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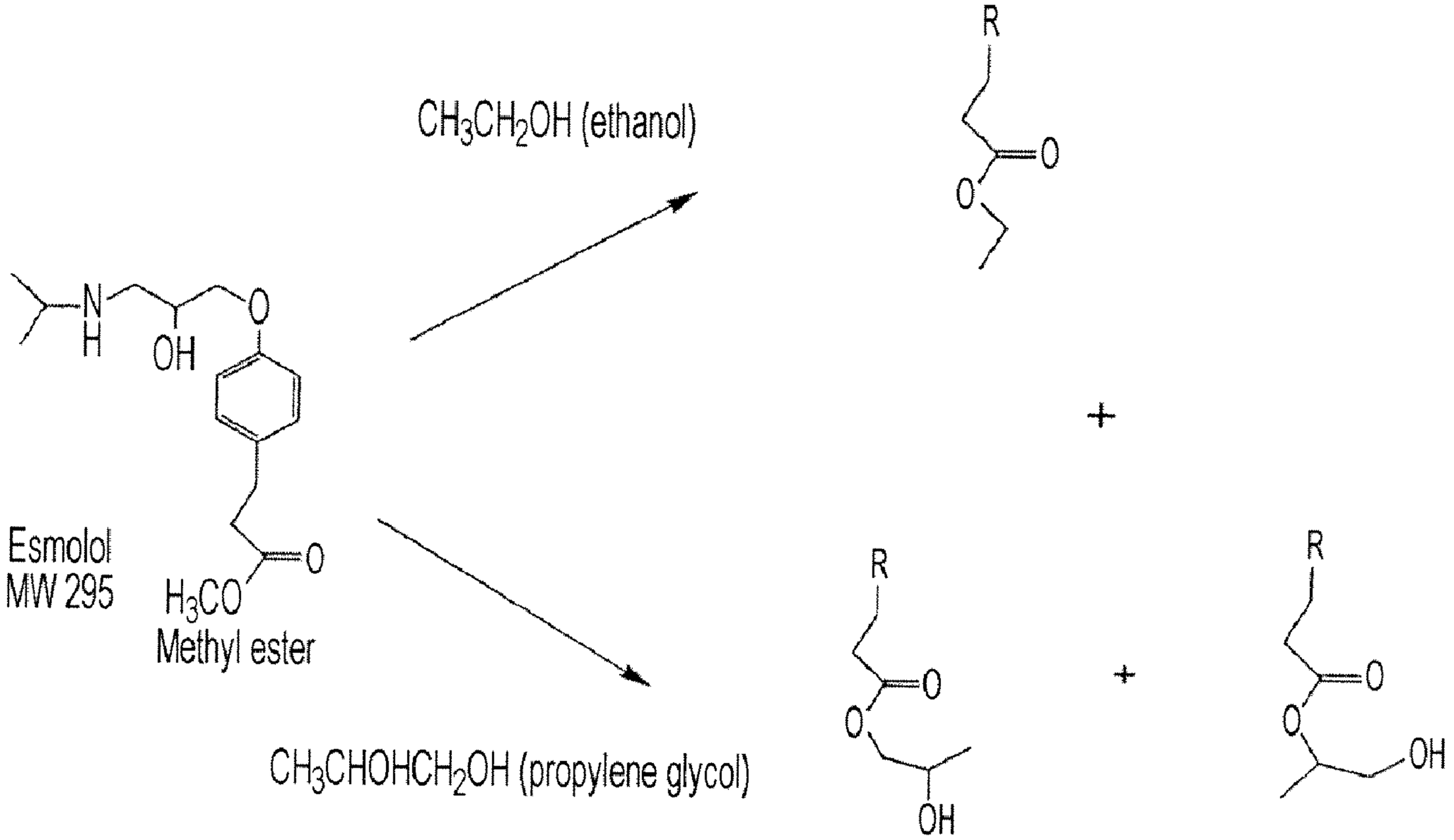
(71) Demandeurs/Applicants:
BAXTER INTERNATIONAL INC., US;
BAXTER HEALTHCARE S.A., CH

(72) Inventeurs/Inventors:
TIWARI, DEEPAK, US;
OWOO, GEORGE, US;
NAYAK, REKHA, US;
BURHOP, KENNETH E., US

(74) Agent: SIM & MCBURNEY

(54) Titre : ESMOLOL CONCENTRE MULTIDOSE COMPORTANT DE L'ALCOOL BENZYLIQUE
(54) Title: MULTI-DOSE CONCENTRATE ESMOLOL WITH BENZYL ALCOHOL

Figure 1. Esmolol Transesterification Reaction



(57) Abrégé/Abstract:
Disclosed are concentrate esmolol injection essentially free from other related esters of esmolol and diluted esmolol compositions. The concentrate esmolol formulation includes from about 25-1000 mg/ml of esmolol and about 1-25 % w/v of benzyl alcohol and

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(57) Abrégé(suite)/Abstract(continued):
the combination thereof. The compositions can also be used as multi-dose compositions. The present invention also discloses diluted, ready-to-use compositions of esmolol prepared by dilution of the present invention concentrates. Also disclosed are methods of making and using the ready-to-use compositions of the present invention.

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(71) Applicants *(for all designated States except US)*: **BAXTER INTERNATIONAL INC.** [US/US]; One Baxter Parkway, DF2-2W, Deerfield, Illinois 60015 (US). **BAXTER HEALTHCARE S.A.** [CH/CH]; Hertistrasse 2, CH-8304 Wallisellen (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TIWARI, Deepak** [US/US]; 53 Vones Lane, Raritan, New Jersey 08869 (US). **OWOO, George** [US/US]; 208 Harding Avenue, North Plainfield, New Jersey 07063 (US). **NAYAK, Rekha** [IN/US]; 13 Arlene Court, Monmouth Junction, New Jersey 08852 (US). **BURHOP, Kenneth, E.** [US/US]; 11009 Sandpiper Court, Spring Grove, Illinois 60081 (US).

(74) Agents: **DEMOOR, Laura, J.** et al.; Baxter Healthcare Corporation, One Baxter Parkway, DF2-2W, Deerfield, Illinois 60015 (US).

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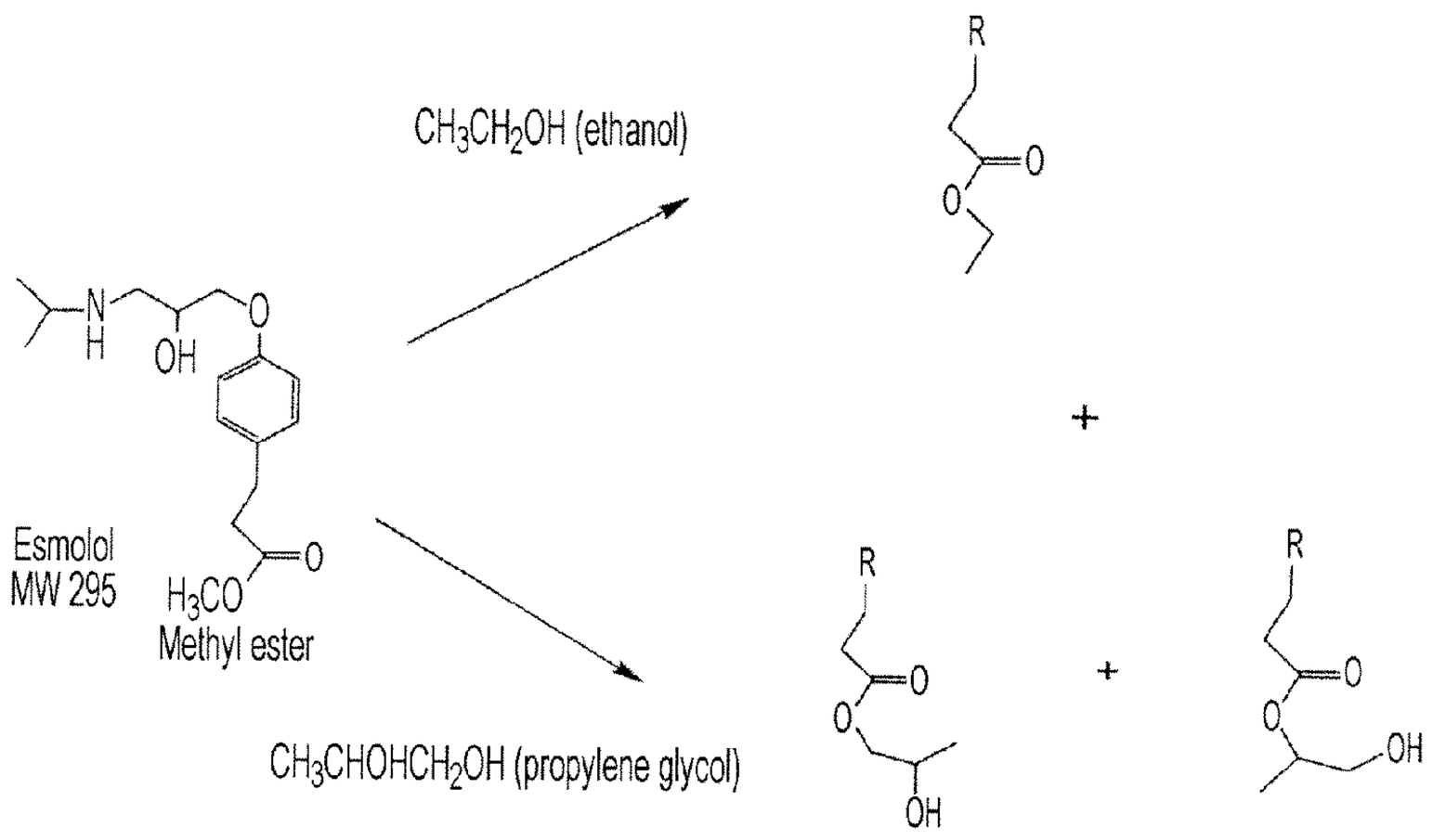
(54) Title: MULTI-DOSE CONCENTRATE ESMOLOL WITH BENZYL ALCOHOL

Figure 1. Esmolol Transesterification Reaction



(57) **Abstract:** Disclosed are concentrate esmolol injection essentially free from other related esters of esmolol and diluted esmolol compositions. The concentrate esmolol formulation includes from about 25-1000 mg/ml of esmolol and about 1-25 % w/v of benzyl alcohol and the combination thereof. The compositions can also be used as multi-dose compositions. The present invention also discloses diluted, ready-to-use compositions of esmolol prepared by dilution of the present invention concentrates. Also disclosed are methods of making and using the ready-to-use compositions of the present invention.

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MULTI-DOSE CONCENTRATE ESMOLOL WITH BENZYL ALCOHOL

BACKGROUND OF THE INVENTION

[0001] The present invention is directed to enhanced stability concentrate esmolol formulations. More specifically, the invention is directed to a concentrate esmolol formulation stabilized with benzyl alcohol. The compositions of the present invention are also suitable as multiple-dose compositions. Additionally, the present invention is directed to ready-to-use, diluted compositions made by dilution of the concentrate esmolol compositions of the present invention.

[0002] Esmolol (and its pharmaceutically acceptable salts, e.g., hydrochloride salt) and related compounds have β-adrenergic blocking activity. β-blockers are therapeutically effective agents for the treatment and prophylaxis of cardiac disorders when administered in the appropriate dosage. Esmolol, which is a short-acting β-blocker, is often times used in acute care settings to control the heart rate of a patient. The short acting property of esmolol is due to its rapid hydrolysis of the labile aliphatic methyl ester group in the blood.

[0003] Ready-to-use isotonic, and concentrate formulations, of esmolol are disclosed in U.S. Patent Nos. 5,017,609, 6,310,094, and 6,528,540, incorporated herein by reference. Methods for making esmolol and methods for treatment or prophylaxis of cardiac disorders using such compounds are disclosed in U.S. Patent 4,387,103, and 4,593,119, incorporated herein by reference. A current commercial esmolol concentrate formulation, covered under U.S. Patent No. 5,017,609, comprises about 250 mg/ml of esmolol hydrochloride, 25% by volume ethanol, 25% by volume propylene glycol, 17 mg/ml sodium acetate trihydrate, and 0.715% by volume of glacial acetic acid. This composition is not intended for direct injection but for subsequent dilution with a suitable diluent.

[0004] The stability of esmolol hydrochloride {methyl 3-[4-[2-hydoxy-3-(isopropylamino)propoxy]phenyl]propionate hydrochloride} in water is mediated by the rate of acid/base catalyzed hydrolysis of the labile aliphatic methyl ester group and it degrades into ASL-8123 {methyl 3-[4-[2-hydoxy-3-(isopropylamino) propoxy]phenyl]propionic acid}. Ready-to-use isotonic formulations address some of the stability issues in a truly aqueous formulation and has only one degradant, ASL-8123. The current commercial concentrate formulation employs excipients (ethanol and propylene glycol) to stabilize the hydrolytic reaction, but those excipients leads to the formation of other related ester degradants.

Therefore, the current commercial esmolol concentrate formulation under long term storage conditions results in the formation of ethyl and propoyl esters of esmolol in addition to ASL-8123. Furthermore the excipients (ethanol and propylene glycol) used to stabilize the current commercial esmolol concentrate formulation have been associated with potential injection site pain or irritation.

[0005] Therefore, it would be desirable to provide a stabilized concentrate esmolol composition that eliminates the formation of related ester degradants, does not include potentially irritating propylene glycol and ethanol excipients, is simpler to make than the prior art concentrate composition and, optionally, can be preserved rendering it applicable for multiple-dose use.

SUMMARY OF THE INVENTION

[0006] In one aspect of the present invention, a concentrate esmolol formulation is provided. The concentrate esmolol formulation comprises about 25-1000 mg/ml of esmolol (or pharmaceutically acceptable salts thereof), about 1 to 25 % by volume of benzyl alcohol and, optionally, from about 0.005 to about 2 molar (M) of a buffering agent. The compositions are pH adjusted to between about 3.5 and about 7.0. Benzyl alcohol, typically used as a preservative, has been surprisingly found to stabilize the concentrate esmolol compositions of the present invention.

[0007] In another aspect of the present invention a ready-to-use composition and a method of dosing such composition is provided. The method comprises the steps of providing a concentrate esmolol formulation of about 25-1000 mg/ml of esmolol (or a pharmaceutically acceptable salt thereof) and 1-25 % weight/volume benzyl alcohol, selecting a volume from the liquid for further dilution with a suitable diluent, followed by injection of the diluted product to the patient.

[0008] An advantage of the present invention is that, unlike prior art concentrate compositions of esmolol, the formulation does not form degredants of other related esters of esmolol.

[0009] Another advantage of the present invention is that it offers the flexibility of multiple-dose use of the formulation without microbial cross-contamination.

[0010] Another advantage of the present invention is that it reduces the potential of injection site pain/irritation contributed by propylene glycol and ethanol excipients.

[0011] Still another advantage of the present invention is that it provides sterile, concentrate esmolol compositions that contain less excipients and are simpler to make than prior art concentrates.

BRIEF DESCRITPION OF THE DRAWING

[0012] FIG. 1 is a chemical scheme depicting the transecterification of esmolol in the presence of ethanol and propylene glycol to yield respective esters.

DETAILED DESCRIPTION OF THE INVENTION

[0013] The compositions of the present invention comprise esmolol, or pharmaceutically acceptable salts thereof, e.g., hydrochloride, and benzyl alcohol. As used herein, "esmolol" refers to esmolol free base and pharmaceutically acceptable salts thereof. The concentration of esmolol in the concentrate ranges from about 25-1000 mg/ml, and preferably is about 250 mg/ml.

[0014] As stated above, the main degradation pathway for esmolol is the hydrolysis of its aliphatic carboxy methyl ester moiety to yield ASL-8123. This degradation depends on the pH, buffer concentrations and concentration of esmolol. The current commercial esmolol concentrate formulation is stabilized by the presence of ethanol and propylene glycol. However, the historical stability data indicate that esmolol in the presence of these solvents undergoes transesterification reactions to yield ethyl and propylene glycol esters of esmolol. (See Figure 1.)

[0015] The compositions of the present invention contain an amount of benzyl alcohol to stabilize the esmolol concentrate compositions. Although benzyl alcohol is typically used as a preservative, it has surprisingly been found to stabilize concentrate esmolol compositions of the present invention. In general, the amount of benzyl alcohol present will depend on the concentration of esmolol present. A typical range of benzyl alcohol in the compositions will be from about 1 to 25 % weight/volume (w/v). Preferably, for esmolol concentrations of 250 mg/ml, benzyl alcohol will be present in a concentration of about 10 % w/v.

[0016] The concentrate of present invention can also include a pharmaceutically acceptable buffer to aid in maintaining the pH in a range of from about 3.5 to about 7.0. Preferably, the pH is maintained between about 4.5 and about 5.5, more preferably between 4.9 and 5.1. Degradation of esmolol occurs most rapidly when the pH is outside the range of

4.0 to 6.0 and is most stable around a pH of about 5.0. Suitable buffers are those buffers that provide sufficient buffering capacity at the desired pH range and are pharmaceutically acceptable for injection into a patient. Examples of buffers useful in the present invention include, but are not limited to, acetate, glutamate, citrate, tartrate, benzoate, lactate, gluconate, phosphate and glycine and conjugate acids thereof. The concentration of the buffer can be from about 0.005 to about 2 M. In a preferred embodiment, the buffering agent comprises a combination of sodium acetate and glacial acetic acid. A preferred combination of buffers can include sodium acetate at from about 0.005 to about 0.3 M and glacial acetic acid at from about 0.05 to about 0.3 M.

[0017] Suitable containers for housing the esmolol concentrate are known in the art. They include vial, syringe and ampoule presentations. Containers may be fabricated of polymeric materials or from glass. Preferred polymeric containers are free of polyvinylchlorine (PVC). Preferably, the container has excellent barrier properties. A preferred container retains a moisture barrier such as glass containers or polymeric containers including barrier layers or secondary packaging. An aluminum overpouch is a preferred moisture barrier for use as secondary packaging for polymeric containers lacking a moisture barrier of their own. Preferred containers should be able to withstand terminal sterilization such as autoclaving.

[0018] The compositions of the present invention are sterile. The compositions are preferably prepared and then sterilized in their final containers by autoclaving. Alternatively, the concentrate can be aseptically prepared or terminally sterilized via autoclaving separately and then placed in sterile containers using an aseptic procedure. Typical autoclave cycles used in the pharmaceutical industry to achieve terminal sterilization of the final product are 121 °C for 15 minutes. The esmolol concentrate of the present invention can be autoclaved at a temperature ranging from 115 to 130 °C for a period of time ranging from about 5 to 40 minutes with acceptable stability. Autoclaving is preferably carried out in the temperature range of about 119 to 122 °C for a period of time ranging from about 10 to 36 minutes.

[0019] In one embodiment the concentrate is housed in a clear glass or plastic syringe and terminally sterilized. These pre-filled syringes can be provided in various volumes to permit quick and easy preparation of either small volume or large volume parental dosage by dispensing the contents of the pre-filled syringes into standard or customized, pre-filled intravenous fluid bags.

[0020] In another embodiment, the concentrate esmolol compositions of the present invention are packaged in sealed vials, preferably of type I treated glass.

[0021] The present invention is also directed to diluted, esmolol compositions made with the esmolol concentrates of the present invention. A practitioner can make a diluted concentration of esmolol with the use of a preferred diluent for infusion into the patient. Suitable diluents include diluents used by practitioners skilled in the art. Typical examples include but are not limited to, sodium chloride solutions, Ringers' or dextrose solutions. While the desired, diluted concentration of esmolol will vary depending on need, typical concentrations range from about 5 to about 25 mg/ml, and preferably 10 mg/ml of esmolol.

[0022] Suitable routes of administration for the diluted compositions of the present invention include intravenous, subcutaneous, intradermal, intramuscular, intraarticular, and intrathecal. The diluted composition is preferably administered by intravenous infusion.

[0023] The following example compositions and method of manufacture further illustrate the invention but should not be construed as limiting its scope.

Example 1

[0024] The following describes the preparation of esmolol concentrate containing 250 mg/mL of esmolol HCl and benzyl alcohol. The concentration of each ingredient of the composition is as follows:

Ingredient	Concentration
Esmolol	250 mg/mL
Sodium Acetate Trihydrate	17mg/mL
Glacial Acetic Acid	0.00715mL/mL
Benzyl Alcohol, USP	10% w/v
Water for Injection, USP	Qs

The equipment and glassware for compounding, filtering, and filling are properly washed and depyrogenated. The filter assembly, filling tube assembly, and other parts and equipment are sterilized. Eighty percent (80%) of the final volume of cool water for injection is collected in a compounding tank. Glacial acetic acid and sodium acetate are then added to the tank. Esmolol hydrochloride is weighed and added to the tank. Required quantity of the benzyl alcohol is weighed and added to the tank. The solution is stirred until all excipients are

dissolved. The solution is then adjusted to pH 5.0 with sodium hydroxide or hydrochloric acid. The solution is brought to final volume with water for injection and mixed. The solution is filled in 10-mL type I treated flint ampoules and sealed. The product is the sterilized at 122°C for 20 minutes.

Example 2

[0025] The stability of esmolol hydrochloride at 55°C in water or water-benzyl alcohol solution is summarized in Tables 1 and 2, respectively. The stability of the formulation of Example 1 at 55 C in water is summarized in Table 3. As demonstrated by the data, the presence of benzyl alcohol greatly reduced the degradation of esmolol (Table 2). And the degradation of esmolol was further reduced when benzyl alcohol is utilized along with the buffer to maintain the pH at 5.0 (Table 3). The absence of propoyl ester degradants peak (at approximate relative retention times of 0.55 and 0.60 – from an HPLC chromatogram) and ethyl ester degradant peak (at approximate relative retention times of 2.10), indicate that the present invention does not contain any of the degradants seen in the prior art current commercial esmolol concentrate formulation. Replacing ethanol and propylene glycol with benzyl alcohol eliminates the transesterification reaction and the formation of ethyl and propylene glycol ester degradants of esmolol, thereby improving the stability and safety profile of the prior art concentrate formulation.

Table 1. Stability of 250 mg/mL Esmolol HCL in water at 55°C

Time Point	pH	% Assay	%ASL-8123	Degradants*
Initial	3.86	101.2	N.D	N.D
1 Week	3.33	87.1	33.8	N.D
2 Weeks	2.43	54.7	45.7	N.D
3 Weeks	2.30	26.7	71.7	N.D
4 Weeks	2.24	14.9	80.7	N.D

*at RRT = 0.55, 0.60 and 2.10

Table 2. Stability of 250 mg/mL Esmolol HCL with 10% Benzyl Alcohol in water at 55°C

Time Point	pH	Assay	%ASL-8123	Degradants*
Initial	3.89	100.7	N.D	N.D
1 Week	3.33	97.1	10.2	N.D
2 Weeks	2.43	82.9	16.3	N.D
3 Weeks	2.30	67.3	31.4	N.D
4 Weeks	2.24	47.0	50.7	N.D

*at RRT = 0.55, 0.60 and 2.10

Table 3. Stability of 250 mg/mL Esmolol HCL with 10% Benzyl Alcohol in buffered water at 55°C

Time Point	pH	% Assay	%ASL-8123	Degradants*
Initial	4.60	106.9	1.24	N.D
1 Week	4.60	101.2	2.70	N.D
4 Weeks	4.60	95.5	9.61	N.D

*at RRT = 0.55, 0.60 and 2.10

Although the present invention has been described by reference to certain preferred embodiments, it should be understood that the preferred embodiments are merely illustrative of the principles of the present invention. Therefore, modifications and/or changes may be made by those skilled in the art without departing from the true spirit and scope of the invention as defined by the appended claims.

What is claimed is:

1. A concentrate esmolol composition comprising:

a) about 25-1000 mg/ml of esmolol; and

b) from about 1-25% w/v of benzyl alcohol;

wherein the composition has a pH of about 3 and 7.

2. The composition of claim 1, further comprising a buffering agent.

3. The composition of claim 2, wherein the buffering agent comprises at least one of acetate, glutamate, citrate, tartrate, benzoate, lactate, gluconate, phosphate and glycine and conjugate acids thereof.

4. The composition of claim 3, wherein the buffering agent comprises sodium acetate and acetic acid.

5. The composition of claim 2, wherein the buffering agent is present in an amount of from about 0.005 to 2 M.

6. The composition of claim 1 comprising:

a) about 250 mg/mL esmolol;

b) about 10 % w/v of benzyl alcohol; and

c) about 0.1 M acetate.

7. The composition of claim 1 comprising:

a) about 50 mg/mL esmolol;

b) about 2 % w/v benzyl alcohol;

c) about 0.1 M acetate .

8. A ready-to-use composition comprising esmolol made by the process of:

a) providing a volume of a first composition comprising about 25-1000 mg/ml of esmolol, and from about 1-25% w/v benzyl alcohol, wherein the first composition has a pH of about 3 to 7; and

b) diluting the volume of the first composition with a volume of a second composition, the second composition comprising a pharmaceutically acceptable diluent for parenteral administration.

9. The composition of claim 8, wherein the first composition further comprises a buffering agent.

10. The composition of claim 9, wherein the buffering agent comprises at least one of acetate, glutamate, citrate, tartrate, benzoate, lactate, gluconate, phosphate and glycine and conjugate acids thereof.

11. The composition of claim 10, wherein the buffering agent comprises sodium acetate and acetic acid.

12. The composition of claim 9, wherein the buffering agent is present in an amount of from about 0.005 to 2 M.

13. The composition of claim 8, wherein the second composition is selected from the group consisting of: phosphate buffered saline, saline, Ringers' solution and dextrose solutions.

14. A method of dosing a patient with an esmolol composition comprising the steps of:

a) providing a volume of a first composition comprising about 25-1000 mg/ml of esmolol, and from about 1-25% w/v benzyl alcohol, wherein the first composition has a pH of about 3 to 7;

b) diluting the volume of the first composition with a volume of a second composition, the second composition comprising a pharmaceutically acceptable diluent for parenteral administration, to form a ready-to-use composition;

c) selecting a volume of the ready-to-use composition; and

d) dosing a patient with the volume of ready-to-use composition.

15. The method of claim 14, wherein the first composition further comprises a buffering agent.

16. The method of claim 15, wherein the buffering agent is present in a concentration of from about 0.005 to 2 M.

17. The method of claim 19, wherein the buffering agent comprises sodium acetate and acetic acid.

18. The method of claim 15, wherein the first composition comprises:

a) about 250 mg/mL esmolol;

b) about 10 % w/v of benzyl alcohol; and

c) about 0.1 M acetate.

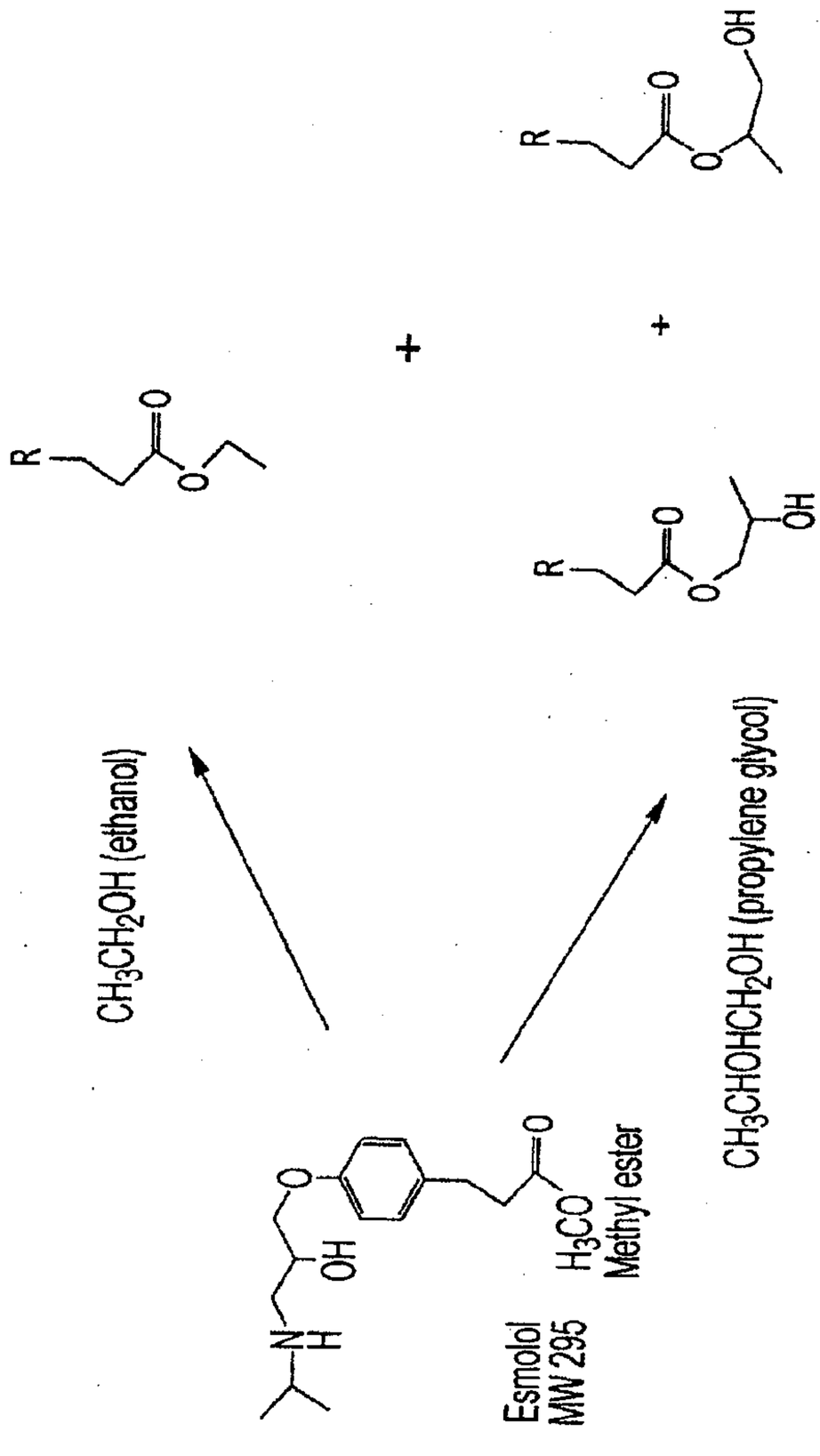
19. The method of claim 15, wherein the first composition comprises about 0.1 M acetate:

a) about 50 mg/mL esmolol;

b) about 2 % w/v benzyl alcohol; and

c) about 50 mg/mL esmolol.

Figure 1. Esmolol Transesterification Reaction



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