Table A. Exemplary Fatty Acid Ester Content of Polysorbate 20

Fatty Acid Ester	Composition (%)	No. of carbons
Caproic	≤ 1	6
Caprylic	≤10	8
Capric	≤ 10	10
Lauric	40 – 60	12
Myristic	14 – 25	14
Palmitic	7 – 15	16
Stearic	≤7	18
Oleic	≤11	18:1
Linolenic	≤ 3	18:3

[005] PS20 can hydrolytically degrade in biopharmaceutical drug products, causing the appearance of visible and sub-visible particles. Enzymes (for example, lipases, esterases, etc.) are believed to cleave PS20 at the ester bond resulting in the formation of free fatty acids (FFAs) and free head groups or polyols. FFAs are poorly soluble in aqueous solutions and may result in visible or sub-visible particle formation either more frequently or earlier in drug product manufacture and storage with substantial implications to long-term protein stability and drug product shelf life.

SUMMARY

[006] The present disclosure provides PS20 formulations with particular fatty acid ester distributions. In some examples, the polysorbate formulations herein may be less susceptible to particle formation by degradation that results in free fatty acids. The present disclosure also relates to formulations comprising the polysorbates. In some examples, these may help to lengthen the shelf life of pharmaceutical formulations and/or reduce waste caused by degraded and expired formulations.

[006a] In one aspect, the present disclosure provides a polysorbate 20 composition comprising fatty acid esters comprising 1.0 % or less caproate, greater than or equal to 2.6 % and less than or equal to 6.6% caprylate, greater than or equal to 2.4 % and less than or equal to 6.4 % caprate, greater than or equal to 55.0 % and less than or equal to 60.0 % laurate, greater than or equal to 14.1 % and less than or equal to 18.1 % myristate, greater than or equal to 7.0 % and less than or equal to 10.9 % palmitate, and less than or equal to 2.0 % stearate.

[006b] In one aspect, the present disclosure provides a pharmaceutical formulation comprising a drug and a pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable excipient comprises: a polysorbate 20 composition comprising fatty acid esters, wherein the fatty acid esters of the polysorbate 20 composition comprise: 1.0 % or less caproate, greater than or equal to 2.6 % and less than or equal to 6.6% caprylate, greater than or equal to 2.4 % and less than or equal to 6.4 % caprate, greater than or equal to 55.0 % and less than or equal to 60.0 % laurate, greater than or equal to 14.1 % and less than or equal to 18.1 % myristate, greater than or equal to 7.0 % and less than or equal to 10.9 % palmitate, and less than or equal to 2.0 % stearate.

[007] Additional objects and advantages will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice. The objects and advantages will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the claims.

[008] The present disclosure provides, inter alia, compositions of PS20 with particular fatty acid ester distributions that may be less susceptible to particle formation by

degradation that results in free fatty acids, and pharmaceutical formulations containing these PS20 compositions. The disclosure herein includes, for example, examples such as the following:

[009] Example 1 is a polysorbate 20 composition comprising fatty acid esters comprising 1 % or less caproate, greater than 2.3 % and less than or equal to 10 % caprylate, greater than 2.8 % and less than or equal to 10 % caprate, greater than 52.1 % and less than or equal to 60 % laurate, greater than or equal to 14 % and less than 18.3 % myristate, greater than or equal to 7 % and less than 11.9 % palmitate, and less than 6.4 % stearate.

[0010] Example 2 is the composition of example 1, comprising greater than 2.5 %, or greater than 3.5 %, or greater than 4 %, or greater than or equal to 4.6 %, and less than or equal to 10 % of caprylate.

[0011] Example 3 is the composition of example 1 or 2, comprising greater than 3 %, or greater than 3.5 %, or greater than 4 %, or greater than or equal to 4.4 %, and less than or equal to 10 % caprate.

[0012] Example 4 is the composition of any one of the previous examples, comprising greater than 53 %, greater than 55 %, greater than 57 %, greater than or equal to 58 % and less than or equal to 60 % laurate.

[0013] Example 5 is the composition of any one of the previous examples, comprising greater than or equal to 14 % and less than 18 %, or less than 17 %, or less than 16.5 %, or less than or equal to 16.1 % myristate.

[0014] Example 6 is the composition of any one of the previous examples, comprising greater than or equal to 7 % and less than 11 %, or less than 10 %, or less than 9.5 %, or less than or equal to 8.9 % palmitate.

[0015] Example 7 is the composition of any one of the previous examples, comprising less than 6 % or less than 5 % or less than 1 % stearate.

[0016] Example 8 is the composition of any one of the previous examples, comprising no detectable stearate.

[0017] Example 9 is the composition of any one of the previous examples, comprising 1 % or less caproate, about 4.6 % caprylate, about 4.4 % caprate, about 58 % laurate, about 16.1 % myristate, about 8.9 % palmitate, and no detectable stearate.

[0018] Example 10 is the composition of any one of the previous examples, comprising 1 % or less caproate, from 4.2 % to 5.1 % caprylate, from 4.0 % to 4.8 % caprate, from 52 % to 60% laurate, from 14.5 % to 17.7 % myristate, from 8.0% to 9.8 % palmitate, and no detectable stearate.

[0019] Example 11 is the composition of any one of the previous examples, comprising 1 % or less caproate, from 4.4 % to 4.8 % caprylate, from 4.2 % to 4.6 % caprate, from 55 % to 60 % laurate, from 15.3 % to 16.9 % myristate, from 8.5 % to 9.3 % palmitate, and no detectable stearate.

[0020] Example 12 is the composition of any one of the previous examples, comprising 1 % or less caproate, from 4.5 % to 4.7 % caprylate, from 4.3 % to 4.5 % caprate, from 56.8 % to 59.1 % laurate, from 15.8 % to 16.4 % myristate, from 8.7 % to 9.1 % palmitate, and no detectable stearate.

[0021] Example 13 is a pharmaceutical formulation comprising a drug and a pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable excipient comprises:

a polysorbate 20 composition comprising fatty acid esters, wherein the fatty acid esters of the polysorbate 20 composition comprise: 1 % or less caproate, greater than 2.3 % and less than or equal to 10 % caprylate, greater than 2.8 % and less than or equal to 10 % caprate, greater than 52.1 % and less than or equal to 60 % laurate, greater than or equal to 14 % and less than 18.3 % myristate, greater than or equal to 7 % and less than 11.9 % palmitate, and less than 6.4 % stearate.

[0022] Example 14 is the pharmaceutical formulation of example 13, wherein the polysorbate 20 composition is from 0.01 % to 0.2 % (w/v) of the formulation.

[0023] Example 15 is the pharmaceutical formulation of example 13 or 14, wherein the drug is a protein, an antibody, an antibody fragment, an enzyme, or a peptide.

[0024] Example 16 is the pharmaceutical formulation of example 15, wherein the drug is a protein.

[0025] Example 17 is the pharmaceutical formulation of example 15, wherein the drug is an antibody.

[0026] Example 18 is the pharmaceutical formulation of any of one of examples 13 to 17, wherein the concentration of drug is from 0.1 % to 30 % (w/v).

[0027] Example 19 is the pharmaceutical formulation of example 18, wherein the concentration of drug is from 5 % to 20 % (w/v).

[0028] Example 20 is the pharmaceutical formulation of any of one of examples 13 to 19, wherein the polysorbate 20 composition is from 0.01% to 0.12%, from 0.01% to 0.08 %, from 0.03 % to 0.1 %, or from 0.04 % to 0.07 %, (w/v) of the formulation.

[0029] Example 21 is the pharmaceutical formulation of any of one of examples 13 to 20, wherein the polysorbate 20 composition is about 0.01 %, 0.02 %, 0.03 %, 0.04 %, 0.05 %, 0.06 %, 0.07 %, 0.08 %, 0.09 %, 0.10 %, 0.11 %, or 0.12 % (w/v) of the formulation.

[0030] Example 22 is the pharmaceutical formulation of any of one of examples 13 to 21, wherein the polysorbate 20 composition is about 0.06 % (w/v) of the formulation.

[0031] Example 23 is the pharmaceutical formulation of any of one of examples 13 to 22, wherein the pH is from 4 to 8, or from 5 to 7.5, or from 6.5 to 7.5, or from 6.8 to 7.2.

[0032] Example 24 is the pharmaceutical formulation of any of one of examples 13 to 23, wherein the pharmaceutically acceptable excipient further comprises water, an alcohol, a sugar, a buffer, a surfactant, a stabilizer, or combinations thereof.

[0033] Example 25 is the pharmaceutical formulation of any of one of examples 13 to 24, wherein the fatty acid esters of the polysorbate 20 composition comprise greater than 2.5 %, or greater than 3.5 %, or greater than 4 %, or greater than or equal to 4.6 %, and less than or equal to 10 % of caprylate.

[0034] Example 26 is the pharmaceutical formulation of any of one of examples 13 to 25, wherein the fatty acid esters of the polysorbate 20 composition comprise greater than 3 %, or greater than 3.5 %, or greater than 4 %, or greater than or equal to 4.4 %, and less than or equal to 10 % caprate.

[0035] Example 27 is the pharmaceutical formulation of any of one of examples 13 to 26, wherein the fatty acid esters of the polysorbate 20 composition

comprise greater than 53 %, greater than 55 %, greater than 57 %, greater than or equal to 58 % and less than or equal to 60 % laurate.

[0036] Example 28 is the pharmaceutical formulation of any of one of examples 13 to 27, wherein the fatty acid esters of the polysorbate 20 composition comprise greater than or equal to 14 % and less than 18 %, or less than 17 %, or less than 16.5 %, or less than or equal to 16.1 % myristate.

[0037] Example 29 is the pharmaceutical formulation of any of one of examples 13 to 28, wherein the fatty acid esters of the polysorbate 20 composition comprise greater than or equal to 7 % and less than 11 %, or less than 10 %, or less than 9.5 %, or less than or equal to 8.9 % palmitate.

[0038] Example 30 is the pharmaceutical formulation of any of one of examples 13 to 29, wherein the fatty acid esters of the polysorbate 20 composition comprise less than 6 % or less than 5 % or less than 1 % stearate.

[0039] Example 31 is the pharmaceutical formulation of any of one of examples 13 to 30, wherein the fatty acid esters of the polysorbate 20 composition comprise no detectable stearate.

[0040] Example 32 is the pharmaceutical formulation of any of one of examples 13 to 31, wherein the fatty acid esters of the polysorbate 20 composition comprise 1 % or less caproate, about 4.6 % caprylate, about 4.4 % caprate, about 58 % laurate, about 16.1 % myristate, about 8.9 % palmitate, and no detectable stearate.

[0041] Example 33 is a polysorbate 20 composition comprising fatty acid esters comprising 1.0 % or less caproate, greater than or equal to 2.6 % and less than or equal to 6.6 % caprylate, greater than or equal to 2.4 % and less than or equal to 6.4 % caprate, greater than or equal to 55.0 % and less than or equal to 60.0 % laurate, greater than or equal to 14.1 % and less than or equal to 18.1 % myristate, greater than or equal to 7.0 % and less than or equal to 10.9 % palmitate, and less than or equal to 2.0 % stearate.

[0042] Example 34 is the composition of example 33, comprising greater than or equal to 3 %, or greater than or equal to 3.5 %, or greater than or equal to 4 %, or greater than or equal to 4.6 %, and less than or equal to 6.6 % of caprylate.

[0043] Example 35 is the composition of example 33 or 34, comprising greater than or equal to 2.6 %, or greater than or equal to 3 %, or greater than or equal to 3.5 %,

or greater than or equal to 4 %, or greater than or equal to 4.4 %, and less than or equal to 6.4 % caprate.

[0044] Example 36 is the composition of any one of examples 33 to 35, comprising greater than or equal to 56 %, greater than or equal to 57 %, greater than or equal to 58 % and less than or equal to 60 % laurate.

[0045] Example 37 is the composition of any one of examples 33 to 36, comprising greater than or equal to 14.1 % and less than or equal to 18 %, or less than or equal to 17 %, or less than or equal to 16 %, or less than or equal to 15 % myristate.

[0046] Example 38 is the composition of any one of examples 33 to 37, comprising greater than or equal to 7 % and less than 10.9 %, or less than or equal to 10 %, or less than or equal to 9 %, or less than or equal to 8 % palmitate.

[0047] Example 39 is the composition of any one of examples 33 to 38, comprising less than or equal to 2 % or less than or equal to 1.5 % or less than or equal to 1 % stearate.

[0048] Example 40 is the composition of any one of examples 33 to 39, comprising no detectable stearate.

[0049] Example 41 is the composition of example 33, comprising 1 % or less caproate, about 4.6 % caprylate, about 4.8 % caprate, about 57.0 % laurate, about 16.2 % myristate, about 9.4 % palmitate, and no detectable stearate.

[0050] Example 42 is the composition of example 33, comprising 1 % or less caproate, from 3.7 % to 5.2 % caprylate, from 3.7 % to 5.2 % caprate, from 56.3 % to 57.2 % laurate, from 15.9 % to 16.9 % myristate, from 8.8 % to 9.7 % palmitate, and no detectable stearate.

[0051] Example 43 is the composition example 33, comprising 1 % or less caproate, from 3.5 % to 5.5 % caprylate, from 3.5 % to 5.5 % caprate, from 55 % to 58 % laurate, from 15 % to 17.5 % myristate, from 8.5 % to 10 % palmitate, and about 0.1 % stearate or less.

[0052] Example 44 is the composition of any one of examples 33 to 43, further comprising, greater than or equal to 5.8 % and less than or equal to 9.8 % oleate, and less than or equal to 2.0 % linoleate.

[0053] Example 45 is a pharmaceutical formulation comprising a drug and a pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable excipient comprises:

a polysorbate 20 composition comprising fatty acid esters, wherein the fatty acid esters of the polysorbate 20 composition comprise: 1.0 % or less caproate, greater than or equal to 2.6 % and less than or equal to 6.6% caprylate, greater than or equal to 2.4 % and less than or equal to 6.4 % caprate, greater than or equal to 55.0 % and less than or equal to 60.0 % laurate, greater than or equal to 14.1 % and less than or equal to 18.1 % myristate, greater than or equal to 7.0 % and less than or equal to 10.9 % palmitate, and less than or equal to 2.0 % stearate.

[0054] Example 46 is the pharmaceutical formulation of example 45, wherein the polysorbate 20 composition is from 0.01 % to 0.2 % (w/v) of the formulation.

[0055] Example 47 is the pharmaceutical formulation of example 45 or 46, wherein the drug is a protein, an antibody, an antibody fragment, an enzyme, or a peptide.

[0056] Example 48 is the pharmaceutical formulation of example 47, wherein the drug is a protein.

[0057] Example 49 is the pharmaceutical formulation of example 47, wherein the drug is an antibody.

[0058] Example 50 is the pharmaceutical formulation of any of one of examples 45 to 49, wherein the concentration of drug is from 0.1 % to 30 % (w/v).

[0059] Example 51 is the pharmaceutical formulation of example 50, wherein the concentration of drug is from 5 % to 20 % (w/v).

[0060] Example 52 is the pharmaceutical formulation of any of one of examples 45 to 51, wherein the polysorbate 20 composition is from 0.01% to 0.12%, from 0.01 % to 0.08 %, from 0.03 % to 0.1 %, or from 0.04 % to 0.07 %, (w/v) of the formulation.

[0061] Example 53 is the pharmaceutical formulation of any of one of examples 45 to 52, wherein the polysorbate 20 composition is about 0.01 %, 0.02 %, 0.03 %, 0.04 %, 0.05 %, 0.06 %, 0.07 %, 0.08 %, 0.09 %, 0.10 %, 0.11 %, or 0.12 % (w/v) of the formulation.

[0062] Example 54 is the pharmaceutical formulation of any of one of examples 45 to 53, wherein the polysorbate 20 composition is about 0.06 % (w/v) of the formulation.

[0063] Example 55 is the pharmaceutical formulation of any of one of examples 45 to 54, wherein the pH is from 4 to 8, or from 5 to 7.5, or from 6.5 to 7.5, or from 6.8 to 7.2.

[0064] Example 56 is the pharmaceutical formulation of any of one of examples 45 to 55, wherein the pharmaceutically acceptable excipient further comprises water, an alcohol, a sugar, a buffer, a surfactant, a stabilizer, or combinations thereof.

[0065] Example 57 is the pharmaceutical formulation of any of one of examples 45 to 56, wherein the fatty acid esters of the polysorbate 20 composition comprise greater than or equal to 3 %, or greater than or equal to 3.5 %, or greater than or equal to 4 %, or greater than or equal to 4.6 %, and less than or equal to 6.6 % of caprylate.

[0066] Example 58 is the pharmaceutical formulation of any one of examples 45 to 57, wherein the fatty acid esters of the polysorbate 20 composition comprises greater than or equal to 2.6 %, or greater than or equal to 3 %, or greater than or equal to 3.5 %, or greater than or equal to 4 %, or greater than or equal to 4.4 %, and less than or equal to 6.4 % caprate.

[0067] Example 59 is the pharmaceutical formulation of any one of examples 45 to 58, wherein the fatty acid esters of the polysorbate 20 composition comprise greater than or equal to 56 %, greater than or equal to 57 %, greater than or equal to 58 % and less than or equal to 60 % laurate.

[0068] Example 60 is the pharmaceutical formulation of any one of examples 45 to 59, wherein the fatty acid esters of the polysorbate 20 composition comprise greater than or equal to 14.1 % and less than or equal to 18 %, or less than or equal to 17 %, or less than or equal to 16 %, or less than or equal to 15 % myristate.

[0069] Example 61 is the pharmaceutical formulation of any one of examples 45 to 60, wherein the fatty acid esters of the polysorbate 20 composition comprise greater

than or equal to 7 % and less than 10.9 %, or less than or equal to 10 %, or less than or equal to 9 %, or less than or equal to 8 % palmitate.

[0070] Example 62 is the pharmaceutical formulation of any one of examples 45 to 61, wherein the fatty acid esters of the polysorbate 20 composition comprise less than or equal to 2 % or less than or equal to 1.5 % or less than or equal to 1 % stearate.

[0071] Example 63 is the pharmaceutical formulation of any one of examples 45 to 62, wherein the fatty acid esters of the polysorbate 20 composition comprise no detectable stearate.

[0072] Example 64 is the pharmaceutical formulation of any one of examples 45 to 63, wherein the fatty acid esters of the polysorbate 20 composition comprise 1 % or less caproate, about 4.6 % caprylate, about 4.8 % caprate, about 57.0 % laurate, about 16.2 % myristate, about 9.4 % palmitate, and no detectable stearate.

[0073] Example 65 is the pharmaceutical formulation of any one of examples 45 to 63, wherein the fatty acid esters of the polysorbate 20 composition comprise 1 % or less caproate, from 3.7 % to 5.2 % caprylate, from 3.7 % to 5.2 % caprate, from 56.3 % to 57.2 % laurate, from 15.9 % to 17.0 % myristate, from 8.8 % to 9.8 % palmitate, and no detectable stearate.

[0074] Example 66 is the pharmaceutical formulation of any one of examples 45 to 63, wherein the fatty acid esters of the polysorbate 20 composition comprise 1 % or less caproate, from 3.5 % to 5.5 % caprylate, from 3.5 % to 5.5 % caprate, from 55 % to 58 % laurate, from 15 % to 17.5 % myristate, from 8.5 % to 10 % palmitate, and about 0.1 % stearate or less.

[0075] Example 67 is the pharmaceutical formulation of any one of examples 45 to 66, wherein the fatty acid esters of the polysorbate 20 composition further comprises, greater than or equal to 5.8 % and less than or equal to 9.8 % oleate, and less than or equal to 2.0 % linoleate.

[0076] Example 68 is the formulation of any one of examples 45 to 67, comprising fewer free fatty acid particles resulting from degradation of fatty acid esters when compared to a formulation comprising a standard polysorbate 20 composition that is subjected to the same storage conditions.

[0077] Example 69 is the formulation of any one of examples 45 to 68, further comprising a higher order ester degrading drug product, wherein up to 10 % more fatty acid esters may be degraded to free fatty acids before free fatty acid particle formation is observed than in an HOE degrading drug product formulation comprising a standard polysorbate 20 composition that otherwise has the identical contents and is stored under the same conditions.

[0078] Example 70 is the formulation of any one of examples 45 to 69, wherein the number of free fatty acid particles produced by metal nucleation of free fatty acids is less than the number of free fatty acid particles produced by metal nucleation of free fatty acids in a formulation comprising a standard polysorbate 20 composition that is otherwise identical in content and storage conditions.

[0079] Example 71 is the composition or formulation of any one of examples 33 to 70, wherein free fatty acids are produced by hydrolytic and/or oxidative degradation of the fatty acid esters.

[0080] Example 72 is the composition or formulation of any one of examples 33 to 70, wherein degradation of fatty acid esters results in free fatty acid particle formation that is delayed relative to free fatty acid particle formation in a composition or formulation comprising a standard polysorbate 20 composition.

[0081] Example 73 is the composition or formulation of example 72, wherein the free fatty acid particles are visible.

[0082] Example 74 is the composition or formulation of example 72, wherein the free fatty acid particles are subvisible.

[0083] Additional objects and advantages will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice. The objects and advantages will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0084] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the claims. The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several exemplary examples and together with the description, serve to explain certain principles described herein.