ORAL DISSOLVABLE FILM AND METHOD OF MANUFACTURING AND USING THE SAME

RELATED APPLICATION

This application claims priority to U.S. Provisional Patent Application No. 62/955,484 filed December 31, 2019; the contents of which are incorporated herein in their entirety.

BACKGROUND OF THE INVENTION

Bioavailability of orally drugs administered is relatively low. Additionally, sensitive active ingredients (e.g., sensitive to moisture, oxygen, light, pH, and/or heat) present difficulties in the selection of the suitable dosage form and the route of administration. This includes those dosage forms configured for oral administration.

Currently, there is a need for pharmaceutical formulations having an increased barrier to moisture, oxygen, light, pH, and heat to thereby confer protection to sensitive active ingredient. There is also a need for an improved bioavailability of less potent and less bioavailable active ingredients which allows the less potent active ingredients to be used at low doses. Additionally, with various pharmaceutical formulations, there is a need for an increased penetration and crossing of the mucus layer by the active ingredients, thereby allowing active ingredients to enter into systemic circulation. The above are desirable while also reducing liver/GI toxicity.

SUMMARY ~~OF THE INVENTION~~

In an aspect of the present disclosure, there is provided a method of forming an oral dissolvable film, the method comprising:

(a) dissolving an active pharmaceutical ingredient in a first solvent-system to form a first mixture, wherein:

(i) when the active pharmaceutical ingredient is lipophilic or hydrophobic, dissolving the active pharmaceutical ingredient in a lipophilic or hydrophobic solvent, in a lipophilic or hydrophobic surfactant, or combination thereof; or

(ii) when the active pharmaceutical ingredient is hydrophilic or lipophobic, dissolving the active pharmaceutical ingredient in a hydrophilic or lipophobic solvent, in a hydrophilic or lipophobic surfactant, or combination thereof;

(b) contacting the first mixture and a lipophilic or hydrophobic surfactant to form a second mixture;

(c) contacting the second mixture with water and a hydrophilic or lipophobic surfactant to form a third mixture;

(d) contacting the third mixture with film forming ingredient to form a slurry; and

(e) casting the slurry on a substrate and curing to form the oral dissolvable film.

The present ~~invention~~disclosure provides for an oral dissolvable film that includes: (a) active pharmaceutical ingredient; (b) surfactant; (c) solvent for the active pharmaceutical ingredient; (d) film matrix; and (e) water; wherein, (1) when the active pharmaceutical ingredient is lipophilic or hydrophobic: (i) the surfactant is lipophilic or hydrophobic, and (ii) the solvent for the active pharmaceutical ingredient is lipophilic or hydrophobic; and (2) when the active pharmaceutical ingredient is lipophobic or hydrophilic: (i) the surfactant is lipophobic or hydrophilic, and (ii) the solvent for the active pharmaceutical ingredient is lipophobic or hydrophilic.

The present ~~invention~~disclosure also provides for an oral dissolvable film that includes: (a) lipophilic active pharmaceutical ingredient; (b) oil carrier for the lipophilic active pharmaceutical ingredient; (c) self–emulsifying lipophilic surfactant for the lipophilic active pharmaceutical ingredient; (d) one or more co–surfactants; (e) one or more hydrophilic surfactants; (f) film matrix; and (g) water.

The present ~~invention~~disclosure also provides for an oral dissolvable film that includes: (a) hydrophilic active pharmaceutical ingredient; (b) water carrier for the hydrophilic active pharmaceutical ingredient; (c) hydrophilic surfactant for the hydrophilic active pharmaceutical ingredient; (d) one or more co–surfactants; (e) one or more self–emulsifying surfactants; (f) film matrix; and (g) water.

The present ~~invention~~disclosure also provides for a method of forming an oral dissolvable film, the method includes: (a) dissolving an active pharmaceutical ingredient in a first solvent-system to form a first mixture, wherein: (i) when the active pharmaceutical ingredient is lipophilic or hydrophobic, dissolving the active pharmaceutical ingredient in a lipophilic or hydrophobic solvent, in a lipophilic or hydrophobic surfactant, or combination thereof; or (ii) when the active pharmaceutical ingredient is hydrophilic or lipophobic, dissolving the active pharmaceutical ingredient in a hydrophilic or lipophobic solvent, in a hydrophilic or lipophobic surfactant, or combination thereof; (b) contacting the first mixture and a lipophilic or hydrophobic surfactant to form a second mixture; (c) contacting the second mixture with water and a hydrophilic or lipophobic surfactant to form a third mixture; (d) contacting the third mixture with film forming ingredient to form a slurry; and (e) casting the slurry on a substrate and curing to form the oral dissolvable film.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for an oral dissolvable film and a method of manufacturing and using the same.

Definitions

The term the following terms have the meanings ascribed to them unless specified otherwise.

The words “comprise,” “comprising,” “include,” “including,” and “includes” when used in this specification and claims are intended to specify the presence of stated substances, features, integers, components, or steps, but they do not preclude the presence or addition of one or more other substances, features, integers, components, steps, or combinations thereof.

CLAIMS

1. An oral dissolvable film comprising:

(a) active pharmaceutical ingredient;

(b) surfactant;

(c) solvent for the active pharmaceutical ingredient;

(d) film matrix; and

(e) water;

wherein,

when the active pharmaceutical ingredient is lipophilic or hydrophobic: (i) the surfactant is lipophilic or hydrophobic, and (ii) the solvent for the active pharmaceutical ingredient is lipophilic or hydrophobic; and

when the active pharmaceutical ingredient is lipophobic or hydrophilic: (i) the surfactant is lipophobic or hydrophilic, and (ii) the solvent for the active pharmaceutical ingredient is lipophobic or hydrophilic.

2. The oral dissolvable film of claim 1, wherein the surfactant is lipophilic or hydrophobic and the solvent for the active pharmaceutical ingredient is lipophilic or hydrophobic.

3. The oral dissolvable film of any one of claims 1-2, wherein the lipophilic or hydrophobic surfactant comprises at least one of Glyceryl Monocaprylate, Propylene Glycol Monocaprylate, Glyceryl Monooleate, Propylene Glycol Monolaurate, Glyceryl Caprylate/ Caprate, Glyceryl Monolinoleate, Sorbitan Monooleate (Span 80), Glyceryl Dibehenate, Propylene Glycol Dilaurate, Glyceryl Tricaprylate/Tricaprate, Glycerol Tricaprylate/Caprate, Decaglycerol Mono and Di Oleate, Oleoyl Macrogolglycerides, Lauroyl Macrogolglycerides, Stearoyl Macrogolglycerides, Stearoyl Polyoxylglycerides, Polyoxyethylene, and Caprylic/Capric Glycerides.

4. The oral dissolvable film of any one of claims 1-3, wherein the lipophilic or hydrophobic surfactant is present in 0.5-40 wt.%.

~~5. The oral dissolvable film of claim 1, wherein the surfactant is lipophobic or hydrophilic and the solvent for the active pharmaceutical ingredient is lipophobic or hydrophilic.~~

~~6. The oral dissolvable film of any one of claims 1 and 5, wherein the lipophobic or hydrophilic surfactant comprises at least one of Poloxamer, Polyoxyl Castor Oil, Polyethylene-polypropylene Glycol, Polyoxyethylene Sorbitan Monolaurate (Tween 20), Tween 80, Polyoxyethylenesorbitan Monostearate (Tween 60), Decyl Glucoside, Lauryl Glucoside, Octyl Glucoside, Triton X-100, Nonoxynol 9, Sodium Lauryl Sulfate, Potassium Lauryl Sulfate, Brij, Glyceryl Laurate, Phospholipids, n-Dodecyl Phosphocholine, and Cholesteryl Esters.~~

~~7. The oral dissolvable film of any one of claims 1 and 5-6, wherein the lipophobic or hydrophilic surfactant is present in 0.5-40 wt.%.~~

~~8. The oral dissolvable film of any one of claims 1-3, wherein the lipophilic or hydrophobic solvent for the active pharmaceutical ingredient comprises at least one of Medium Chain Triglycerides Oil, Coconut Oil, Corn Oil, Olive Oil, Palm Oil, Canola Oil, Safflower Oil, Sesame Oil, Propylene Glycol Monocaprylate, Propylene Glycol Monolaurate, Glyceryl Monolinoleate, Cetyl Alcohol, Stearyl Alcohol, Cetostearyl Alcohol, and Oleyl Alcohols.~~

~~9. The oral dissolvable film of any one of claims 1-3 and 8, wherein the lipophilic or hydrophobic solvent for the active pharmaceutical ingredient is present in 0.5-40 wt.%.~~

~~10. The oral dissolvable film of any one of claims 1 and 5-7, wherein the lipophobic or hydrophilic solvent for the active pharmaceutical ingredient comprises water.~~

~~11. The oral dissolvable film of any one of claims 1, 5-7, and 10, wherein the lipophobic or hydrophilic solvent for the active pharmaceutical ingredient is present in 0.5-20 wt.%.~~

~~12. The oral dissolvable film of any one of claims 1-11, wherein the active pharmaceutical ingredient is lipophilic or hydrophobic.~~

~~13. The oral dissolvable film of any one of claims 1-11, wherein the active pharmaceutical ingredient is lipophobic or hydrophilic.~~

~~14. The oral dissolvable film of any one of claims 1-13, wherein the active pharmaceutical ingredient comprises a cannabinoid, terpene, flavonoid, or combination thereof.~~

~~15. The oral dissolvable film of any one of claims 1-13, wherein the active pharmaceutical ingredient comprises at least one of cyclosporine, ritonavir, saquinavir, amprenavir, valproic acid, calcitriol, bexarotene, tretinoin, isotretinoin, tipranavir, and pharmaceutically acceptable salts thereof.~~

~~16. The oral dissolvable film of any one of claims 1-13, wherein the active pharmaceutical ingredient comprises a psychedelic agent.~~

~~17. The oral dissolvable film of any one of claims 1-13, wherein the active pharmaceutical ingredient comprises a psychedelic agent comprising at least one of Lysergic acid diethylamide (LSD); 3,4-Methylenedioxymethamphetamine (MDMA); N,N-Dimethyltryptamine (DMT); Psilocybin, Mescaline, and Ibogaine.~~

~~18. The oral dissolvable film of any one of claims 1-13, wherein the active pharmaceutical ingredient comprises ivermectin.~~

~~19. The oral dissolvable film of any one of claims 1-18, comprising the active pharmaceutical ingredient in at least 10 wt.%.~~

~~20. The oral dissolvable film of any one of claims 1-19, wherein the film matrix comprises a plasticizer, and film former.~~

~~21. The oral dissolvable film of any one of claims 1-20, wherein the film matrix comprises a plasticizer comprising at least one of Propylene Glycol, Glycerin, Triacetin, Triethyl Citrate, and Polyethylene Glycol.~~

~~22. The oral dissolvable film of any one of claims 1-21, wherein the film matrix comprises a plasticizer present in 0.5-20 wt.%.~~

~~23. The oral dissolvable film of any one of claims 1-23, wherein the film matrix comprises a film former comprising at least one of Pullulan, Gum Arabic, Guar Gum, Maltodextrin, Microcrystalline Cellulose, Chitosan, Pectin, Carrageenan, HPMC, HPC, Modified Corn Starch, Carbopol 974P, Carbopol 934P, Kollidon 25, Soluplus, Lycoat NG73, Kollicoat, Polyox N-10, Polyox N-80, Polyox N-750, Methocel E4M, Methocel E10M, and Sodium CMC.~~

~~24. The oral dissolvable film of any one of claims 1-23, wherein the film matrix comprises a film former present in 1-60 wt.%.~~

~~25. The oral dissolvable film of any one of claims 1-24, further comprising a co-solvent.~~

~~26. The oral dissolvable film of any one of claims 1-25, further comprising a co-solvent comprising at least one of Diethylene Glycol Monoethyl Ether and Caprylocapryol Polyoxyl-8 Glycerides.~~

~~27. The oral dissolvable film of any one of claims 1-26, further comprising a co-solvent present in 0.5-40 wt.%.~~

~~28. The oral dissolvable film of any one of claims 1-27, further comprising at least one of an antioxidant, antimicrobial agent, flavoring agent, coloring agent, and sweetener.~~

~~29. The oral dissolvable film of clam 1, comprising:~~

~~(a) lipophilic active pharmaceutical ingredient;~~

~~(b) oil carrier for the lipophilic active pharmaceutical ingredient;~~

~~(c) self-emulsifying lipophilic surfactant for the lipophilic active pharmaceutical ingredient;~~

~~(d) one or more co-surfactants;~~

~~(e) one or more hydrophilic surfactants;~~

~~(f) film matrix; and~~

~~(g) water.~~

30. The oral dissolvable film of clam 1, comprising:

(a) hydrophilic active pharmaceutical ingredient;

(b) water carrier for the hydrophilic active pharmaceutical ingredient;

(c) hydrophilic surfactant for the hydrophilic active pharmaceutical ingredient;

(d) one or more co- surfactants;

(e) one or more self- emulsifying surfactants;

(f) film matrix; and

(g) water.

31. The oral dissolvable film of any one of claims 1-30, configured to self-emulsify within 20 seconds upon contact with an oral mucosal surface of a subject.

32. The oral dissolvable film of any one of claims 1-31, configured to form an oil- in- water (O/W) emulsion within 20 seconds upon contact with an oral mucosal surface of a subject.

33. The oral dissolvable film of any one of claims 1-32, configured to form an oil- in- water (O/W) emulsion having an average droplet size of 0.1 microns to 120 microns within 20 seconds upon contact with an oral mucosal surface of a subject.

34. The oral dissolvable film of any one of claims 1-33, configured to form an oil- in- water (O/W) emulsion having an average droplet size of

d(10): 0.5-10 micron,

d(50): 1-20 micron, and

d(90): 15-100 micron

within 20 seconds upon contact with an oral mucosal surface of a subject.

35. The oral dissolvable film of any one of claims 1-34, suitable for oral administration (PO), buccal administration, sublingual administration, or mucosal administration.

~~36. The oral dissolvable film of any one of claims 1-35, having a moisture content of 3-13 wt.%.~~

~~37. The oral dissolvable film of any one of claims 1-36, configured to disintegrate within 15 minutes upon buccal administration to a subject.~~

~~38. The oral dissolvable film of any one of claims 1-36, configured to disintegrate within 30 seconds upon oral (PO) administration to a subject.~~

~~39. The oral dissolvable film of any one of claims 1-36, configured for in vitro disintegration (USP<701> In-vitro Disintegration method) within 30 seconds.~~

~~40. The oral dissolvable film of any one of claims 1-39, exhibiting at least one pharmacokinetic parameter selected from, (i) Tmax of between about 45 min to about 120 min, (ii) Cmax of at least 3.5 ng/ml, and (iii) AUC_{0-t} of at least 13 ng/hr/ml.~~

~~41. The oral dissolvable film of any one of claims 1-40, exhibiting at least one pharmacokinetic parameter selected from, (i) Tmax of 1.5 hr, (ii) Cmax of 4.4 ng/ml, and (iii) AUC_{0-t} of 13.5 ng/hr/ml.~~

~~42. The oral dissolvable film of any one of claims 1-41, exhibiting an in vivo dissolution time of no more than 20 minutes.~~

~~43. The oral dissolvable film of any one of claims 1-42, exhibiting an in vivo dissolution time of between about 10 minutes to about 15 minutes.~~

~~44. The oral dissolvable film of any one of claims 1-43, exhibiting a bioavailability of at least 15%.~~

~~45. The oral dissolvable film of any one of claims 1-43, exhibiting a bioavailability of at least 18%.~~

~~46. The oral dissolvable film of any one of claims 1-45, exhibiting a stability of at least about 96% after nine months as measured under 40°C/75% RH accelerated conditions.~~

~~47. The oral dissolvable film of any one of claims 1-45, exhibiting a stability of 100% after three months as measured under 25°C/60% RH accelerated condition, or 40°C/75% RH accelerated conditions.~~

~~48~~1. A method of forming an oral dissolvable film, the method comprising:

(a) dissolving an active pharmaceutical ingredient in a first solvent-system to form a first mixture, wherein:

(i) when the active pharmaceutical ingredient is lipophilic or hydrophobic, dissolving the active pharmaceutical ingredient in a lipophilic or hydrophobic solvent, in a lipophilic or hydrophobic surfactant, or combination thereof; or

(ii) when the active pharmaceutical ingredient is hydrophilic or lipophobic, dissolving the active pharmaceutical ingredient in a hydrophilic or lipophobic solvent, in a hydrophilic or lipophobic surfactant, or combination thereof;

(b) contacting the first mixture and a lipophilic or hydrophobic surfactant to form a second mixture;

(c) contacting the second mixture with water and a hydrophilic or lipophobic surfactant to form a third mixture;

(d) contacting the third mixture with film forming ingredient to form a slurry; and

(e) casting the slurry on a substrate and curing to form the oral dissolvable film.

2~~49~~. The method of claim 1~~48~~, wherein the film forming ingredient comprises at least one of mucoadhesive polymer, plasticizer, binder, filler, bulking agent, saliva stimulating agent, stabilizing and thickening agent, gelling agent, flavoring agent, taste masking agent, coloring agent, pigment, lubricant, release modifier, adjuvant, sweetening agent, solubilizer & emulsifier, fragrance, emulsifier, surfactant, pH adjusting agent, buffering agent, lipid, glidant, stabilizer, antioxidant, anti-tacking agent, humectant, solvent, permeation enhancer, and preservative.

3~~50~~. The method of claim 1~~any one of claims 48-49~~, wherein the lipophilic or hydrophobic solvent comprises an oil.

4~~51~~. The method of claim 1~~any one of claims 48-49~~, wherein the hydrophilic or lipophobic solvent comprises an aqueous liquid.

5~~52~~. The method of claim 1~~any one of claims 48-51~~, wherein the curing is carried out in a hot air oven at an air temperature of between about 38°C to about 110°C.

6~~53~~. The method of claim 1~~any one of claims 48-52~~, wherein the curing is carried out in a hot air oven at an air temperature of between about 45°C to about 80°C

7~~54~~. The method of claim 1~~any one of claims 48-53~~, wherein the curing is carried out in a hot air oven (at an air temperature of 50°C–70°C).

8~~55~~. The method of claim 1~~any one of claims 48-54~~, wherein the curing is carried out at a speed of between about 0.8 feet/min to about 2.5 feet/min.

9~~56~~. The method of claim 1~~any one of claims 48-55~~, wherein the curing is carried out at a speed of between about 0.8 feet/min to about 1.0 feet/min.

10~~57~~. The method of claim 1~~any one of claims 48-56~~, wherein the curing is carried out at a speed of between about 2.0 feet/min to about 2.5 feet/min.

11. The method of claim 1, wherein the oral dissolvable film comprises:

(a) hydrophilic active pharmaceutical ingredient;

(b) water carrier for the hydrophilic active pharmaceutical ingredient;

(c) hydrophilic surfactant for the hydrophilic active pharmaceutical ingredient;

(d) one or more co–surfactants;

(e) one or more self–emulsifying surfactants;

(f) film matrix; and

(g) water.

12. The method of claim 1, wherein the oral dissolvable film is configured to self-emulsify within 20 seconds upon contact with an oral mucosal surface of a subject.

13. The method of claim 1, wherein the oral dissolvable film is configured to form an oil–in–water (O/W) emulsion within 20 seconds upon contact with an oral mucosal surface of a subject.

14. The method of claim 1, wherein the oral dissolvable film is configured to form an oil–in–water (O/W) emulsion having an average droplet size of 0.1 microns to 120 microns within 20 seconds upon contact with an oral mucosal surface of a subject.

15. The method of claim 1, wherein the oral dissolvable film is configured to form an oil–in–water (O/W) emulsion having an average droplet size of

d(10): 0.5-10 micron,

d(50): 1-20 micron, and

d(90): 15-100 micron

within 20 seconds upon contact with an oral mucosal surface of a subject.

16. The method of claim 1, wherein the oral dissolvable film is suitable for oral administration (PO), buccal administration, sublingual administration, or mucosal administration.

17. The method of claim 1, wherein the oral dissolvable film has a moisture content of 3–13 wt.%.

18. The method of claim 1, wherein the oral dissolvable film is configured to disintegrate within 15 minutes upon buccal administration to a subject.

19. The method of claim 1, wherein the oral dissolvable film is configured to disintegrate within 30 seconds upon oral (PO) administration to a subject.

20. The method of claim 1, wherein the oral dissolvable film is configured for in vitro disintegration (USP<701> In-vitro Disintegration method) within 30 seconds.

21. The method of claim 1, wherein the oral dissolvable film exhibits at least one pharmacokinetic parameter selected from, (i) Tmax of between about 45 min to about 120 min, (ii) Cmax of at least 3.5 ng/ml, and (iii) AUC_{0-t} of at least 13 ng/hr/ml.

22. The method of claim 1, wherein the oral dissolvable film exhibits at least one pharmacokinetic parameter selected from, (i) Tmax of 1.5 hr, (ii) Cmax of 4.4 ng/ml, and (iii) AUC_{0-t} of 13.5 ng/hr/ml.

23. The method of claim 1, wherein the oral dissolvable film exhibits an in vivo dissolution time of no more than 20 minutes.

24. The method of claim 1, wherein the oral dissolvable film exhibits a bioavailability of at least 15%.

25. The method of claim 1, wherein the oral dissolvable film exhibits a stability of at least about 96% after nine months as measured under 40°C/75% RH accelerated conditions.