BCS system classifies APIs according to their solubility and permeability characteristics, where BCS Class II APIs are characterized by low solubility and high permeability, and BCS Class III APIs are characterized by high solubility and low permeability. Although some PEs can help Class II and III APIs overcome the oral mucosa barrier, it is difficult to predict which PEs will work with a given API. The selection of appropriate PEs for each type of API is largely based on empirical, trial-and-error experience, and most work on PEs to date has focused on improving drug permeation of intestinal and dermal tissues. The effect of PEs on pre-gastric absorption through the oral mucosal tissue, especially in a freeze-dried orally dissolvable tablet (ODT) format, is less established. As a result, formulations are often unsuccessful, and the required reformulation activities increase drug development time and incur additional development costs.

[0006] Disclosed herein are pharmaceutical formulations and compositions and methods of making thereof utilizing appropriate PEs for a given Class II and/or Class III API.

[0007] In one aspect, the present disclosure refers to a pharmaceutical composition comprising: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of less than 0.1 mg/mL and a log P value greater than 2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, a micelle, or a fatty acid; a matrix former; and a structure former. In some examples, a pharmaceutical composition includes a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of less than 0.1 mg/mL and a log P value greater than 2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, a micelle, or a fatty acid; a matrix former; and a structure former. In some examples, the permeation enhancer comprises a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10. In some examples, a molar ratio of API to the surfactant is 5:1 to 1:5 and/or the pharmaceutical composition comprises 0.5-20 wt.% the surfactant. In some examples, the pharmaceutical composition includes a pH modifier. In some examples, the permeation enhancer comprises a bile salt. In some examples, a molar ratio of API to the bile salt is 15:1 to 1:15 and/or the pharmaceutical composition comprises 1-20 wt.% the bile salt. In some examples, the permeation enhancer comprises a fatty acid. In some examples, a molar ratio of API to fatty acid is 3:1 to 1:3 and/or the pharmaceutical composition comprises 0.25-5 wt.% fatty acid. In some examples, the permeation enhancer comprises counterions. In some examples, a molar ratio of API to counterions is 6:1 to 1:6 and/or the pharmaceutical composition comprises 0.1-25 wt.% counterions. In some examples, the pharmaceutical composition includes a pH modifier. In some examples, the pharmaceutical composition includes 25-60 wt.% matrix former. In some examples, the matrix former comprises gelatin, pullulan, starch, or combinations thereof.

In some examples, the gelatin comprises fish gelatin, bovine gelatin, porcine gelatin, or combination thereof. In some examples, the gelatin is fish gelatin and the fish gelatin is high molecular weight fish gelatin. In some examples, the pharmaceutical composition includes 20-45 wt.% structure former. In some examples, the structure former comprises mannitol. In some examples, the pharmaceutical composition comprises 1-35 wt.% the BCS Class II API or pharmaceutically acceptable salt or solvate thereof.

[0008] In one aspect, the present disclosure refers to a pharmaceutical composition comprising: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 0.1-1 mg/mL and a log P value of 1-2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, or a micelle; a matrix former; and a structure former. In some examples, a pharmaceutical composition includes: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 0.1-1 mg/mL and a log P value of 1-2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, or a micelle; a matrix former; and a structure former. In some examples, the permeation enhancer comprises a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10. In some examples, a molar ratio of API to surfactant is 5:1 to 1:5 and/or the pharmaceutical composition comprises 0.5-20 wt.% surfactant. In some examples, the permeation enhancer comprises a bile salt. In some examples, a molar ratio of API to bile salt is 15:1 to 1:15 and/or the pharmaceutical composition comprises 1-20 wt.% bile salt. In some examples, the permeation enhancer comprises counterions. In some examples, a molar ratio of API to counterions is 6:1 to 1:6 and/or the pharmaceutical composition comprises 0.1-25 wt.% counterions. In some examples, the pharmaceutical composition includes a pH modifier. In some examples, the pharmaceutical composition includes 1-35 wt.% the pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 0.1-1 mg/mL and a log P value of 1-2.5. In some examples, the pharmaceutical composition includes 25-60 wt.% matrix former. In some examples, the matrix former comprises gelatin, pullulan, starch, or combinations thereof. In some examples, the gelatin comprises fish gelatin, bovine gelatin, porcine gelatin, or combination thereof. In some examples, the gelatin is fish gelatin and the fish gelatin is high molecular weight fish gelatin. In some examples, the pharmaceutical composition includes 20-45 wt.% structure former. In some examples, the structure former comprises mannitol.

[0009] In one aspect, the present disclosure refers to a pharmaceutical composition comprising: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 1-10 mg/mL and a log P value of less than 1; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, or a bile salt; a matrix former; and a structure former. In some examples, a pharmaceutical composition includes: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active

pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 1-10 mg/mL and a log P value of less than 1; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, or a bile salt; a matrix former; and a structure former. In some examples, the permeation enhancer comprises a bile salt. In some examples, a molar ratio of API to bile salt is 15:1 to 1:15 and/or the pharmaceutical composition comprises 1-20 wt.% bile salt. In some examples, the permeation enhancer comprises counterions. In some examples, a molar ratio of API to counterions is 6:1 to 1:6 and/or the pharmaceutical composition comprises 0.1-25 wt.% counterions. In some examples, the pharmaceutical composition includes a pH modifier. In some examples, a pharmaceutical composition includes 25-60 wt.% matrix former. In some examples, the matrix former comprises gelatin, pullulan, starch, or combinations thereof. In some examples, the gelatin comprises fish gelatin, bovine gelatin, porcine gelatin, or combination thereof. In some examples, the gelatin is fish gelatin and the fish gelatin is high molecular weight fish gelatin. In some examples, the pharmaceutical composition includes 20-45 wt.% structure former. In some examples, the structure former comprises mannitol. In some examples, the pharmaceutical composition includes 1-35 wt.% the BCS Class III API or pharmaceutically acceptable salt or solvate thereof.

[0010] In one aspect, the present disclosure refers to a pharmaceutical composition comprising: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 10-33 mg/mL and a log P value of less than 1; a permeation enhancer comprising at least one selected from the group of counterions or a pH modifier; a matrix former; and a structure former. In some examples, a pharmaceutical composition includes a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 10-33 mg/mL and a log P value of less than 1; a permeation enhancer comprising at least one selected from the group of counterions or a pH modifier; a matrix former; and a structure former. In some examples, the permeation enhancer comprises counterions. In some examples, a molar ratio of API to counterions is 6:1 to 1:6 and/or the pharmaceutical composition comprises 0.1-25 wt.% counterions. In some examples, the pharmaceutical composition includes 25-60 wt.% matrix former. In some examples, the matrix former comprises gelatin, pullulan, starch, or combinations thereof. In some examples, the gelatin comprises fish gelatin, bovine gelatin, porcine gelatin, or combination thereof. In some examples, the gelatin is fish gelatin and the fish gelatin is high molecular weight fish gelatin. In some examples, the pharmaceutical compositions include 20-45 wt.% structure former. In some examples, the structure former comprises mannitol. In some examples, the pharmaceutical composition includes 1-35 wt.% the pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class

II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 10-33 mg/mL and a log P value of less than 1.

[0011] In some examples, the pharmaceutical composition is a solid dosage form. In some examples, a method of treating a patient includes placing the solid dosage form in an oral cavity of a person in need of the treatment. In some examples, the placement in the oral cavity is placement on or under the tongue or in the buccal or pharyngeal region. In some examples, the pharmaceutical composition is provided for use in therapy. In one aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein, for use in therapy. In some examples, the pharmaceutical composition is provided for use in a method of treating a patient, the method comprising placing the pharmaceutical composition in an oral cavity of a person in need of the treatment. Placement in the oral cavity may be placement on or under the tongue or in the buccal or pharyngeal region. In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a patient, wherein the medicament is to be placed in an oral cavity of a person in need of the treatment.

[0012] In one aspect, the present disclosure refers to a method of forming a solid dosage form, the method comprising: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of less than 0.1 mg/mL and a log P value greater than 2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, a micelle, or a fatty acid; 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, a method of forming a solid dosage form includes: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of less than 0.1 mg/mL and a log P value greater than 2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, a micelle, or a fatty acid; 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, the permeation enhancer comprises a surfactant with a hydrophilic lipophilic balance greater than 10. In some examples, the pharmaceutical formulation comprises 0.01-5 wt.% the surfactant. In some examples, the surfactant has a concentration of 0.1-30 x its critical micellar concentrations (CMC) in the pharmaceutical formulation. In some examples, the surfactant has a concentration of 0.5-3 x CMC in the pharmaceutical formulation. In some examples, the pharmaceutical formulation has a molar ratio of API to the surfactant of 5:1 to 1:5. In some examples, the permeation enhancer comprises a bile salt. In some examples, the pharmaceutical formulation comprises 0.25-5 wt.% bile salt. In some examples, the bile salt has a concentration of 0.5-5 x CMC in the pharmaceutical formulation. In some examples, the pharmaceutical formulation has a molar ratio of API to the bile salt of 15:1 to 1:15. In some examples, the molar ratio is 5:1 to 1:5. In some examples, the permeation enhancer comprises a fatty acid. In some examples, the pharmaceutical formulation comprises 0.03-0.15 wt.% fatty acid. In some examples, the

pharmaceutical formulation has a molar ratio of API to fatty acid of 3:1 to 1:3. In some examples, the permeation enhancer comprises counterions. In some examples, the pharmaceutical formulation comprises 0.025-5 wt.% counterions. In some examples, the pharmaceutical formulation has a molar ratio of API to counterions of 6:1 to 1:6. In some examples, the molar ratio is 3:1 to 1:3. In some examples, the pharmaceutical formulation comprises a pH modifier. In some examples, the pharmaceutical formulation comprises 0.1-5 wt.% the BCS Class II API or pharmaceutically acceptable salt or solvate thereof.

[0013] In one aspect, the present disclosure refers to method of forming a solid dosage form, the method comprising: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 0.1-1 mg/mL and a log P value 1-2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, or a micelles; 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, a method of forming a solid dosage form includes: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 0.1-1 mg/mL and a log P value 1-2.5; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, a surfactant with a hydrophilic lipophilic balance (HLB) greater than 10, a bile salt, or a micelles; 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, the permeation enhancer comprises a surfactant with a hydrophilic lipophilic balance greater than 10. In some examples, the pharmaceutical formulation comprises 0.01-5 wt.% the surfactant. In some examples, the surfactant has a concentration 0.1-30 x its critical micellar concentrations (CMC) of in the pharmaceutical formulation. In some examples, the surfactant has a concentration of 0.5-3 x CMC in the pharmaceutical formulation. In some examples, the pharmaceutical formulation has a molar ratio of API to the surfactant of 5:1 to 1:5. In some examples, the permeation enhancer comprises a bile salt. In some examples, the pharmaceutical formulation comprises 0.25-5 wt.% bile salt. In some examples, the bile salt has a concentration of 0.5-5 x CMC in the pharmaceutical formulation. In some examples, the pharmaceutical formulation has a molar ratio of API to the bile salt of 15:1 to 1:15. In some examples, the molar ratio is 5:1 to 1:5. In some examples, the permeation enhancer comprises counterions. In some examples, the pharmaceutical formulation comprises 0.025-5 wt.% counterions. In some examples, the pharmaceutical formulation has a molar ratio of API to counterions of 6:1 to 1:6. In some examples, the molar ratio is 3:1 to 1:3. In some examples, the pharmaceutical formulation comprises a pH modifier. In some

examples, the pharmaceutical formulation comprises 0.1-5 wt.% BCS Class II API or pharmaceutically acceptable salt or solvate thereof.

[0014] In one aspect, the present disclosure refers to a method of forming a solid dosage form, the method comprising: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 1-10 mg/mL and a log P value less than 1; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, or a bile salt; 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, a method of forming a solid dosage form includes: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 1-10 mg/mL and a log P value less than 1; a permeation enhancer comprising at least one selected from the group of counterions, a pH modifier, or a bile salt; 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, the permeation enhancer comprises a bile salt. In some examples, the pharmaceutical formulation comprises 0.25-5 wt.% bile salt. In some examples, the bile salt has a concentration of 0.5-5 x CMC in the pharmaceutical formulation. In some examples, the pharmaceutical formulation has a molar ratio of API to the bile salt of 15:1 to 1:15. In some examples, the molar ratio is 5:1 to 1:5. In some examples, the permeation enhancer comprises counterions. In some examples, the pharmaceutical formulation comprises 0.025-5 wt.% counterions. In some examples, the pharmaceutical formulation has a molar ratio of API to counterions of 6:1 to 1:6. In some examples, the pharmaceutical formulation comprises a pH modifier. In some examples, the molar ratio is 3:1 to 1:3. In some examples, the pharmaceutical formulation comprises 0.1-5 wt.% BCS Class III API or pharmaceutically acceptable salt or solvate thereof.

[0015] In one aspect, the present disclosure refers to a method of forming a solid dosage form, the method comprising: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 10-33 mg/mL and a log P value less than 1; a permeation enhancer comprising at least one selected from the group of counterions or a pH modifier, 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, a method of forming a solid dosage form includes: dosing a pharmaceutical formulation into a preformed mold, wherein the pharmaceutical formulation comprises: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class III active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 10-33 mg/mL and a log P value less than 1; a permeation enhancer comprising at least one selected from the group of counterions or a pH modifier, 1-10 wt.% matrix former; and 1-10 wt.% of a structure former; freezing the dosed pharmaceutical formulation; and freeze-drying the frozen pharmaceutical formulation to form the dosage form. In some examples, the permeation enhancer comprises counterions. In some examples, the pharmaceutical formulation comprises 0.025-5 wt.% counterions. In some examples, the pharmaceutical formulation has a molar ratio of API to counterions of 6:1 to 1:6. In some examples, the molar ratio is 3:1 to 1:3. In some examples, the

pharmaceutical formulation comprises a pH modifier. In some examples, the pharmaceutical formulation comprises 0.1-5 wt.% BCS Class III API or pharmaceutically acceptable salt or solvate thereof. In some examples, the matrix former comprises gelatin, pullulan, starch, or combinations thereof. In some examples, the gelatin comprises fish gelatin, bovine gelatin, porcine gelatin, or combination thereof. In some examples, the gelatin is fish gelatin and the fish gelatin is high molecular weight fish gelatin. In some examples, the structure former comprises mannitol.

[0016] In one aspect, the present disclosure refers to a pharmaceutical composition comprising: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 0.1-1 mg/mL and a log P value of 1-2.5; a permeation inhibitor comprising at least one selected from the group of a surfactant with a hydrophilic lipophilic balance (HLB) less than 10 or a fatty acid; a matrix former; and a structure former. In some examples, a pharmaceutical composition includes: a pharmaceutically effective amount of a biopharmaceutics classification system (BCS) Class II active pharmaceutical ingredient (API) or pharmaceutically acceptable salt or solvate thereof having a solubility of 0.1-1 mg/mL and a log P value of 1-2.5; a permeation inhibitor comprising at least one selected from the group of a surfactant with a hydrophilic lipophilic balance (HLB) less than 10 or a fatty acid; a matrix former; and a structure former. In some examples, the permeation inhibitor comprises a fatty acid. In some examples, the pharmaceutical composition comprises 0.25-0.5 wt.% fatty acid. In some examples, the pharmaceutical composition has a molar ratio of API to fatty acid of 3:1 to 1:3. In some examples, the permeation inhibitor comprises the surfactant with a HLB less than 10. In some examples, a molar ratio of API to surfactant is 5:1 to 1:5.

[0017] 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.

[0018] 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.

BRIEF DESCRIPTION OF THE FIGURES

[0019] FIG. 1A shows various pharmaceutical pre-formulations (binary mixture of API and permeation enhancer) and piroxicam pharmaceutical compositions (ODTs) tested for permeability herein when surfactants are used as permeation agents.