porcine serum albumin, are described in Raun *et al.*, EUR. JNL. ENDOCR. (1998) 139:552-561. EP 0736039 B1 mentions numerous acid addition salts of compounds structurally related to ipamorelin, but makes no mention of ways to improve the solubility of ipamorelin in injection solutions, while improving the molecule's stability.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure provides a solution of ipamorelin solubilized by two molar equivalents of acetic acid (hereinafter referred to as "ipamorelin diacetate"), useful as finished injection and infusion solutions, methods of making the finished solutions, and novel intermediates and raw materials used in the methods, which do not lead to excessive instability, precipitation or degradation of the ipamorelin. Thus, in a first principal embodiment the ~~invention~~disclosure provides novel injection and infusion solutions of ipamorelin diacetate comprising:

a) ipamorelin solubilized by approximately two molar equivalents of acetic acid (ipamorelin diacetate), in an amount of from 0.001 to 20% based on the weight of the free base of ipamorelin;

b) a molar excess of acid, preferably acetic acid, in an amount sufficient to give a pH of at least 3 and less than 7;

c) optionally from 0.1 to 30% of one or more formulation aids; and

d) water q.s. to 100%; all percentages based on the total weight of the solution.

In one aspect, there is provided an injection or infusion solution of ipamorelin comprising:

a) ipamorelin solubilized by two molar equivalents of acetic acid (ipamorelin diacetate), in an amount of from 0.001 to 20%, based on the weight of the free base of ipamorelin;

b) a molar excess of acid, preferably acetic acid, in an amount sufficient to give a pH of at least 3 and less than 7;

c) optionally from 0.1 to 30% of one or more formulation aids; and

d) water q.s. to 100%; all percentages based on the total weight of the solution.

The present ~~invention~~disclosure also relates to a method of producing injection and infusion solutions of ipamorelin diacetate *in situ*, at a concentration of ipamorelin of from 0.001 to 20%, without isolating the diacetate salt after formation, comprising:

a) mixing ipamorelin free base and acetic acid at a molar ratio of approximately 1:2 to form an aqueous solution of ipamorelin diacetate;

b) mixing said ipamorelin diacetate with from 0.1 to 30% of one or more formulation aids, optionally including one or more excess acids, without isolating said ipamorelin diacetate in solid form; and

c) optionally mixing said ipamorelin diacetate with additional water so that the final concentration of ipamorelin is from 0.001 to 20%, based on the total weight of the solution and the weight of the free base of ipamorelin.

In this context, the term "mixing" is given a broad meaning, so that steps (a), (b) and (c) can occur simultaneously, sequentially or in any order. In a particularly preferred embodiment, the one or more formulation aids comprises a tonicifying effective amount of one or more tonicity agents. In another preferred embodiment, the one or more formulation aids comprises a pH adjusting agent, in an amount sufficient to yield a predetermined pH.

In yet another embodiment, the ~~invention~~disclosure provides ipamorelin diacetate. Still further, the ~~invention~~disclosure relates to intermediates used in the manufacture of the pharmaceutical solutions of the present ~~invention~~disclosure. Thus, in another embodiment the ~~invention~~disclosure provides an intermediate ipamorelin solution solubilized by acetic acid having an ipamorelin:acid molar ratio of about 1:2.

Compared with previously known injection solutions of ipamorelin, the solutions according to the ~~invention~~disclosure have the advantage of improved stability when stored for prolonged periods of time. In like manner, the methods of production, and intermediates and raw materials used in the methods, ensure the stability of ipamorelin during the product's shelf life.

Additional embodiments and advantages of the ~~invention~~disclosure 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 of the ~~invention~~disclosure. The embodiments and advantages of the ~~invention~~disclosure 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 ~~invention~~disclosure, as claimed.

DESCRIPTION OF THE FIGURES

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description serve to explain the principles of the invention.