FORMULATION FOR ORAL DELIVERY OF PROTEINS, PEPTIDES AND SMALL MOLECULES WITH POOR PERMEABILITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority of U.S. Provisional Application No. 62/832,508, filed April 11, 2019, the entire contents of which are incorporated herein by reference.

FIELD OF THE DISCLOSURE

[0002] This disclosure relates to a formulation for oral delivery of proteins, peptides and small molecules with poor permeability. More specifically, this disclosure relates to a pharmaceutical formulation intended for oral delivery of any molecule synthetic or natural with poor permeability or salts or solvates thereof having a therapeutic activity.

BACKGROUND OF THE INVENTION

[0003] Poorly permeable molecules are compounds that have poor absorption through the intestinal membrane. As such, they are administered intravenously or subcutaneously. Because of their poor absorption through the intestinal membrane, their clinical use is considerably restricted given the need to be administered IV and dosed several times a day (e.g., insulin for diabetics). These poorly permeable compounds are identified as BCS class III and class IV compounds in the classification proposed by Amidon GL et al in *A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability* (Pharm Res. 1995 Mar;12(3):413-20.), which is hereby incorporated by reference in its entirety.

SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a pharmaceutical formulation, comprising:

a synthetic or natural poorly permeable calcitonin gene-related peptide (CGRP) inhibitor or salt or solvate thereof in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids in an amount of 10-50 wt.% of the total weight of the formulation.

[0003b] In another aspect of the present disclosure, there is provided a delayed release pharmaceutical dosage form comprising:

a pharmaceutical formulation comprising:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the delayed release dosage form is a coated dosage form whose release is pH dependent.

[0003c] In a further aspect of the present disclosure, there is provided a pharmaceutical formulation for use in treating a patient, wherein an effective amount of the pharmaceutical formulation is to be administered to the patient, and wherein the pharmaceutical formulation comprises:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids in an amount of 10-50 wt.% of the total weight of the formulation.

[0004] Applicants have developed formulations for orally administered molecules with poor permeability. The molecule may be a CGRP inhibitor. These formulations are highly beneficial for patients that require dosing several times a day. In order to prepare such formulations for oral delivery of poorly permeable CGRP inhibitors, Applicants had to overcome at least this poor permeability against the intestinal membrane; and for some of those inhibitors in particular peptides and proteins the chemical and physical instability in the gastrointestinal tract and specifically, the loss of activity due to acidic conditions in the

stomach; and enzymatic degradation throughout the intestine. Accordingly, Applicants developed delayed release coated dosage form that can deliver poorly permeable CGRP inhibitors in the intestine with *in-situ* production of permeation enhancer to increase its bioavailability.

[0005] In U.S. Patent No. 9,259,389, the inventors found that a digestible reverse emulsion can increase bioavailability of oligosaccharides. Unexpectedly, Applicants found that a solution of lipid excipients with a poorly permeable molecule dispersed as a powder in the formulation can allow better results of bioavailability for this specific class of molecules (i.e., BCS Class III and Class IV compounds in the classification proposed by Amidon GL et al (Pharm Res. 1995 Mar;12(3):413-20.)). Specifically, Applicants found that for poorly permeable molecules, specifically BCS Class III protein and peptide compounds, the formulation without addition of water can be beneficial. Without being bound by any theory, it is believed that water tends to cause this class of the poorly permeable molecules to aggregate together. More particularly, Applicants found that when they did not include water in the formulation comprising a solution of lipid based excipients with the poorly permeable BCS Class III protein or peptide molecule or salt dispersed as a powder in the formulation, higher results of bioavailability were achieved for this specific class of molecules. In contrast, the removal of water was detrimental for saccharides of U.S. Patent No. 9,259,389.

[0006] In addition, Applicants can increase the drug load when the API can be dispersed as a powder without the need to solubilize the active pharmaceutical ingredient ("API") in water given there is no need to solubilize the API. Furthermore, the formulation is inherently more physically stable because lipid excipients can be in solution as a single phase. Thus, there may be no need to add a stabilizing agent such as silicon dioxide to stabilize the phases. In some examples, a thickener may be added for manufacturing purposes to maintain homogeneity of the API powder in suspension during the process. In some examples, the thickener can be silicon dioxide. Lastly, compared to other formulations found in literature using excipients such as permeation enhancers, the formulations disclosed herein can use only generally recognized as safe excipients or already marketed ingredients.

[0007] In some examples, a pharmaceutical formulation comprising a synthetic or natural poorly permeable CGRP inhibitors or salt or solvate thereof in an amount 0.01-20 wt.% of the total weight of the formulation; a lipophilic phase comprising triglycerides of

fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and at least one lipophilic surfactant comprising partial esters of polyol and fatty acids in an amount of 10-50 wt.% of the total weight of the formulation. In some examples, the synthetic or natural poorly permeable CGRP inhibitors or salt or solvate thereof is a CGRP antibody, a CGRP receptor antibody, an antigen-binding fragment from a CGRP antibody or a CGRP receptor antibody, a CGRP infusion inhibitory protein, a CGRP bio-neutralizing agent, a small molecule CGRP receptor antagonist, a small molecule CGRP inhibitor, or a polypeptide CGRP inhibitor. In some examples, the small molecule CGRP receptor antagonist is (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500). In some examples, the formulation comprises at least one hydrophilic surfactant with a hydrophilic lipophilic balance ("HLB") above 10 in an amount of 1-30 wt.% of the total weight of the formulation. In some examples, the at least one hydrophilic surfactant is selected from the group consisting of polyoxyethylene (20) monooleate, PEG 8 caprylic/capric glycerides, PEG 6 caprylic/capric glycerides, poly(oxyethylene)(4)Lauryl ether and mixtures thereof. In some examples, the triglycerides of fatty acids are medium chain fatty acids. In some examples, the lipophilic surfactant comprises a mixture of mono and diglyceride of medium chain fatty acids. In some examples, the formulation does not include water. In some examples, a delayed release pharmaceutical dosage form comprises any of the formulations described above, wherein the delayed release dosage form is a coated dosage form whose release is pH dependent. In some examples, a method for treating a patient comprises administering to a person in need thereof an effective amount of any of the formulations described above.

[0008] Additional advantages will be readily apparent to those skilled in the art from the following detailed description. The examples and descriptions herein are to be regarded as illustrative in nature and not restrictive.

[0009] All publications, including patent documents, scientific articles and databases, referred to in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication were individually incorporated by reference. If a definition set forth herein is contrary to or otherwise inconsistent with a definition set forth in the patents, applications, published applications and other publications that are herein incorporated by reference, the definition set forth herein prevails over the definition that is incorporated herein by reference.

CLAIMS

1. A pharmaceutical formulation, comprising:

a synthetic or natural poorly permeable calcitonin gene-related peptide (CGRP) inhibitor or salt or solvate thereof in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids in an amount of 10-50 wt.% of the total weight of the formulation.

2. The formulation of claim 1, wherein the synthetic or natural poorly permeable CGRP inhibitor is a CGRP antibody, a CGRP receptor antibody, an antigen-binding fragment from a CGRP antibody or a CGRP receptor antibody, a CGRP infusion inhibitory protein, a CGRP bio-neutralizing agent, a small molecule CGRP receptor antagonist, a small molecule CGRP inhibitor, or a polypeptide CGRP inhibitor.

3. The formulation of claim 1, wherein the synthetic or natural poorly permeable CGRP inhibitor is a small molecule CGRP receptor antagonist.

4. The formulation of claim 3, wherein the small molecule CGRP receptor antagonist is (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500).

5. The formulation of claim 1, further comprising at least one hydrophilic surfactant with a hydrophilic lipophilic balance (“HLB”) above 10 in an amount of 1-30 wt.% of the total weight of the formulation.

6. The formulation of claim 5, wherein the at least one hydrophilic surfactant is selected from the group consisting of polyoxyethylene (20) monooleate, PEG 8 caprylic/capric glycerides, PEG 6 caprylic/capric glycerides, poly(oxyethylene)(4)Lauryl ether and mixtures thereof.

7. The formulation of claim 1, wherein the triglycerides of fatty acids are medium chain fatty acids.

8. The formulation of claim 1, wherein the lipophilic surfactant comprises a mixture of mono and diglyceride of medium chain fatty acids.

9. The formulation of claim 1, wherein the formulation does not include water.

10. A delayed release pharmaceutical dosage form comprising:

a pharmaceutical formulation comprising:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the delayed release dosage form is a coated dosage form whose release is pH dependent.

11. A pharmaceutical formulation for use in treating a patient, wherein an effective amount of the pharmaceutical formulation is to be administered to the patient, and wherein the pharmaceutical formulation comprises:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids in an amount of 10-50 wt.% of the total weight of the formulation.

12. The pharmaceutical formulation for use of claim 11, wherein the synthetic or natural poorly permeable CGRP inhibitor is a CGRP antibody, a CGRP receptor antibody, an antigen-binding fragment from a CGRP antibody or a CGRP receptor antibody, a CGRP infusion inhibitory protein, a CGRP bio-neutralizing agent, a small molecule CGRP receptor antagonist, a small molecule CGRP inhibitor, or a polypeptide CGRP inhibitor.

13. The pharmaceutical formulation for use of claim 11, wherein the synthetic or natural poorly permeable CGRP inhibitor is a small molecule CGRP receptor antagonist.

14. The pharmaceutical formulation for use of claim 13, wherein the small molecule CGRP receptor antagonist is (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500).

15. The pharmaceutical formulation for use of claim 11, wherein the pharmaceutical formulation comprises at least one hydrophilic surfactant with a hydrophilic lipophilic balance (“HLB”) above 10 in an amount of 1-30 wt.% of the total weight of the formulation.

16. The pharmaceutical formulation for use of claim 15, wherein the at least one hydrophilic surfactant is selected from the group consisting of polyoxyethylene (20) monooleate, PEG 8 caprylic/capric glycerides, PEG 6 caprylic/capric glycerides, poly(oxyethylene)(4)Lauryl ether and mixtures thereof.

17. The pharmaceutical formulation for use of claim 11, wherein the triglycerides of fatty acids are medium chain fatty acids.

18. The pharmaceutical formulation for use of claim 11, wherein the lipophilic surfactant comprises a mixture of mono and diglyceride of medium chain fatty acids.

19. The pharmaceutical formulation for use of claim 11, wherein the formulation does not include water.

20. The pharmaceutical formulation for use of claim 11, wherein the pharmaceutical formulation is in a delayed release dosage form comprising a coated dosage form whose release is pH dependent.