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(54) **PHARMACEUTICAL FORMULATIONS OF BIVALIRUDIN AND PROCESSES OF MAKING THE SAME**

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See application file for complete search history.

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(57) **ABSTRACT**

Pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin as the active ingredient, and a method of preparing the pharmaceutical batch(es) or pharmaceutical formulation(s). The pharmaceutical batch(es) or pharmaceutical formulation(s) may have a maximum impurity level of Asp^{9}-bivalirudin that does not exceed about 0.6%. Also, the pharmaceutical batch(es) or pharmaceutical formulation(s) may have a reconstitution time that does not exceed about 42 seconds. The method of preparing the pharmaceutical batch(es) or pharmaceutical formulation(s) may comprise dissolving bivalirudin in a solvent to form a first solution, efficiently mixing a pH-adjusting solution with the first solution to form a second solution in which the pH-adjusting solution may comprise a pH-adjusting solution solvent, and removing the solvent and the pH-adjusting solution solvent from the second solution.

20 Claims, No Drawings

PHARMACEUTICAL FORMULATIONS OF BIVALIRUDIN AND PROCESSES OF MAKING THE SAME

INCORPORATION BY REFERENCE

The foregoing applications, and all documents cited therein or during their prosecution ("appln cited documents") and all documents cited or referenced in the appln cited documents, and all documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

FIELD OF THE INVENTION

Various embodiments of the present invention are generally directed towards a method for preparing a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin as the active ingredient. Some embodiments of the present invention are also directed towards a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin as the active ingredient. For example, certain embodiments of the present invention relate to pharmaceutical batch(es) or pharmaceutical formulation(s) of a drug product having reduced levels of a major degradation product, i.e., Asp^9-bivalirudin, which may contribute to improved stability and shelf-life. In some embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In various embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) of the present invention are characterized by a reconstitution time that does not exceed about 42 seconds. Various embodiments of the invention further generally relate to an injectable dosage form comprising a pharmaceutical formulation and a vehicle, and methods of administering the injectable dosage form.

BACKGROUND OF THE INVENTION

Anticoagulants are substances that prevent blood from clotting. They are commonly used during percutaneous coronary intervention (PCI) and other catherization techniques in order to reduce bleeding complications. One class of anticoagulants is direct thrombin inhibitors that disrupt the activity of thrombin, an important protein in the coagulation cascade. In particular, bivalirudin (ANGIOMAX®), which directly inhibits thrombin by specifically binding to both its catalytic site and to the anion-binding exosite, is regarded as a highly effective anticoagulant for use during catherization procedures.

Bivalirudin, also known as Hirulog-8, is a synthetic congener of the naturally occurring thrombin peptide inhibitor hirudin, which is found in the saliva of the medicinal leech *Hirudo medicinalis*. Hirudin consists of 65 amino acids, although shorter peptide segments have proven to be effective as thrombin inhibitors. U.S. Pat. No. 5,196,404 (incorporated herein by reference) discloses bivalirudin among these shorter peptides that demonstrate an anticoagulant activity. However, in contrast to hirudin, bivalirudin is a reversible

In light of the medical and therapeutic applications of bivalirudin, it is essential that the bivalirudin formulation maintains a high level of purity. The bivalirudin formulation is a compounded formulation containing bivalirudin, e.g., bivalirudin undergoes a compounding process following its synthesis so that it is usable and stable for medical and therapeutic applications.

Impurities such as Asp^9-bivalirudin (deamidation of asparagine at position 9 of bivalirudin to aspartic acid) and D-Phe^{12}-bivalirudin (isomerization of L-phenylalanine at position 12 of bivalirudin to the D-isomer) may be generated during the synthesis of bivalirudin. Consequently, processes for synthesizing bivalirudin have been developed to minimize the generation of impurities. However, impurities can also be produced during the compounding process, i.e., the process to generate a formulation of bivalirudin. It has been shown that various compounding processes can result in formulations that have up to 12% of Asp^9-bivalirudin, which may affect product stability and shelf-life. Therefore, development of a compounding process for formulating bivalirudin that consistently generates formulations having low levels of impurities is desirable.

Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

Various embodiments of the present invention relates to a compounding process for preparing a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient. In certain embodiments, the compounding process comprises (i) dissolving bivalirudin in a solvent to form a first solution; (ii) efficiently mixing a pH-adjusting solution with the first solution to form a second solution, wherein Asp^9-bivalirudin in the second solution is minimized; and (iii) removing the solvent from the second solution.

In some embodiments, the pH of the second solution does not exceed about 8. In some embodiments, the pH of the second solution does not exceed about 7. In further embodiments, the pH of the second solution does not exceed about 6.

In certain embodiments, efficient mixing is achieved by adding the pH-adjusting solution to the first solution, by adding the first solution to the pH-adjusting solution, or a combination thereof. In some embodiments, the pH-adjusting solution is added to the first solution in portions. In further embodiments, the pH-adjusting solution is added to the first solution at a constant rate.

In some embodiments, efficient mixing is achieved by using one or more mixing devices. In certain embodiments, the mixing device is selected from a group consisting of a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. In some embodiments, the mixing device is a homogenizer, a paddle mixer, or a combination thereof.

In further embodiments, the efficient mixing is achieved through high shear mixing.

In certain embodiments, removal of the solvent from the second solution is achieved through lyophilization.

In some embodiments, the compounding process may further comprise sterilization of the second solution before removal of the solvent. In certain embodiments, sterilization is achieved by aseptic filtration.

Various embodiments of the present invention also relate to

invention. In certain embodiments, a pharmaceutical batch (es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In some embodiments, a pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum total impurity level that does not exceed about 2%. In additional embodiments, a pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

In addition, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) prepared by a compounding process comprising: (i) dissolving bivalirudin in a solvent to form a first solution; (ii) efficiently mixing a pH-adjusting solution with the first solution to form a second solution; and (iii) removing the solvent from the second solution.

In certain embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In some embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.4%. In further embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.3%.

In some embodiments of the present invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum total impurity level that does not exceed about 2%. In certain embodiments, the maximum total impurity level does not exceed about 1%. In additional embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5%.

In other embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds. In some embodiments, the maximum reconstitution time does not exceed about 30 seconds. In further embodiments, the maximum reconstitution time does not exceed about 21 seconds.

In some embodiments of the present invention, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In additional embodiments, the bulking agent is a sugar. In further embodiments, the sugar is mannitol.

In certain embodiments, efficient mixing is achieved by adding the pH-adjusting solution to the first solution, by adding the first solution to the pH-adjusting solution, or a combination thereof. In some embodiments, the pH-adjusting solution is added to the first solution at a constant rate. In further embodiments, efficient mixing is achieved by using one or more mixing devices. In yet additional embodiments, the efficient mixing is achieved through high shear mixing.

Moreover, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) prepared by a compounding process comprising: (i) dissolving bivalirudin in a solvent to form a first solution; (ii) efficiently mixing a pH-adjusting solution with the first solution to form a second solution; and (iii) removing the solvent from the second solution; wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%.

Certain embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) prepared by a compounding process comprising: (i) dissolving bivalirudin in a solvent to form a first solution; (ii) efficiently mixing a pH-adjusting solution with the first solution to form a second solution; and (iii) removing the solvent from the second solution; wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

Furthermore, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof. Some embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%.

In some embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.4%. In certain embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.3%.

In additional embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is further characterized by a maximum total impurity level that does not exceed about 2%. In certain embodiments, the maximum total impurity level does not exceed about 1%. In some embodiments, the maximum total impurity level does not exceed about 0.5%.

In certain embodiments of the invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) is further characterized by a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5%.

In some embodiments, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In further embodiments, the bulking agent is a sugar. In yet additional embodiments, the sugar is mannitol.

Some embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

In certain embodiments, the maximum reconstitution time does not exceed about 30 seconds. In some embodiments, the maximum reconstitution time does not exceed about 21 seconds.

In some embodiments of the invention, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In further embodiments, the bulking agent is a sugar. In yet additional embodiments, the sugar is mannitol.

Also, various embodiments of the present invention relate

ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%, a maximum total impurity level that does not exceed about 2%, and a maximum reconstitution time that does not exceed about 42 seconds.

These and other embodiments are disclosed or are obvious from and encompassed by, the following Detailed Description.

DETAILED DESCRIPTION

Various embodiments of the present invention relate to a compounding process for preparing a pharmaceutical batch(es) of a drug product, which results in pharmaceutical formulations comprising bivalirudin and a pharmaceutically acceptable carrier. Certain embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product, resultant pharmaceutical formulation(s) comprising bivalirudin and a pharmaceutically acceptable carrier, and an injectable dosage form comprising the pharmaceutical formulation and a vehicle.

As used here, "batch" or "pharmaceutical batch" refers to material produced by a single execution of a compounding process of various embodiments of the present invention. "Batches" or "pharmaceutical batches" as defined herein may include a single batch, wherein the single batch is representative of all commercial batches (see generally, Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5225.1, Guidance on the Packaging of Test Batches at 1), and wherein the levels of, for example, Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time represent levels for all potential batches made by said process. "Batches" may also include all batches prepared by a same compounding process.

The term "drug product" herein refers to an active ingredient and a pharmaceutically acceptable carrier.

The term "formulation" or "pharmaceutical formulation" refers to a unit dose of an active pharmaceutical ingredient and a pharmaceutically acceptable carrier, which is prepared by the various processes in certain embodiments of the present invention. In the case of the present pharmaceutical formulation, the active pharmaceutical ingredient is bivalirudin.

The term "carrier" refers to any component of the pharmaceutical batch(es) or pharmaceutical formulation(s) that, for example, serves as a bulking agent or functions as a stabilizing agent for the active ingredient. A bulking agent refers to any material that fills or provides volume to the active ingredient. Examples of appropriate bulking agents may include, but are not limited to, sugars such as mannitol, sucrose, lactose, fructose and trehalose.

A stabilizing agent refers to any material which serves to minimize degradation of the active ingredient. Examples of stabilizing agents may include, but are not limited to, antioxidants, buffering agents, preservatives, etc.

Bivalirudin has the chemical name of D-Phenylalanyl-L-Prolyl-L-Arginyl-L-Prolyl-Glycyl-Glycyl-Glycyl-Glycyl-L-Asparagyl-Glycyl-L-Aspartyl-L-Phenylalanyl-L-Glutamyl-L-Glutamyl-L-Isoleucyl-L-Prolyl-L-Glutamyl-L-Glutamyl-L-Tyrosyl-L-Leucine trifluoroacetate (salt) hydrate and has a molecular weight of 2180 daltons. Bivalirudin is made up of the amino acid sequence: (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-

thesis, solution-phase peptide synthesis, or a combination of solid-phase and solution-phase procedures (e.g., U.S. Pat. No. 5,196,404; Okayama et al., *Chem. Pharm. Bull.* 1996, 44: 1344-1350; Steinmetzer et al., *Eur. J. Biochem.* 1999, 265: 598-605; PCT Patent Application WO 91/02750).

As described above, Asp^9-bivalirudin is formed due to deamidation of asparagine at position 9 of bivalirudin to aspartic acid. The amino acid sequence of Asp^9-bivalirudin is: (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 2). Further, D-Phe^{12}-bivalirudin is generated from isomerization of L-phenylalanine at position 12 of bivalirudin to the D-isomer. The amino acid sequence of D-Phe^{12}-bivalirudin is (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-(D-Phe)-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 3)

Bivalirudin inhibits blood clotting by binding to thrombin, a key serine protease in blood clot formation. This synthetic 20 amino acid peptide binds to thrombin at the catalytic site and at the anion-binding exocite, thereby inhibiting thrombin. Thrombin plays a central role in hemostasis. The coagulation pathway initiates clotting when thrombin, a serine protease, converts fibrinogen into fibrin. Additionally, thrombin activates Factor XIII into Factor XIIIa (the latter which links fibrin polymers covalently), Factors V and VIII (which promote thrombin generation), and platelets (which help propagate the thrombus).

The method of delivery of bivalirudin may be through intravenous administration. Bivalirudin may be supplied in single-use vials as a white lyophilized sterile cake. Each single-use vial may contain about 250 mg of bivalirudin. When reconstituted with a sterile aqueous solution for injection, the product yields a clear to opalescent, colorless to slightly yellow, solution. Such a solution has a pH of about 5-6.

The pharmaceutical batch(es) or pharmaceutical formulation(s) according to certain embodiments of the present invention may be used in any application which requires altered or inhibited thrombin activity. The pharmaceutical batch(es) or pharmaceutical formulation(s) may be used to alter or inhibit the coagulation cascade, for example, as an anticoagulant.

Approved indications include treatment in patients with unstable angina undergoing percutaneous translumnial coronary angioplasty; administration with the provisional use of glycoprotein IIb/IIIa inhibitor for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI); and treatment in patients with, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. Also, the pharmaceutical batch(es) or pharmaceutical formulation(s) according to various embodiments of the present invention can be used for the prevention and treatment of venous thromboembolic disease.

Process for Preparing a Pharmaceutical Batch(es) or a Pharmaceutical Formulation(s)

Various embodiments of the present invention relate to a compounding process for preparing a pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin.

1) Dissolving Bivalirudin in a Solvent to Form a Bivalirudin Solution

In the compounding process of various embodiments of the present invention, bivalirudin may be dissolved in a solvent to form a bivalirudin solution. Bivalirudin may be commercially

between about 0.010 g/mL and about 1 g/mL, or between about 0.050 g/mL and about 0.1 g/mL. Solvents may include aqueous and non-aqueous liquids, including but not limited to, mono- and di-alcohols such as methanol, ethanol, isopropyl alcohol, and propylene glycol; polyhydric alcohols such as glycerol and polyethylene glycol; buffers; and water.

The solvent may comprise carriers such as sugars. For example, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. Alternatively, the sugar may be a sugar alcohol, such as sorbitol or mannitol. The quantity of carrier in the solvent may be adjusted to provide a pharmaceutical batch or pharmaceutical formulation preferably having a ratio of the carrier to the active ingredient of between about 5:1 and about 1:10, or between about 1:1 and about 1:4, or more preferably about 1:2.

Bivalirudin can be dissolved in the solvent by methods known in the art, preferably by adding the bivalirudin to the solvent. For example, bivalirudin may be added to the solvent rapidly, slowly, in portions, at a constant rate, at a variable rate, or a combination thereof. A mixing device known in the art may be used to dissolve bivalirudin. Examples of mixing devices may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing device may be applied at a mixing rate between about 100 and about 2000 rpm, or between about 300 and about 1500 rpm. The solution resulting from dissolving the bivalirudin in the solvent is referred to here as the "bivalirudin solution" or alternatively the "first solution."

2) Mixing a pH-Adjusting Solution with the Bivalirudin Solution to Form a Compounding Solution

The compounding process may comprise mixing a pH-adjusting solution with the bivalirudin solution to form a compounding solution. The pH-adjusting solution may be prepared before, after, or simultaneously with, the bivalirudin solution.

The pH-adjusting solution may comprise a base dissolved in a solvent, wherein the solvent is referred to here as the "pH-adjusting solution solvent." In other words, the solution resulting from the combination of the base with the pH-adjusting solution solvent is referred to here as the "pH-adjusting solution." The pH-adjusting solution may also comprise a neat base such as pyridine or a volatilizable base such as ammonium carbonate.

The base may be an organic base or an inorganic base. The terms "inorganic base" and "organic base," as used herein, refer to compounds that react with an acid to form a salt; compounds that produce hydroxide ions in an aqueous solution (Arrhenius bases); molecules or ions that capture hydrogen ions (Bronsted-Lowry bases); and/or molecules or ions that donate an electron pair to form a chemical bond (Lewis bases). In certain processes, the inorganic or organic base may be an alkaline carbonate, an alkaline bicarbonate, an alkaline earth metal carbonate, an alkaline hydroxide, an alkaline earth metal hydroxide, an amine, or a phosphine. For example, the inorganic or organic base may be an alkaline hydroxide such as lithium hydroxide, potassium hydroxide, cesium hydroxide, or sodium hydroxide; an alkaline carbonate such as calcium carbonate or sodium carbonate; or an alkaline bicarbonate such as sodium bicarbonate.

Solvents may include aqueous and non-aqueous liquids, including but not limited to, mono- and di-alcohols such as methanol, ethanol, isopropyl alcohol, and propylene glycol; [illegible]

may comprise carriers such as dissolved sugars. For instance, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. The sugar may also be a sugar alcohol, such as sorbitol or mannitol. The quantity of the carrier in the pH-adjusting solution solvent may be adjusted to provide the final product as described above.

The base is mixed or dissolved in the pH-adjusting solution solvent. The mixing or dissolution can be performed by methods known in the art. For instance, the base may be added to the pH-adjusting solution solvent rapidly, slowly, in portions, at a constant rate, at a variable rate, or a combination thereof. Also, a mixing device known in the art may be used to mix the base and the pH-adjusting solution solvent. Examples of mixing devices may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing device may be applied at a mixing rate between about 100 and about 1500 rpm, or between about 300 and about 1200 rpm. The base is added/mixed with the pH-adjusting solution solvent in a quantity that will result in a pH-adjusting solution that is characterized as being between about 0.01 N and about 5 N, or between about 0.1 N and 1 N.

The pH-adjusting solution may then be mixed with the bivalirudin solution. This mixing may occur by adding the pH-adjusting solution to the bivalirudin solution. Alternatively, the bivalirudin solution may be added to the pH-adjusting solution, or the pH-adjusting solution and the bivalirudin solution may be added simultaneously (into a separate vessel), or there may be a combination of these addition methods thereof. It is important during the adding or mixing of the pH-adjusting solution and the bivalirudin solution that pH is controlled. See below. The solution resulting from mixing the pH-adjusting solution and the bivalirudin solution is referred to here as the "compounding solution," or the "second solution." The compounding solution or the second solution can refer to the bivalirudin solution during or after the pH-adjusting solution is added, or can refer to the pH-adjusting solution during or after the bivalirudin solution is added, or can refer to the resulting solution formed during or after both the pH-adjusting solution and the bivalirudin solution are added together.

The mixing of the pH-adjusting solution and the bivalirudin solution may occur under controlled conditions. For example, temperature may be controlled by means known in the art, such as by mixing the pH-adjusting solution and the bivalirudin solution in a vessel inside a cooling jacket. The temperature may be set between about 1° C. and about 25° C., or between about 2° C. and about 10° C. In some instances, the temperature may exceed 25° C. for limited periods of time. Also, the mixing of the pH-adjusting solution and the bivalirudin solution may occur under controlled conditions such as under nitrogen, etc.

The pH-adjusting solution will be efficiently mixed with the bivalirudin solution to form the compounding solution. Efficient mixing of the pH-adjusting solution with the bivalirudin solution will minimize levels of Asp^9-bivalirudin in the compounding solution. "Minimize" as used herein refers to the generation of a level of Asp^9-bivalirudin in the compounding solution that is less than about 0.6%, or less than about 0.4%, or less than about 0.3%.

Critical to the efficient mixing is the fact that the isoelectric point of bivalirudin is about 3.6. As the bivalirudin solution itself has a pH of between about 2.5 and about 2.8, and the compounding solution is adjusted to a final pH of between [illegible]

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