Transmucosal and transdermal delivery systems

Field of the Art

[001] The present invention relates generally to transmucosal (typically oral and/or nasal) and transdermal delivery systems and methods for making such delivery systems.

Background

[002] Oral formulations for the delivery of vitamins, minerals and active pharmaceutical ingredients include tablets, capsules (hard and soft shelled), lozenges, powders, emulsions and liquids. In order to benefit from such formulations and ensure optimum absorption of the vitamins, minerals or active pharmaceutical ingredients the subject must have a well functioning gastrointestinal system that ensures adequate absorption via the gastrointestinal tract. Not all subjects have a well functioning gastrointestinal system and therefore can not make use of such oral formulations. It is therefore beneficial to produce formulations that can be absorbed transdermal^ or via the oral and/or nasal mucosa, for example via the highly vascularized oral-buccal mucosa, such that the vitamins, minerals or active pharmaceutical ingredients are provided direct access to the body's systemic circulation system via capillaries thereby bypassing the gastrointestinal tract.

[003] Many active pharmaceutical ingredients, for example insulin, are typically administered via needle and syringe, and the like such as pens, jet injectors and pumps. Many people find such administration devices to be daunting, uncomfortable and generally inconvenient. It is therefore beneficial to produce formulations that can be absorbed via the oral and/or nasal mucosa, for example via the highly vascularized buccal/sublingual mucosa, such that the insulin is provided direct access to the body's systemic circulation system via capillaries thereby avoiding the need to break the skin.

[004] The present inventors have found that transdermal and transmucosal (oral and/or nasal) delivery systems comprising at least one non-ionic surfactant; at least one polyol; and at least one active agent can be successfully administered bypassing the gastrointestinal tract and avoiding the need to break the skin.

Summary of the Disclosure

[005] In one embodiment, there is provided a transmucosal and/or transdermal delivery system comprising at least one non-ionic surfactant; at least one polyol; and at least one active agent. The transmucosal delivery may be via the oral mucosa and/or the nasal muscosa.

[005a] Disclosed herein is a micellized transmucosal and/or transdermal delivery system formulated as a fine mist spray comprising: at least one non-ionic surfactant, wherein the non-ionic surfactant has a Hydrophile-Lipophile (HLB) value of from 12 to 16; at least one polyol; and at least one active agent, wherein the delivery system has a viscosity of from 5 cP to 35 cP when measured at 25°C.

[006] In certain embodiments the delivery system further comprises at least one oil. The at least one oil may be ethyl oleate, ethyl linoleate, caproic acid, caprylic acid, capric acid, or lauric acid, or a combination thereof. In particular embodiments the at least one oil is a natural oil or is derived from a natural oil. Typically the natural oil is coconut oil, palm kernel oil, palm oil, lemon oil, or sunflower oil, or a combination thereof.

[007] Typically the at least one non-ionic surfactant is selected from the group consisting of a polyethoxylated castor oil, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monoleate and tocopheryl polyethylene glycol succinate. In one embodiment the at least one non-ionic surfactant is a polyethoxylated castor oil. The at least one non-ionic surfactant may be obtained by reacting castor oil or hydrogenated castor oil with ethylene oxide. In one embodiment the at least one non-ionic surfactant is a polyethoxylated castor oil. In another embodiment the at least one non-ionic surfactant comprises glycerol polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, free polyethylene glycols and ethoxylated glycerol. In another embodiment the at least one non-ionic surfactant comprises glycerol polyethylene glycol hydroxystearate, fatty acid glycerol polyglycol esters, polyethylene glycols and glycerol ethoxylate.

[008] Typically the at least one polyol is selected from the group consisting of glycerol and propylene glycol. In one embodiment the at least one polyol is glycerol. In another embodiment the at least one polyol is propylene glycol.

[009] Typically the active agent is a pharmaceutically active ingredient. In exemplary embodiments the at least one active agent is selected from the group consisting of a vitamin, a mineral, a hormone, an amino acid, a peptide, a fatty acid, an antioxidant, a plant extract, a nutraceutical, a statin, an immunosuppressive agent, an antibiotic, a sedative, a steroid, a proton pump inhibitor (PPI), a selective serotonin reuptake inhibitor (SSRI), an angiotensin converting enzyme (ACE) inhibitor and combinations thereof.

[0010] In particular embodiments the active agent is a statin. The stain may be fat soluble or water soluble. In one embodiment the fat soluble statin is atorvastatin. In an exemplary embodiment the atorvastatin is atorvastatin calcium. In some embodiments the fat soluble statin is provided in oil or an oil mixture. In certain embodiments the at least one fat soluble statin is provided in ethanol or an ethanol and oil solution. In particular embodiments the statin is a water soluble statin. In one embodiment the water soluble statin is rosuvastatin. In an exemplary embodiment the atorvastatin is rosuvastatin calcium.

[0011] In some embodiments the at least one active agent is a vitamin. Typically, the vitamin is selected from the group consisting of vitamin A, vitamin B, vitamin C, vitamin D, vitamin E and vitamin K. In particular embodiments the vitamin is selected from the group consisting of vitamin B1 , vitamin B2, vitamin B5, vitamin B6, vitamin B7, vitamin B9 and vitamin B12. In one embodiment the vitamin is vitamin B12. The vitamin B12 may be methylcobalamin and/or cyanocobalamin. In another embodiment the vitamin is B6. The vitamin B6 may be pyridoxine hydrochloride. In particular embodiments the vitamin is D2 or vitamin D3. In one embodiment the vitamin D3 is cholecalciferol. In particular embodiments the vitamin is vitamin E. In one embodiment the vitamin E is d-alpha-tocopherol. In particular embodiments the vitamin is vitamin K2. In one embodiment the vitamin K2 is menaquinone-4 or menaquinone-7. In one embodiment the vitamin is a combination of vitamin D3 and vitamin K2.

[0012] In some embodiments the at least one active agent is an antioxidant. The antioxidant may be Coenzyme Q10.

[0013] In some embodiments the at least one active agent is a plant extract. The plant extract may be a natural extract or a synthetic version thereof. The plant extract may be resveratrol, cannabis, or hemp oil.

[0014] In some embodiments the at least one active agent is a mineral. Typically, the mineral is selected from the group consisting of zinc, calcium, chromium, cooper, iron, magnesium, manganese, phosphorus, potassium. In one embodiment the mineral is zinc.

[0015] In some embodiments the at least one active agent is a hormone. The hormone may be selected from the group consisting of melatonin, insulin, testosterone, progesterone and estrogen. The testosterone may be testosterone propionate. In an exemplary embodiment the hormone may be insulin. In another exemplary embodiment the hormone may be progestogen. In yet another exemplary embodiment the hormone may be beta-estradiol.

[0016] In another embodiment, the delivery system further comprises water. Typically, the ratio of water to the at least one active agent, at least one non-ionic surfactant and at least one polyol is from about 3:1 to about 2:1 by weight.

[0017] In another embodiment the delivery system further comprises a non-aqueous solvent or a mixture of a non-aqueous solvent and water. In certain embodiments the delivery system comprises ethanol and/or water.

[0018] In another embodiment, the delivery system further comprises at least one flavour. The at least one flavour may be a natural oil. The natural oil is typically peppermint oil or orange oil.

[0019] In another embodiment, the delivery system further comprises at least one acidulant. The at least one acidulant may be citric acid.

[0020] In another embodiment, the delivery system further comprises at least one preservative. The at least one preservative may be potassium sorbate or phenoxyethanol.

[0021] In another embodiment, the delivery system further comprises at least one sweetener. The at least one sweetener may be a natural sweetener. In one embodiment the natural sweetener is stevia.

[0022] In one embodiment the at least one non-ionic surfactant has an Hydrophile-Lipophile Balance (HLB) value of from about 8 to about 20. In particular embodiments the at least one non-ionic surfactant has an Hydrophile-Lipophile Balance (HLB) value of from about 12 to about 16.

[0023] The viscosity of the delivery system may be about 5 cP to about 35 cP. In one embodiment the viscosity of the delivery system is from about 10 cP to about 20 cP.

[0024] The average size of particles in the delivery system may be up to about 300 nm. In one embodiment the average particle size is from about 1 nm to about 200 nm. In another embodiment the average particle size is from about 5 nm to about 100 nm.

[0025] In one embodiment the ratio of the at least one active agent to the at least one non-ionic surfactant may be from about 1 :5 to about 1 :15 by weight. In one embodiment the ratio of the at least one non-ionic surfactant to the at least one polyol is from about 2:1 to about 1.5:1 by weight.

[0026] Also provided are oral and/or nasal transmucosal delivery systems and transdermal delivery systems comprising: at least one non-ionic surfactant; at least one polyol; and at least one active agent, wherein the at least one non-ionic surfactant has an Hydrophile-Lipophile Balance (HLB) value of from about 12 to about 16; the delivery system has a viscosity of from about 5 cP to about 35 cP; the delivery system has an average particle size of about <200 nm; the ratio of the at least one active agent to the at least one non-ionic surfactant is from about 1 :5 to about 1 :15 by weight; and the ratio of the at least one non-ionic surfactant to the at least one polyol is from about 2:1 to about 1.5:1 by weight. In a particular embodiment the viscosity of the delivery system is from about 10 cP to about 20 and/or the particle size of the delivery system is from about from about 1 nm to about 200 nm.

[0027] In one embodiment, there is provided a method for preventing and/or reducing blood cholesterol in a subject, the method comprising administering an effective amount of the delivery

system as defined herein to the subject, wherein the active agent in the delivery system is a statin.

[0027a] Disclosed herein is the use of a delivery system as defined herein in the manufacture of a medicament for reducing blood cholesterol in a subject in need thereof, wherein the active agent in the delivery system is a statin.

[0028] In one embodiment, there is provided a method for treating dyslipidemia in a subject, the method comprising administering an effective amount of the delivery system as defined herein to the subject, wherein the active agent in the delivery system is a statin.

[0028a] Disclosed herein is the use of a delivery system as defined herein in the manufacture of a medicament for treating dyslipidemia, wherein the active agent in the delivery system is a statin.

[0029] A method for preventing and/or treating cardiovascular disease in a subject, the method comprising administering an effective amount of the delivery system as defined herein to the subject, wherein the active agent in the delivery system is a statin.

[0029a] Disclosed herein is the use of a delivery system as defined herein in the manufacture of a medicament for preventing and/or treating cardiovascular disease, wherein the active agent in the delivery system is a statin.

[0030] A method for treating diabetes, for regulating blood glucose levels and/or for preventing or treating hyperglycaemia in a subject, the method comprising administering an effective amount of the delivery system as defined hereinto the subject, wherein the active agent in the delivery system is insulin.

[0030a] Disclosed herein is the use of a delivery system as defined herein in the manufacture of a medicament for treating diabetes, for regulating blood glucose levels and/or for preventing or treating hyperglycaemia, wherein the active agent in the delivery system is insulin.

Detailed Description

[0031] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the disclosure belongs. Although any methods and materials similar or equivalent to those described herein can

Claims

1. A micellized transmucosal and/or transdermal delivery system formulated as a fine mist spray comprising:
at least one non-ionic surfactant, wherein the non-ionic surfactant has a Hydrophile-Lipophile (HLB) value of from 12 to 16;
at least one polyol; and
at least one active agent,
wherein the delivery system has a viscosity of from 5 cP to 35 cP when measured at 25°C.

2. The delivery system of claim 1, wherein the delivery system is delivered vial the oral or nasal mucosa.

3. The delivery system of claim 1 or 2, further comprising at least one oil.

4. The delivery system of claim 3, wherein the at least one oil is ethyl oleate, ethyl linoleate, caproic acid, caprylic acid, capric acid, or lauric acid, or a combination thereof.

5. The delivery system of claim 4, wherein the at least one oil is a natural oil or is derived from a natural oil.

6. The delivery system of claim 5, wherein the natural oil is coconut oil, palm kernel oil, palm oil, lemon oil, or sunflower oil, or a combination thereof.

7. The delivery system of any one of claims 1 to 6, wherein the at least one non-ionic surfactant is selected from the group consisting of a polyethoxylated castor oil, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monoleate, tocopheryl polyethylene glycol succinate and mixtures thereof.

8. The delivery system of any one of claims 1 to 6, wherein the at least one non-ionic surfactant is obtained by reacting castor oil or hydrogenated castor oil with ethylene oxide.

9. The delivery system of any one of claims 1 to 7, wherein the at least one non-ionic surfactant comprises one or more of glycerol polyethylene glycol ricinoleate, glycerol

polyethylene glycol hydroxystearate, fatty acid esters of polyethylene glycol, fatty acid glycerol polyglycol esters, polyethylene glycols, free polyethylene glycols and ethoxylated glycerol.

10. The delivery system of any one of claims 1 to 9, wherein the at least one polyol is selected from the group consisting of glycerol and propylene glycol.

11. The delivery system of any one of claims 1 to 10, further comprising a non-aqueous solvent or a mixture of a non-aqueous solvent and water.

12. The delivery system of any one of claims 1 to 10, further comprising ethanol or water.

13. The delivery system of any one of claims 1 to 12, wherein the at least one active agent is provided in an alcohol and oil solution.

14. The delivery system of any one of claims 1 to 13, wherein the at least one active agent is selected from a vitamin, a mineral, a hormone, an amino acid, a peptide, a fatty acid, an antioxidant, a plant extract, a nutraceutical, a statin, an immunosuppressive agent, an antibiotic, a sedative, a steroid, a proton pump inhibitor (PPI), a selective serotonin reuptake inhibitor (SSRI), an angiotensin converting enzyme (ACE) inhibitor and combinations thereof.

15. The delivery system of claim 14, wherein the statin is a fat soluble statin or a water soluble statin.

16. The delivery system of claim 15, wherein the fat soluble statin is atorvastatin calcium.

17. The delivery system of claim 15, wherein the water soluble statin is rosuvastatin calcium.

18. The delivery system of claim 14, wherein the at least one active agent is insulin.

19. The delivery system of claim 14, wherein the vitamin is selected from the group consisting of vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, vitamin B1, vitamin B2, vitamin B5, vitamin B6, vitamin B7, vitamin B9, vitamin B12 and combinations thereof.

20. The delivery system of claim 14, wherein the at least one active agent is a combination of vitamin D3 and vitamin K2 or a combination of vitamin B12 and vitamin E.

21. The delivery system of claim 14, wherein the antioxidant is Coenzyme Q10.

22. The delivery system of claim 14, wherein the plant extract is a natural extract or a synthetic version thereof.

23. The delivery system of claim 22, wherein the plant extract comprises resveratrol, a cannabis extract or one or more cannabinoids, or is hemp seed oil.

24. The delivery system of claim 14, wherein the mineral is selected from the group consisting of zinc, calcium, chromium, copper, iron, magnesium, manganese, phosphorus, potassium.

25. The delivery system of claim 14, wherein the hormone is selected from the group consisting of melatonin, testosterone, insulin, progesterone and estrogen.

26. The delivery system of claim 25, wherein the testosterone is testosterone propionate.

27. The delivery system of any one of claims 1 to 26, further comprising at least one flavour, at least one acidulant, at least one preservative, and/or at least one sweetener.

28. The delivery system of claim 27, wherein the at least one flavour is a natural oil.

29. The delivery system of claim 27, wherein the at least one acidulant is citric acid.

30. The delivery system of claim 27, wherein the at least one preservative is potassium sorbate or phenoxyethanol.

31. The delivery system of claim 27, wherein the at least one sweetener is a natural sweetener.

32. The delivery system of any one of claims 1 to 31, wherein the ratio of the at least one

active agent to the at least one non-ionic surfactant is from 1:5 to 1:15 by weight.

33. The delivery system of any one of claims 1 to 31, wherein the ratio of the at least one non-ionic surfactant to the at least one polyol is from 2:1 to 1.5:1 by weight.

34. Use of a delivery system of any one of claims 1 to 33 in the manufacture of a medicament for reducing blood cholesterol in a subject in need thereof, wherein the active agent in the delivery system is a statin.

35. Use of a delivery system of any one of claims 1 to 33 in the manufacture of a medicament for treating dyslipidemia, wherein the active agent in the delivery system is a statin.

36. Use of a delivery system of any one of claims 1 to 33 in the manufacture of a medicament for preventing and/or treating cardiovascular disease, wherein the active agent in the delivery system is a statin.

37. Use of a delivery system of any one of claims 1 to 33 in the manufacture of a medicament for treating diabetes, for regulating blood glucose levels and/or for preventing or treating hyperglycaemia, wherein the active agent in the delivery system is insulin.