VASOPRESSIN FORMULATIONS FOR USE IN TREATMENT OF HYPOTENSION

CROSS REFERENCE

This Application is a continuation-in-part of U.S. application Ser. No. 15/289,640, filed Oct. 10, 2016, which is a continuation-in-part of U.S. application Ser. No. 14/717,877, filed May 20, 2015, which is a continuation of U.S. application Ser. No. 14/610,499, filed Jan. 30, 2015, each of which is incorporated herein by reference in its entirety.

BACKGROUND

Vasopressin is a potent endogenous hormone, responsible for maintaining plasma osmolality and volume in most mammals. Vasopressin can be used clinically in the treatment of sepsis and cardiac conditions, and in the elevation of patient's suffering from low blood pressure. Current formulations of vasopressin suffer from poor long-term stability.

INCORPORATION BY REFERENCE

Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Feb. 6, 2017 is named 47956702503_SL.txt and is 5184 bytes in size.

SUMMARY OF THE INVENTION

In some embodiments, the invention provides a pharmaceutical composition comprising, in a unit dosage form: a) from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin, or a pharmaceutically-acceptable salt thereof; and b) a polymeric pharmaceutically-acceptable excipient in an amount that is from about 1% to about 10% by mass of the unit dosage form or the pharmaceutically-acceptable salt thereof, wherein the unit dosage form exhibits from about 5% to about 10% less degradation of the vasopressin or the pharmaceutically-acceptable salt thereof after storage for about 1 week at about 60° C. than does a corresponding unit dosage form, wherein the corresponding unit dosage form consists essentially of: A) vasopressin, or a pharmaceutically-acceptable salt thereof; and B) a buffer having acidic pH.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a chromatogram of a diluent used in vasopressin assay.

FIG. **2** is a chromatogram of a sensitivity solution used in a vasopressin assay.

FIG. **3** is a chromatogram of an impurity marker solution used in a vasopressin assay.

FIG. **4** is a zoomed-in depiction of the chromatogram in FIG. **3**.

FIG. **5** is a chromatogram of a vasopressin standard solution.

FIG. **6** is a chromatogram of a sample vasopressin preparation.

FIG. **7** is a UV spectrum of a vasopressin sample.

FIG. **8** is a UV spectrum of a vasopressin standard.

FIG. **9** plots vasopressin stability across a range of pH as determined experimentally.

FIG. **10** illustrates the effects of various stabilizers on vasopressin stability.

FIG. **11** plots vasopressin stability across a range of pH at 25° C.

FIG. **12** plots vasopressin impurities across a range of pH at 25° C.

FIG. **13** plots vasopressin stability across a range of pH at 40° C.

FIG. **14** plots vasopressin impurities across a range of pH at 40° C.

FIG. **15** illustrates vasopressin impurities across a range of pH at 25° C.

FIG. **16** illustrates vasopressin impurities across a range of pH at 40° C.

FIG. **17** illustrates the effect of pH on vasopressin at 25° C.

FIG. **18** illustrates the effect of pH on vasopressin at 40° C.

FIG. **19** depicts the % LC of vasopressin formulations stored for 15 months at 25° C.

DETAILED DESCRIPTION

Vasopressin and Peptides of the Invention.

Vasopressin, a peptide hormone, acts to regulate water retention in the body and is a neurotransmitter that controls circadian rhythm, thermoregulation, and adrenocorticotrophic hormone (ACTH) release. Vasopressin is synthesized as a pro-hormone in neurosecretory cells of the hypothalamus, and is subsequently transported to the pituitary gland for storage. Vasopressin is released upon detection of hyperosmolality in the plasma, which can be due to dehydration of the body. Upon release, vasopressin increases the permeability of collecting ducts in the kidney to reduce renal excretion of water. The decrease in renal excretion of water leads to an increase in water retention of the body and an increase in blood volume. At higher concentrations, vasopressin raises blood pressure by inducing vasoconstriction.

Vasopressin acts through various receptors in the body including, for example, the V1, V2, V3, and oxytocin-type (OTR) receptors. The V1 receptors occur on vascular smooth muscle cells, and the major effect of vasopressin action on the V1 receptor is the induction of vasoconstriction via an increase of intracellular calcium. V2 receptors occur on the collecting ducts and the distal tubule of the kidney. V2 receptors play a role in detection of plasma volume and osmolality. V3 receptors occur in the pituitary gland and can cause ACTH release upon vasopressin binding. OTRs can be found on the myometrium and vascular smooth muscle. Engagement of OTRs via vasopressin leads to an increase of intracellular calcium and vasoconstriction.

Vasopressin is a nonapeptide, illustrated below (SEQ ID NO. 1):