United States Patent [19]

Escobar et al.

[11] **Patent Number: 5,017,609**

[45] **Date of Patent: May 21, 1991**

[54] **PHARMACEUTICAL COMPOSITION AND METHOD OF TREATMENT OR PROPHYLAXIS OF CARDIAC DISORDERS**

[75] Inventors: **Agustin Escobar**, Aquadilla, P.R.; **Dietmar Wagenknecht**, Zion, Ill.; **Ahmad W. Malick**, Edison, N.J.

[73] Assignee: **E. I. Du Pont de Nemours and Company**, Wilmington, Del.

[21] Appl. No.: **437,293**

[22] Filed: **Nov. 16, 1989**

Related U.S. Application Data

[63] Continuation of Ser. No. 289,501, Dec. 23, 1988, abandoned, which is a continuation of Ser. No. 810,547, Dec. 18, 1985, abandoned, which is a continuation-in-part of Ser. No. 598,061, Apr. 9, 1984, abandoned.

[51] **Int. Cl.**[5] **A61K 31/24**

[52] **U.S. Cl.** **514/538**; 514/821

[58] **Field of Search** 514/510, 511, 522, 524, 514/529, 532, 534, 538, 821

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,742,023	6/1973	Koppe et al.	260/471 R
3,872,147	3/1975	Koppe et al.	260/465
4,146,630	3/1979	Kampe et al.	546/207
4,191,765	3/1980	Fritsch et al.	424/248.53
4,346,093	8/1982	Friebe et al.	546/271
4,387,103	6/1983	Erhardt et al.	560/22
4,829,086	5/1989	Bodor	514/538

FOREIGN PATENT DOCUMENTS

0041491	12/1981	European Pat. Off.	514/538

OTHER PUBLICATIONS

Remington's Pharmaceutical Sciences, 16th ed. (1980), pp. 214, 238, 1253–1256 and 1463–1468.

Morrison and Boyd, *Organic Chemistry*, 3rd Edition, Sec. 20.16, p. 675.

L. H. Smith, *Journal of Applied Chemistry and Biotechnology*, 28(3):201–212 (1978).

Hisashi Nogami et al., *Chemical and Pharmaceutical Bulletin*, vol. 10, pp. 1158–1160 (1962).

Joseph M. Talmage et al., *Journal of Pharmaceutical Sciences*, vol. 57, No. 6, pp. 1073–1074 (Jun. 1968).

Pharmaceuticals, vol. 66, p. 6499, 68878k (1967).

H. A. Garrera et al., *Rev. Latinoamer, Quim.*, 7:4–8 (1976).

P. B. Sheth et al., *Journal of Pharmaceutical Sciences*, vol. 56, No. 8, pp. 983–986 (Aug. 1967).

M. Balakrishnan et al., *Tetrahedron Letters*, No. 45, pp. 4617–4620 (1972).

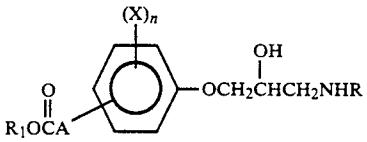
H. A. Garrera et al., *Rev. Latinoamer, Quim.*, 5:201–205 (1974).

Primary Examiner—Joseph A. Lipovsky

Attorney, Agent, or Firm—Bernard, Rothwell & Brown

[57] **ABSTRACT**

A pharmaceutical composition is disclosed, which contains a short-acting β-blocking compound of the formula



wherein R_1 may be an alkyl, cycloalkyl, alkenyl, alkynyl, alkyl carboxymethyl, aryl carboxymethyl, aryl or aralkyl, A may be an alkylene or alkenylene, X may be independently amino, hydrogen, halogen, hydroxy, alkoxy, aryloxy, aralkyl, cyano, amido or trifluoromethyl, n is an integer from 1 to about 4, R may be an alkyl, propargyl, dimethylpropargyl or hydroxyalkyl; or a pharmaceutically acceptable salt thereof in a hydroalcoholic solution further containing a physiologically acceptable buffering agent, ethanol and a physiologically acceptable liquid polyhydric compound. A method for treatment or prophylaxis of cardiac disorders using the composition of the present invention is also disclosed.

10 Claims, 2 Drawing Sheets

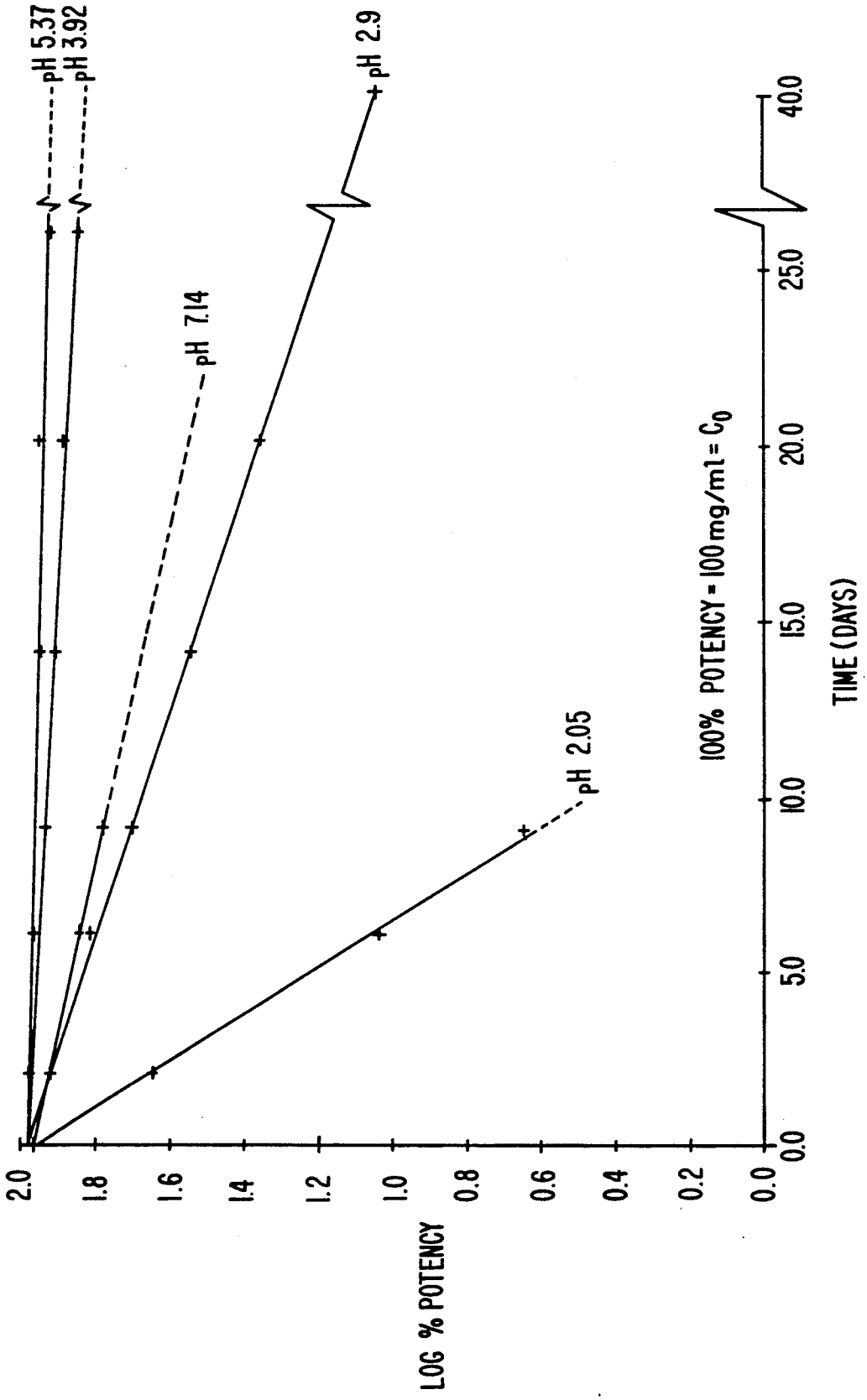
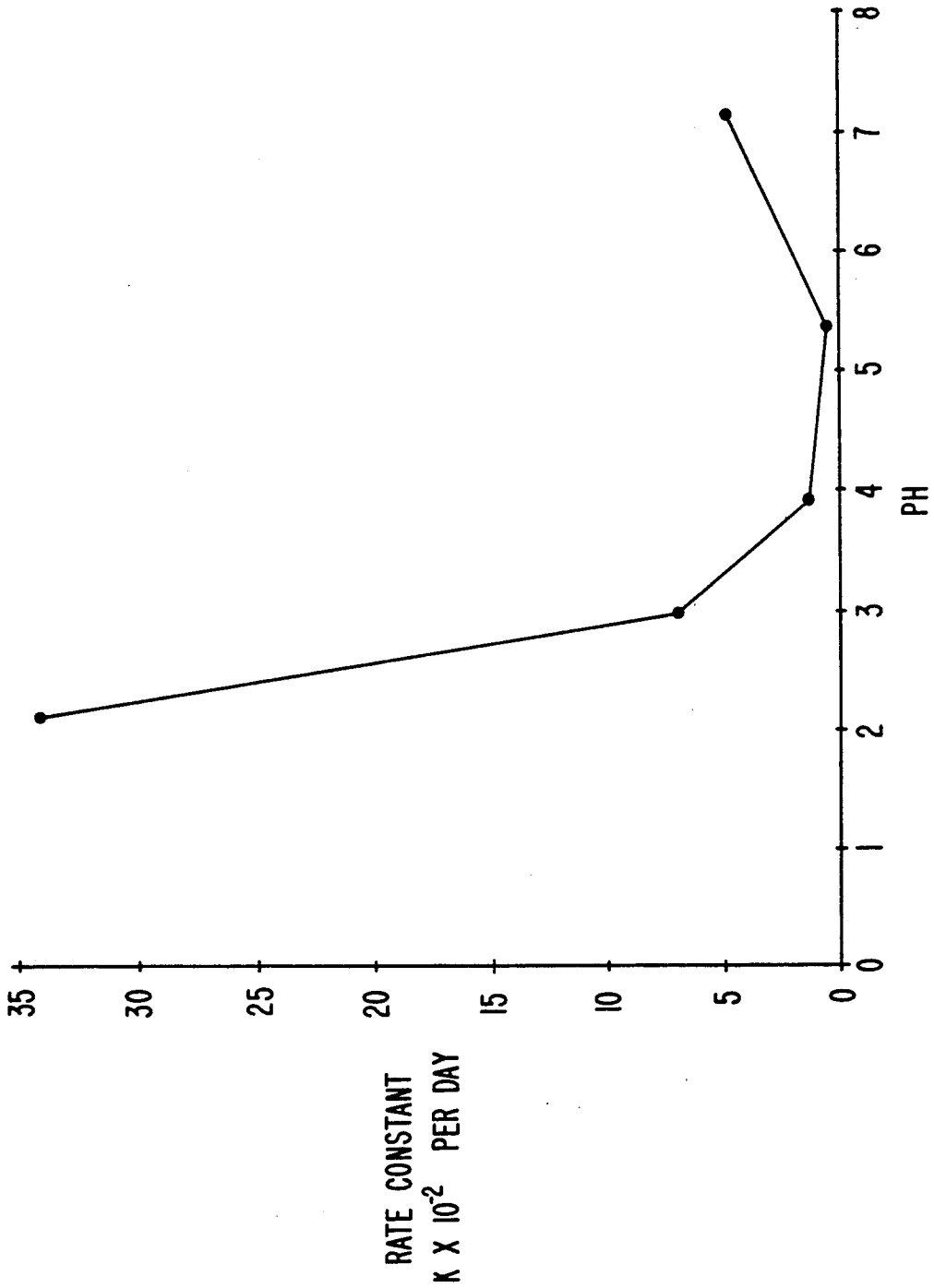


FIG. 1.

FIG. 2.



PHARMACEUTICAL COMPOSITION AND METHOD OF TREATMENT OR PROPHYLAXIS OF CARDIAC DISORDERS

This is a continuation of application Ser. No. 07/289,501, filed Dec. 23, 1988, now abandoned which is a continuation of application Ser. No. 810,547, filed Dec. 18, 1985, now abandoned which is a continuation-in-part of Ser. No. 598,061, filed Apr. 9, 1984, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to pharmaceutical compositions which contain short-acting β-adrenergic blocking agents. More particularly, the invention concerns novel compositions in which ester-containing β-blocking drugs are stabilized against hydrolysis during shipping and storage.

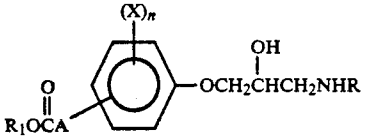
In the past, the emphasis in β-blocker research has been to develop stable drugs which could be administered to cardiac patients over relatively long periods of time. However, often it is desirable in the critical care setting to quickly reduce heart work or improve rhythmicity during a cardiac crisis, e.g., during or shortly after a myocardial infarction. Conventional β-blocking agents can be employed for such treatment, but their long durations of action can cause undesirable side effects.

Recently, certain compounds containing ester functions have been found to possess β-adrenergic blocking activity. (See U.S. Pat. No. 4,387,103 to Erhardt, et al., June 7, 1983.) These compounds generally have a short duration of action in vivo, and do not possess the disadvantages of the conventional β-blockers described above. The ester groups in these compounds have, however, been found to be somewhat unstable in aqueous environments, such as intravenous infusion solutions. The practical effect of this instability is that conventional compositions containing the compounds have relatively short shelf lives, thus making commercial distribution and storage difficult.

Therefore, there remains a need for pharmaceutical preparations of short-acting β-blockers which are stable in vitro and have a relatively long storage life.

SUMMARY OF THE INVENTION

In accordance with the present invention, disclosed herein is a pharmaceutical composition for the treatment or prophylaxis of cardiac disorders in a mammal comprising from about 0.1 to about 30% by weight of a β-adrenergic blocking compound having the formula



where R_1 is an alkyl having from 1 to about 6 carbon atoms, cycloalkyl of from 3 to about 5 carbon atoms, alkenyl of from 2 to about 5 carbon atoms, alkynyl of from 3 to about 5 carbon atoms, alkyl carboxymethyl where the alkyl is from 1 to about 5 carbon atoms, aryl carboxymethyl in which the aryl portion contains from 6 to about 10 carbon atoms, aryl of from 6 to about 10 carbon atoms, or aralkyl wherein the alkyl portion contains from 1 to about 6 carbon atoms and the aryl portion represents substituted or unsubstituted monocyclic or polycyclic aromatic ring systems of from 6 to about 10 carbon atoms; A is an alkylene from about 1 to about 5 carbon atoms, or alkenylene of from 2 to about 5 carbon atoms; X is independently amino, hydrogen, halogen, hydroxy, alkoxy, aryloxy, aralkyl, cyano, amido, or trifluoromethyl; n is an integer from 1 to about 4; R is alkyl having from 1 to about 5 carbon atoms, propargyl, dimethylpropargyl, or hydroxyalkyl having from 1 to about 6 carbon atoms; and its pharmaceutically acceptable salts in a hydroalcoholic solution further comprising from about 0.05 to about 2 molar physiologically acceptable buffering agent; from about 5 to about 60% by volume ethanol; from about 5 to about 60% by volume of a physiologically acceptable liquid polyhydric compound; and said hydroalcoholic solution having a pH of from about 4.0 to about 6.0. A method for the treatment or prophylaxis of cardiac disorders in a mammal comprising parenteral administration of the composition of the invention to such mammal is also disclosed.

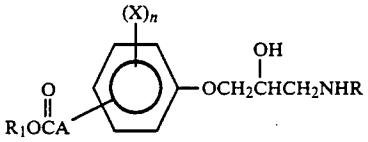
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: A graphic depiction of the effect of various pH levels on the potency of methyl 3-(p-phenoxypropanolamine) propionate over time.

FIG. 2: A graphic depiction of rate of degradation of methyl 3-(p-phenoxypropanolamine) propionate at 55° C. and at various pH levels.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, it has been discovered that a stable pharmaceutical composition possessing a relatively long shelf life can be prepared using short-acting, ester-containing β-blockers of the formula:



where R_1 may be an alkyl having from 1 to about 6 carbon atoms such as methyl, ethyl, propyl, t-butyl, isopentyl, and the like; cycloalkyl of from 3 to about 5 carbon atoms such as cyclopropyl, cyclopentyl, methyl cyclopropyl, and the like; alkenyl of from 2 to about 5 carbon atoms such as ethenyl, propenyl, 2-methyl-2-butenyl, and the like; alkynyl of from 3 to about 5 carbon atoms such as ethynyl, propynyl, 3-methyl-1-butynyl, and the like; alkyl carboxymethyl where the alkyl is from 1 to about 5 carbon atoms such as methyl carboxymethyl, ethyl carboxymethyl, propyl carboxymethyl, and the like; aryl carboxymethyl in which the aryl portion contains from 6 to about 10 carbon atoms such as phenyl carboxymethyl, napthyl carboxymethyl and the like; aryl of from 6 to about 10 carbon atoms such as phenyl, 2-tolyl, 2-methoxyphenyl, naphthyl, and the like; or aralkyl in which the alkyl portion contains from 1 to about 6 carbon atoms and the aryl portion represents substituted or unsubstituted monocyclic or polycyclic aromatic ring systems of from 6 to about 10 carbon atoms such as benzyl, phenethyl, 1-naphthylpropyl, 3,4-dimethoxyphenethyl, naphthylethyl, and the like.

A may be an alkylene from about 1 to about 5 carbon atoms such as methylene, ethylene, propylene, and the like; or alkenylene of from 2 to about 5 carbon atoms such as ethenylene, propenylene, isobutylenylene, and the like.

X is independently amino, hydrogen, halogen, hydroxy, alkoxy of from about 1 to about **10** carbon atoms such as methoxy, ethoxy and the like, of from about 6 to about 10 carbon atoms such as phenyloxy and the like, wherein the alkyl portion contains from 1 to about 6 carbon atoms and the aryl portion contains from 6 to about 10 carbon atoms such as phenylmethyl, p-methylbenzylmethyl dimethylbenzyl, phenyl t-butyl, 3,4-dimethoxyphenethyl and the like, (preferably dimethylbenzyl, phenyl t-butyl, 3,4-dimethoxyphenethyl), cyano, amido, or trifluoromethyl, and n is an integer from 1 to about 4.

R may be an alkyl having from 1 to about 5 carbon atoms such as methyl, ethyl, propyl, t-butyl, isopentyl, and the like; propargyl; dimethylpropargyl; or hydroxyalkyl having from 1 to about 6 carbon atoms such as hydroxymethyl, hydroxyethyl, 2-hydroxypentyl and the like.

In preferred compounds, R_1 is ethyl or methyl, A is ethylene, X is hydrogen, the

group is in the para position with respect to the side chain containing the —R group, and/or —R is represented by —W—B where —W— is an alkylene containing from 1 to about 10 carbon atoms, and —B is $—NR_2COR_3$, $—NR_2CONR_3R_4$, $—NR_2SO_2R_3$, $—NR_2SO_2NR_3R_4$, $—NR_2COOR_5$ or $—NHR_6$, where R_2, R_3, R_4 and R_5 may each be hydrogen, lower alkyl of from about 1 to about 10 carbon atoms, lower alkoxyalkyl of from 1 to about 10 carbon atoms, lower alkoxyaryl wherein the alkoxy portion contains from 1 to about 6 carbon atoms and the aryl portion contains from 6 to about 10 carbon atoms, lower cycloalkyl of from 3 to about 10 carbon atoms, lower alkenyl of from 1 to about 10 carbon atoms, lower alkynyl of from 1 to about 10 carbon atoms, aryl of from 6 to about 10 carbon atoms, heteroaryl of from about 4 to about **10** carbon atoms or aralkyl wherein the alkyl portion contains from 1 to about 6 carbon atoms and the aryl portion contains from 6 to about 10 **carbon atoms, except that** R_3 and R_5 are not hydrogen when B is $—NR_2SO_2R_3$ or $—NR_2COOR_5$, or R_3 and R_4 may together with N form a 5-to 7-membered heterocyclic group, and R_6 is unsubstituted or substituted pyridinyl, phenyl, naphthyl or indoyl the optional R_6 substituents being the same as X defined above. In one embodiment, R_2, R_3, R_4 and R_5 are hydrogen, or R_3 and R_4 together with N form a 5–7 membered heterocyclic group.

In one embodiment, R_1 is lower alkyl of from 1 to about 5 carbon atoms or lower alkenyl of from 2 to about 5 carbon atoms; A is alkylene of up to about 3 carbon atoms; X is lower alkyl of from 1 to about 10 carbon atoms, lower alkenyl of from 2 to about 10 carbon atoms, lower alkynyl of from 2 to about 10 carbon atoms, lower alkoxy of from 1 to about 10 carbon atoms, halogen, acetamido, amino, nitro, alkylamino of from 1 to about 10 carbon atoms, hydroxy, lower hydroxyalkyl of from 1 to about 10 carbon atoms, or cyano; n is an integer of from about 1 to about 4; R is lower alkyl of from 1 to about 10 carbon atoms or aralkyl wherein the alkyl portion contains from about 1 to about 6 carbon atoms and the aryl portion contains from about 6 to about 10 carbon atoms. According to this embodiment, the R_1-containing group preferably is in the ortho- or para-position with respect to the R-containing group. Preferably, R_1 is a lower alkyl or alkenyl group having from 1 to about 3 carbon atoms, and X is hydrogen, lower alkoxy of from 1 to about 5 carbon atoms, lower alkyl of from 1 to about 5 carbon atoms, halogen or cyano. When the X substituent is a halogen, X preferably is fluorine. R_1 preferably is methyl or ethyl, with methyl being particularly preferred. According to this embodiment, R preferably is lower alkyl of from 1 to about 5 carbon atoms or aralkyl wherein the alkyl portion contains from 1 to about 5 carbon atoms and the aryl portion contains from 6 to about 10 carbon atoms. In particularly preferred embodiments, R is isopropyl, t-butyl or 3,4-dimethoxyphenethyl, and X is hydrogen with n being 4. When R_1 is methyl or ethyl, A preferably is ethylene, and R is isopropyl, t-butyl or 3,4-dimethoxyphenethyl. Most preferably, R is isopropyl.

Methods for producing the above-described compounds are known in the prior art. For example, U.S. Pat. No. 4,387,103 to Erhardt et al. (incorporated herein by reference) discloses methods for preparing above-defined compounds wherein A is alkylene. Methods for preparing above-defined compounds wherein A is alkenylene are described in U.S. Pat. No. 4,191,765 to Fritsch et al. (incorporated herein by reference).

The above-described β-blocking compounds may be separated into optically active enantiomers using conventional methods. While both configurations are active β-blockers, the l-isomers have been found to be more active than their dextrorotary counterparts.

In one embodiment of the present invention, the composition contains a pharmaceutically acceptable acid addition salt of an above described β-blocking compound, e.g., a hydrochloride, sulfate, phosphate, gluconate, tartrate, etc. salt.

The composition of the present invention consists of a hydroalcoholic solution containing an above described β-blocking compound (or its pharmaceutically acceptable salt) at a concentration of from about 0.1 to about 30% by weight. Concentrations of less than about 0.1% (weight) of the β-blocking compounds in solutions generally do not provide effective β-blocking activity at practical infusion rates, while there is generally no added benefit to having concentrations greater than about 30% (weight) of the β-blocker in solution. In particularly preferred compositions, the concentration of β-blocking compound in solution is from about 1 to about 30% by weight.

One component of the hydroalcoholic solution is ethanol, preferably at a concentration of from about 5 to about 60% by volume. Ethanol has been found to be important in the stabilization of the β-blocking compound according to the present invention.

The hydroalcoholic solution also contains a physiologically acceptable liquid polyhydric compound, preferably at a concentration of from about 5 to about 60% by volume. Physiologically acceptable liquid polyhydric compounds include, but are not limited to, alkyls of from 1 to about 10 carbon atoms having two or more adjacent hydroxyl groups such as ethylene glycol, propylene glycol, glycerol and the like; polyethyleneglycols having a molecular weight of from about 200 to

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.