,
wherein:
the hydrophilic matrix former is present in a concentration from 10 %w/w to 30 %w/w hydroxypropyl methylcellulose;
the PDE inhibitor is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, or polymorphic forms thereof.

7. The modified release tablet formulation according to any one of claims 1 to 6, wherein the hydrophilic matrix former comprises hydroxypropylmethylcellulose.

8. The modified release tablet formulation according to any one of claims 1 to 7, wherein the hydrophilic matrix former is present in a concentration from 15 %w/w to 25 %w/w hydroxypropylmethylcellulose.

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

10. The modified release tablet formulation according to any one of claims 4 to 9, wherein the hydroxypropylmethylcellulose is hypromellose 2910, hypromellose 2208, or mixtures thereof.

11. The modified release tablet formulation according to any one of claims 4 to 9, wherein the hydroxypropylmethylcellulose is hypromellose 2910.

12. The modified release tablet formulation according to any one of claims 4 to 9, wherein the hydroxypropylmethylcellulose is hypromellose 2208.

13. The modified release tablet formulation according to any one of claims 1 to 12, wherein the one or more pharmaceutically acceptable excipients comprise a filler selected from lactose monohydrate and microcrystalline cellulose, and mixtures thereof.

14. The modified release tablet formulation according to claim 13, wherein the fillers are present in a concentration from 30 % to 78%w/w of lactose monohydrate and from 0 to 40 %w/w of microcrystalline cellulose.

15. The modified release tablet formulation according to claim 13 or claim 14, wherein the filler is lactose monohydrate.

16. The modified release tablet formulation according to claim 15, wherein the lactose monohydrate is present in a concentration from 30 % to 78 %w/w.

17. The modified release tablet formulation according to claim 15 or claim 16, wherein the lactose monohydrate is present in a concentration of 71 %w/w.

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

19. The modified release tablet formulation according to claim 18, wherein the glidant is colloidal silicon dioxide.

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

21. The modified release tablet formulation according to claim 18 or claim 19, wherein the glidant is present in a concentration of 0.5 %w/w.

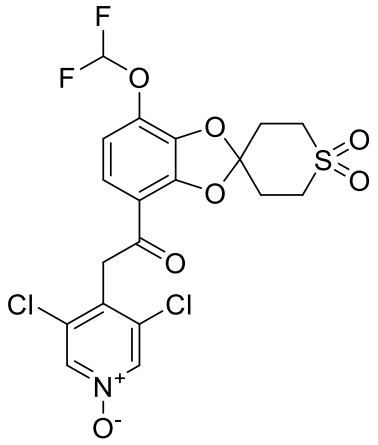
22. The modified release tablet formulation according to any one of claims 1 to 21, wherein one of the pharmaceutically acceptable excipients is a lubricant.

23. The modified release tablet formulation according to claim 22, wherein the lubricant is magnesium stearate.

24. The modified release tablet formulation according to claim 22 or claim 23, wherein the lubricant is present in a concentration from 0.1 %w/w to 2 %w/w.

25. The modified release tablet formulation according to claim 22 or claim 23, wherein the lubricant is present in a concentration of 1.0 %w/w.

26. A modified release tablet formulation comprising:
(i) a PDE inhibitor;
(ii) from 15 %w/w to 25 %w/w of a hydrophilic matrix former, wherein the hydrophilic matrix former is hydroxypropyl methylcellulose; and
(iii) from 30 %w/w to 78 %w/w lactose monohydrate;
wherein the PDE inhibitor is a compound of the formula (I):



(I).

27. The modified release tablet formulation according to any one of claims 1 to 26, wherein the compound of formula (I) is in micronized form.

28. The modified release tablet formulation according to any one of claims 1 to 27, wherein the compound of formula (I) has a particle size distribution with $D_{50} \leq 5$ µm.

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

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

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

32. The modified release tablet formulation according to any one of claims 1 to 28, wherein the PDE inhibitor is present in an amount of 20 mg.

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

34. The modified release tablet formulation according to any one of claims 1 to 28, wherein the PDE inhibitor is present in an amount of 40 mg.

35. The modified release tablet formulation according to any one of claims 1 to 34, further comprising a pharmaceutically acceptable coating system.

36. The modified release tablet formulation according to claim 35, wherein the coating system is a PVA-based coating system.

37. The modified release tablet formulation according to claim 36, wherein the coating is present in an amount from 3% to 5% weight gain of the tablet formulation.

38. The modified release tablet formulation according to claim 36, wherein the coating is present in an amount of 4% weight gain of the tablet formulation.

39. The modified release tablet formulation according to claim 35, wherein the coating system comprises a coating system selected from: a hydroxypropyl methylcellulose-based coating system, a polyvinyl alcohol-based coating system, a polyvinyl alcohol-polyethylene glycol-based coating system and an ethylcellulose based functional barrier membrane coating system.

40. The modified release tablet formulation according to claim 6, wherein the formulation consists of 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) ethanone, 17.5 %w/w hypromellose, 77.7 %w/w lactose monohydrate, 0.5 %w/w colloidal silicon dioxide, and 1.0 %w/w magnesium stearate.

41. The modified release tablet formulation according to claim 6, wherein the formulation consists of 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) ethanone, 17.5 %w/w hypromellose, 71.0 %w/w lactose monohydrate, 0.5 %w/w colloidal silicon dioxide, and 1.0 %w/w magnesium stearate.

42. The modified release tablet formulation according to claim 40 or claim 41, wherein the 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) ethanone has a particle size distribution with $D_{50} \leq 5$ µm.

43. The modified release tablet formulation according to any one of claims 40 to 42, wherein the modified release tablet formulation further comprises a polyvinyl alcohol (PVA) based coating system.

44. The modified release tablet formulation according to claim 43, wherein the coating is present in an amount of from 3% to 5% weight gain of the tablet formulation.

45. The modified release tablet formulation according to claim 43, wherein the coating is present in an amount of 4% weight gain of the tablet formulation.

46. The modified release tablet formulation according to any one of claims 1 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 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 according to 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 according to claim 46, or the use of claim 47, wherein the dermal disease or condition is psoriasis vulgaris.

50. The modified release tablet formulation for use according to claim 46, or the use of claim 47, wherein the dermal disease or condition is moderate to severe psoriasis vulgaris.

51. The modified release tablet formulation for use according to claim 46, or the use of claim 47, wherein the dermal disease or condition is atopic dermatitis.