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(54) **STORAGE STABLE SINCALIDE FORMULATIONS**

(71) Applicant: **MAIA Pharmaceuticals, Inc.**, Princeton, NJ (US)

(72) Inventor: **Srikanth Sundaram**, Somerset, NJ (US)

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(57) **ABSTRACT**

Disclosed herein are solid compositions that comprise sincalide and are storage stable and which lack a buffer, and optionally, also lack a surfactant/solubilizer, wherein such compositions are storage stable. Also disclosed herein are liquid compositions that comprise sincalide, wherein such compositions are storage stable, and may lack buffer and/or surfactant/solubilizer. Also provided are methods of making and administering the solid or liquid storage stable compositions to a patient in need of, e.g., for the treatment, prevention, and/or diagnosis of gall bladder- and/or pancreatic disorders; or other diagnostic imaging.

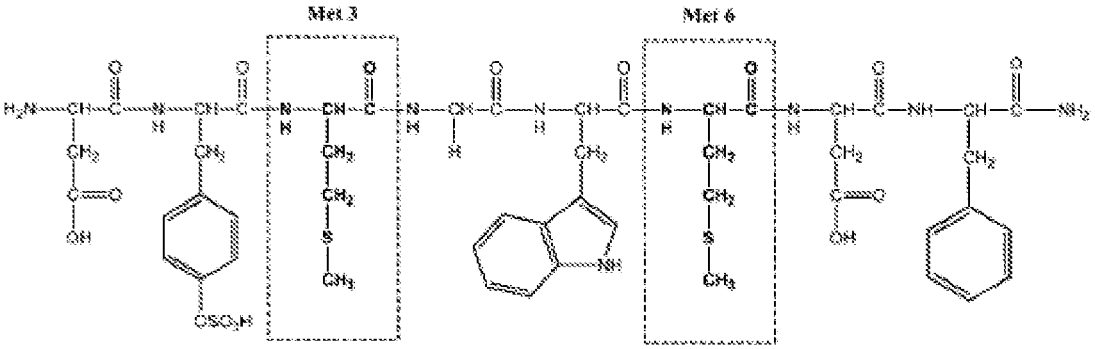
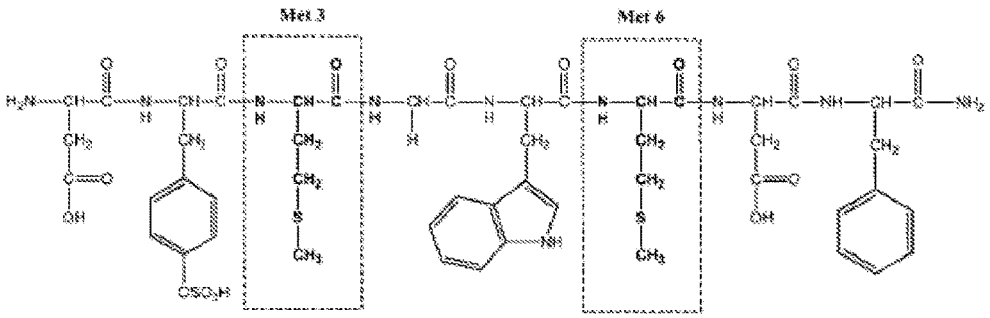


FIGURE 1



STORAGE STABLE SINCALIDE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 60/550,484, filed Aug. 25, 2017, and entitled "Storage Stable Sincalide Formulations" which application is hereby incorporated by reference.

TECHNICAL FIELD

[0002] Disclosed herein are storage stable solid compositions of sincalide that are substantially free of buffers (and optionally surfactants/solubilizers), methods of making and using the compositions, and kits comprising the compositions. Also disclosed herein are storage stable liquid compositions of sincalide, methods of making and using the compositions, and kits comprising the liquid compositions. Such liquid compositions may also be substantially free of buffers (and optionally surfactants/solubilizers).

BACKGROUND OF THE INVENTION

[0003] Sincalide is a cholecystopancreatic-gastrointestinal hormone peptide for parenteral administration. The active pharmaceutical ingredient, 1-De(5-oxo-L-glutamine-5-L-proline)-2-de-L-methioninecaerulein or "sincalide" (CAS #25126-32-3), is a synthetically prepared C-terminal octapeptide of cholecystokinin (CCK-8), with the following amino acid sequence: Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2.

[0004] Sincalide (KINEVAC® Sincalide for Injection) was first approved by Food and Drug Administration (FDA) in 1976, and was supplied as a sterile, nonpyrogenic, lyophilized white powder in containing nominally 5 μg sincalide, 45 mg sodium chloride as a bulking/tonicity agent, and sodium hydroxide or hydrochloric acid to adjust the pH to pH 5.5-6.5. The 5-mL Type I glass vial was sealed under a nitrogen headspace with a relative humidity (RH) of less than 30% in the headspace of the vial (Huber RC (1978) *J. Pharm. Sci.* 67(9): 1239-1243). This two-ingredient formulation was approved with an 18-month shelf life when stored at −20° C. or below (U.S. Pat. No. 3,937,819; FDA Summary Basis of Approval for NDA 017697). The recommended storage temperature is reported to be −4° C. elsewhere (Sargent NE (1976) *Am. J. Roentgenol.* 127: 267-271). This two-ingredient formulation (Sincalide for Injection) was incorporated into the U.S. Pharmacopeia, USP 24, NF 19, Jan.1, 2000, but the monograph remained unenforceable and was withdrawn in 2011.

[0005] Various drawbacks in the manufacturing and analysis of the two-ingredient formulation of sincalide have been reported (U.S. Pat. No. 6,803,046). For example, the potency of the two-ingredient formulation was analyzed using a guinea pig gallbladder contraction bioassay, with a wide acceptance range of 80-125%. This bioassay was reportedly unable to distinguish between the bioactivity of sincalide and the bioactivity of sincalide degradants. Accordingly, a 20% overage of sincalide was required in previous sincalide formulations to compensate for the limitations of the bioassay (U.S. Pat. No. 6,803,046, supra). The complex functional bioassay not suitable for use as a public standard and its attempts to replace the functional bioassay with a quantitative chemical assay were not successful. Another lyophilized formulation of Sincalide (KINEVAC®) was approved in 2002, and contained the following ingredients: 170 mg mannitol as a bulking agent/tonicity adjuster; 30 mg of lysine, 15 mg of arginine, and 4 mg of methionine as stabilizers; 2 mg of pentetic acid as a chelator; 0.04 mg of sodium metabisulfite as a stabilizer/antioxidant; 0.005 mg of polysorbate (Tween) 20 as a surfactant/solubilizer; 9 mg potassium phosphate dibasic as a buffer; and hydrochloric acid and/or sodium hydroxide to adjust the pH to 6.0 to 8.0 (Daily Med "Label: Kinevac—sincalide injection, powder, lyophilized, for solution" NIH: U.S. National Library of Medicine, last updated Jul. 13, 2015; U.S. Pat. No. 6,803,046, supra). The purity of this formulation was assessed by a sincalide-specific assay such as high-performance liquid chromatography (HPLC).

[0006] The current formulation of KINEVAC® has been in recurrent shortages: it was first listed in the FDA Drug Shortages database from June 2013 to December 2015, and is currently on the FDA shortage list again since Mar. 1, 2017. Additionally, the current formulation of KINEVAC® appears to have issues with stability, as in January 2015, FDA approved a request to have KINEVAC's® shelf-life reduced from 24 months to 15 months when stored at 25° C.

[0007] There is thus need for additional solid formulations of sincalide with pharmaceutically acceptable stability profiles.

[0008] Additionally, ready-to-use (e.g., ready-to-dilute) formulations for sincalide are currently not available. Lyophilized products must be reconstituted in the appropriate diluent with the appropriate volume of the diluent prior to administration to the patient. In some cases, the reconstituted solution may further need to be diluted prior to use. Additional drug preparation steps such as reconstitution and dilution can result in errors in the drug preparation process (wrong drug-preparation error as defined by ASHP Guidelines on Preventing Medication Errors in Hospitals). Medication errors compromise patients' health and safety, their confidence in the health care system, and increase healthcare costs. This ASHP guideline thus recommends the use of medications in ready-to-administer forms whenever possible.

[0009] There is thus need for ready-to-use, including ready-to-dilute, liquid formulations of sincalide that are storage stable and eliminate or reduce the potential for drug preparation errors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. **1** is the chemical structure of sincalide.

SUMMARY OF THE INVENTION

[0011] Described herein are solid (lyophilized) or liquid (aqueous ready-to-use (e.g., ready-to-dilute) formulations, reconstituted formulations, etc.) of sincalide that are surprisingly stable in storage. See, e.g., Tables 3, 5-8. Such stability is unexpected in light of the stability profile of previous sincalide formulations that demonstrated a shelf-life of less than 18 months in long term storage (25° C.) conditions in lyophilized forms. Such unexpected findings

[0012] More surprising is the demonstration herein that an aqueous solution of sincalide may have a shelf-life of at least 3 months, 6 months, or 12 months in long term storage (2°-8° C.) conditions. Such aqueous sincalide compositions may also lack a buffer or also lack both a buffer and surfactant/solubilizer.

[0013] Compositions comprising the storage stable formulations, methods of making the compositions, kits comprising the compositions (e.g., in appropriate vials, and optionally a fluid portion (e.g., Water for Injection) for reconstituting the lyophilized compositions described herein), and use of the compositions, e.g., in therapeutic, diagnostic, and/or imaging methods, are provided.

[0014] Described herein are compositions comprising sincalide, wherein the compositions have an unexpected shelf-life. The sincalide compositions described herein may be in the form of a lyophilized powder, e.g., may be solid, for example, one which is packaged under a vacuum or partial vacuum.

[0015] In some embodiments, described herein is a solid (lyophilized) composition comprising sincalide, wherein the shelf-life of the solid (lyophilized) composition is at least 18 months, or, for example, at least 24 months when stored at 25° C. and 60% relative humidity, e.g., wherein after 18 months (or 24 months) of storage at 25° C. and 60% relative humidity, and as measured by HPLC, the composition comprises

[0016] (a) less than 5% total impurities,

[0017] (b) retains at least 90% of active sincalide

[0018] (c) less than 2% of any individual impurity, and

[0019] (d) any combination of (a)-(c),

and wherein the solid (lyophilized) composition does not comprise dibasic potassium phosphate.

[0020] In some embodiments, described herein is a solid (lyophilized) composition comprising sincalide, wherein the shelf-life of the solid (lyophilized) composition is at least 15 months when stored at 25° C. and 60% relative humidity, e.g., wherein after 15 months of storage at 25° C. and 60% relative humidity, and as measured by HPLC, the composition comprises

[0021] a) less than 5% total impurities,

[0022] b) retains at least 90% of active sincalide

[0023] c) less than 2% of any individual impurity, and

[0024] d) any combination of (a)-(c),

and wherein the solid (lyophilized) composition does not comprise dibasic potassium phosphate.

[0025] In some further embodiments, described herein is a solid (lyophilized) composition comprising sincalide, wherein the shelf-life of the solid (lyophilized) composition is at least 12 months when stored at 25° C. and 60% relative humidity, e.g., wherein after 12 months of storage at 25° C. and 60% relative humidity, and as measured by HPLC, the composition comprises

[0026] (a) less than 4% total impurities,

[0027] (b) retains at least 90% of active sincalide

[0028] (c) less than 1.5% of any individual impurity, and

[0029] (d) any combination of (a)-(c),

and wherein the solid (lyophilized) composition does not comprise dibasic potassium phosphate.

[0030] In some other further embodiments, described herein is a solid (lyophilized) composition comprising sincalide, wherein the shelf-life of the solid (lyophilized) composition is at least 18 months when stored at 25° C. and 60% relative humidity, e.g., wherein after 9 months of storage at 25° C. and 60% relative humidity, and as measured by HPLC, the composition comprises

[0031] (a) less 2.5% total impurities,

[0032] (b) retains at least 95% of active sincalide

[0033] (c) less than 1.5% of any individual impurity, and

[0034] (d) any combination of (a)-(c),

and wherein the solid (lyophilized) composition does not comprise dibasic potassium phosphate.

[0035] In some embodiments, the solid (lyophilized) composition does not comprise a phosphate buffer. In some embodiments, the solid (lyophilized) composition does not comprise any buffers. In some further embodiments, the solid (lyophilized) compositions do not comprise buffer and also do not comprise surfactant/solubilizer.

[0036] The solid compositions described herein include, for example, pharmaceutical sincalide compositions including: a therapeutically effective amount of sincalide; 1 to 4 mg pentetic acid; 15 to 45 mg arginine hydrochloride; 2 to 8 mg methionine; 7.5 to 30 mg lysine hydrochloride; 0.02 to 1 mg sodium metabisulfite; 85 to 340 mg mannitol; and have a pH from 6.5 to 7.5, wherein the composition does not contain a buffer having a pKa within one unit of the pH, and wherein the composition is storage stable. Such compositions can be a lyophilized powder, and can be packaged under a vacuum.

[0037] Compositions described herein may be liquid, e.g., in the form of a ready-to-use aqueous sincalide solution which exhibits storage stability. For example, the aqueous sincalide solutions described herein, after being stored for 6 months at 2°-8° C. contain less than 5% total impurities, more than 90% of active sincalide, and less than 2% of any individual impurity.

[0038] Also described herein is a liquid (e.g., an aqueous ready-to-use composition, a reconstituted lyophilized composition, etc.) comprising sincalide, wherein the shelf-life of the aqueous composition is at least 18 months when stored at 2°-8° C., e.g., wherein after 18 months of storage at 2°-8° C., and as measured by HPLC, the composition comprises

[0039] (a) less than 5% total impurities,

[0040] (b) at least 90% of active sincalide

[0041] (c) less than 2% of any individual impurity, and

[0042] (d) any combination of (a)-(c).

[0043] Also described herein is a liquid (e.g., an aqueous ready-to-use composition, a reconstituted lyophilized composition, etc.) comprising sincalide, wherein the shelf-life of the aqueous composition is at least 18 months when stored at 2°-8° C., e.g., wherein after 15 months of storage at 2°-8° C., and as measured by HPLC, the composition comprises

[0044] (a) less than 5% total impurities,

[0045] (b) at least 90% of active sincalide

[0046] (c) less than 2% of any individual impurity, and

[0047] (d) any combination of (a)-(c).

[0048] Also described herein a liquid (e.g., an aqueous ready-to-use composition, a reconstituted lyophilized composition, etc.) composition comprising sincalide, wherein the shelf-life of the aqueous composition is at least 12 months when stored at 2°-8° C., e.g., wherein after 12 months of storage at 2°-8° C., and as measured by HPLC, the composition comprises

[0051] (c) less than 2% of any individual impurity, and

[0052] (d) any combination of (a)-(c).

[0053] Also described herein is a liquid (e.g., an aqueous ready-to-use composition, a reconstituted lyophilized composition, etc.) composition comprising sincalide, wherein the shelf-life of the aqueous composition is at least 6 months when stored at 25° C./65% relative humidity, e.g., wherein after 6 months of storage at 2°-8° C., and as measured by HPLC, the composition comprises

[0054] (a) less than 5% total impurities,

[0055] (b) at least 90% of active sincalide

[0056] (c) less than 2% of any individual impurity, and

[0057] (d) any combination of (a)-(c).

[0058] Also described herein is a liquid (e.g., an aqueous ready-to-use composition, a reconstituted lyophilized composition, etc.) composition comprising sincalide, wherein the shelf-life of the aqueous composition is at least 3 months when stored at 25° C./65% relative humidity, e.g., wherein after 3 months of storage at 2°-8° C., and as measured by HPLC, the composition comprises

[0059] (a) less than 5% total impurities,

[0060] (b) at least 90% of active sincalide

[0061] (c) less than 2% of any individual impurity, and

[0062] (d) any combination of (a)-(c).

[0063] In some embodiments, the liquid composition does not comprise dibasic potassium phosphate. In some embodiments, the liquid composition does not comprise a phosphate buffer. In some embodiments, the liquid composition does not comprise any buffers. In some embodiments, the liquid compositions do not comprise any buffers and do not comprise any surfactant/solubilizer.

[0064] Other embodiments of such compositions can be ready-to-use aqueous solutions, for example, comprising: a therapeutically effective amount of sincalide; 0.4 to 5 mg/mL pentetic acid; 6 to 30 mg/mL arginine hydrochloride; 0.8 to 5 mg/mL methionine; 3 to 15 mg/mL lysine hydrochloride; 0.008 to 1 mg/mL sodium metabisulfite; and 34 to 170 mg/mL mannitol, exhibiting storage stability, such that the compositions, for example, stored at 2°-8° C. for 6 months contain less than 5% total impurities, more than 90% active sincalide, and less than 2% of any individual impurity. Such aqueous compositions may lack a buffer, or optionally may additionally lack a surfactant/solubilizer

[0065] The solid or liquid sincalide compositions described herein may comprise a stabilizer and/or a bulking agent/tonicity adjuster. In some embodiments, the stabilizer is selected from the group consisting of pentetic acid, arginine hydrochloride, L-methionine, L-lysine hydrochloride, sodium metabisulfite, and a combination thereof. In some embodiments, the bulking agent/tonicity adjuster comprises mannitol.

[0066] In particular embodiments, compositions described herein may comprise sincalide, wherein the composition does not contain a buffer (e.g., does not contain a phosphate buffer, such as dibasic potassium phosphate), and wherein the composition is stable in storage. Sincalide compositions described herein may further comprise a stabilizer (e.g., pentetic acid, arginine hydrochloride, L-methionine, L-lysine hydrochloride, sodium metabisulfite, or combinations thereof) and/or a bulking agent/tonicity adjuster (e.g., mannitol). The sincalide compositions described herein may comprise polysorbate 80). Some particular sincalide compositions described herein contain neither dibasic potassium phosphate, nor polysorbate 20.

[0067] The sincalide compositions described herein may contain chelators (e.g. pentetic acid), stabilizers (e.g., combinations of L-arginine hydrochloride, L-methionine, L-lysine hydrochloride, and sodium metabisulfite), and bulking agents/tonicity adjusters (e.g., mannitol), buffers (e.g., dibasic potassium phosphate), and surfactants/solubilizers (e.g., polysorbate 20).

[0068] The description also includes methods of making storage stable sincalide compositions by mixing: a therapeutically effective amount of sincalide; and an excipient, wherein the excipient consists essentially of: at least one stabilizer; at least one bulking agent/tonicity adjuster; at least one chelator, or any combination of these (e.g., L-arginine hydrochloride, L-methionine, L-lysine hydrochloride, sodium metabisulfite, mannitol, and pentetic acid.), and water, wherein the composition has a pH from 6.5 to 7.5, and the storage stable solid sincalide composition does not contain a buffer having a pKa within one unit of the pH, or neither contains a buffer nor a surfactant/solubilizer. Such methods of making storage stable solid sincalide compositions can also include lyophilizing the mixture of sincalide, excipients and water, e.g., under a vacuum.

[0069] Aqueous sincalide compositions can also be made by mixing: a therapeutically effective amount of sincalide; and excipients, wherein the excipients comprise: at least one stabilizer; at least one bulking agent/tonicity adjuster; at least one chelator, or any combination of these (e.g., L-arginine hydrochloride, L-methionine, L-lysine hydrochloride, sodium metabisulfite, mannitol, and pentetic acid.), and water, wherein the composition has a pH from 6.5 to 7.5. These storage stable aqueous sincalide compositions also may lack a buffer having a pKa within one unit of the pH, or lack both a buffer and a surfactant/solubilizer.

[0070] The description also includes methods for the treatment, prevention, and/or diagnosis of gall bladder- and/or pancreatic disorders; or other diagnostic imaging a patient in need thereof by administering to the patient pharmaceutical sincalide compositions described herein (containing excipients, for example, L-arginine hydrochloride, L-methionine, L-lysine hydrochloride, sodium metabisulfite, mannitol, and pentetic acid).

[0071] Also described herein are kits comprising the described compositions optionally also including a fluid component.

DETAILED DESCRIPTION

[0072] Described herein are solid formulations of sincalide that are surprisingly as stable and/or more stable than KINEVAC® even though the compositions lack a buffer (e.g., lack dibasic potassium phosphate, lack any phosphate buffer, and/or lack any buffer), and optionally, lack both a buffer and a surfactant/solubilizer. In addition, described here are liquid formulations of sincalide which display storage stability, and optionally lack a buffer or lack both a buffer and surfactant/solubilizer. Since sincalide may be administered as an intravenous bolus or by intravenous infusion or by intramuscular administration, there is a need for aqueous liquid formulations of sincalide that are storage

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