

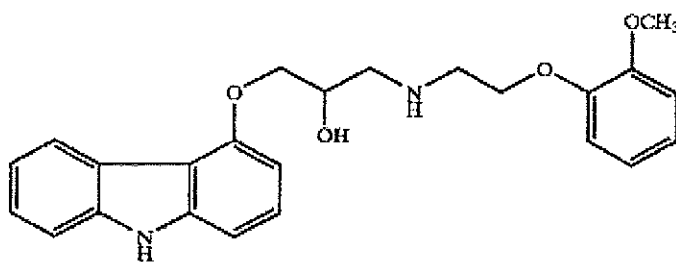
CONTROLLED RELEASE CARVEDILOL FORMULATION

FIELD OF THE INVENTION

The present invention relates to a controlled released carvedilol formulation for less frequent, preferably once daily administration. More specifically, the present invention also relates to the use of such controlled released formulation in the treatment and/or prophylaxis of one or more conditions in subjects suffering from, for example, cardiovascular disorders

BACKGROUND OF THE INVENTION

The chemical name of carvedilol is ((±)1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]-amino]-2-propanol), the structure of which is shown as follows:



Carvedilol is a nonselective beta-adrenergic blocking agent with vasodilatory actions due to alpha-adrenoreceptor blockage. It is commonly used for the treatment of cardiovascular diseases, such as hypertension, congestive heart failure or left ventricular dysfunction following myocardial infarction. The anti-hypertensive actions of carvedilol result primarily from alpha-adrenoreceptor blockage, whereas the beta-adrenergic blocking action prevents the unwanted side effect, mainly reflex tachycardia, when used in the treatment of hypertension.

However, carvedilol has certain disadvantages in the treatment of medical conditions. For example, carvedilol is known to have solubility and stability problems and poor bioavailability. It is a weak base, so the solubility depends on the pH value. At pH values in the pharmaceutically relevant range of 1 to 8, the solubility of carvedilol in aqueous media increases from about 0.01 mg/ml to about 1 mg/ml. Furthermore, carvedilol presents low solubility in water, gastric fluid (simulated, TS, pH1.1) and intestinal fluid (simulated, TS without pancreatin, pH 7.5). Carvedilol also presents a narrow absorption window. The relative absorption of

carvedilol in the jejunum, ileum and colon is reported as 56%, 28% and 7% respectively. (See, e.g., WO2003/028718 and Nolte et al (Arzneimittelforschung 49(9):745-9,1999)) Carvedilol's solubility and absorption limitations dictate immediate release commercial formulations for carvedilol that are administered twice a day. (See, e.g., Coreg® Prescribing Information)

5 Given the disadvantages and currently available carvedilol formulations, a need exists for a controlled release formulation of carvedilol that provides adequate bioavailability and extended release duration, allowing for a less frequent dosage requirement.

SUMMARY OF THE INVENTION

10 The present invention is a controlled release formulation of carvedilol with adequate bioavailability and extended release duration. The formulation comprises a therapeutically effective amount of carvedilol or a pharmaceutically acceptable salt thereof, a matrix forming polymer, a solubility enhancer, and a pharmaceutically acceptable carrier.

15 The invention further provides a controlled release formulation of carvedilol with two or more subunits, wherein at least one subunit comprises a therapeutically effective amount of carvedilol or a pharmaceutically acceptable salt thereof, a matrix forming polymer, a pharmaceutically acceptable carrier and wherein at least one subunit comprises a therapeutically effective amount of carvedilol or a pharmaceutically acceptable salt thereof, a matrix forming
20 polymer, a solubility enhancer, and a pharmaceutically acceptable carrier.

Particularly, the present invention provides a controlled release formulation, comprising:

- (a) a therapeutically effective amount of carvedilol free base or carvedilol salt thereof;
- (b) a matrix forming polymer comprising one or more of the following: about 20% to about 60% by weight (e.g. about 25% to about 35% by weight) of Methocel K15M, about
25 15% to about 20% by weight of Methocel K100M, about 25% to about 35% by weight of Methocel E4M, about 35% to about 45% by weight of Eudragit RSPO, or about 35% to about 55% by weight of WSR N12NF;
- (c) a solubility enhancer comprising one or more of the following: about 25% to about 55% by weight of Povidone, about 25% to about 35% by weight of PEG6000, or about
30 35% to about 45% by weight of HPC-L; and
- (d) an excipient comprising one or more of the following: about 15% to about 35% by

weight of corn starch, or about 0.1% to about 2% by weight of magnesium stearate.

The present invention also provides a controlled release formulation, comprising two or more subunits wherein at least one of said subunits is an immediate release carvedilol subunit comprising a therapeutically effective amount of carvedilol free base or carvedilol salt thereof, a matrix forming polymer, a solubility enhancer and a pharmaceutically acceptable carrier, and wherein at least one of said subunits is a slow release carvedilol subunit comprising a therapeutically effective amount of carvedilol free base or carvedilol salt thereof, a matrix forming polymer and a pharmaceutically acceptable carrier.

According to one embodiment of the present invention, the carvedilol is free base carvedilol.

According to one embodiment of the present invention, the matrix forming polymer comprises one or more of the following: hydroxypropyl methylcellulose (HPMC), polyoxethylene oxide, alginate, methylcellulose, ethycellulose, methacrylic copolymer, or hydroethylmethylcellulose (HEMC).

According to one embodiment of the present invention, the solubility enhancer comprises one or more of the following: hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), or sodium lauryl sulfate (SLS).

According to one embodiment of the present invention, the pharmaceutically acceptable carrier comprises one or more of the following: lactose, corn starch or magnesium stearate.

The present invention further provides a controlled release formulation, comprising:

A. One or more immediate release subunits, comprising;

- (i) a therapeutically effective amount of carvedilol free base or carvedilol salt thereof;
- (ii) about 4% to about 5 % by weight of a matrix forming polymer comprising one or more of the following: hydroxypropyl methylcellulose (HPMC), polyoxethylene oxide, alginate, methylcellulose, ethycellulose, a methacrylic copolymer, or hydroethylmethylcellulose (HEMC); and
- (iii) about 0.01% to about 0.1% by weight of an excipient; and

B. One or more slow release subunits, comprising;

- (i) a therapeutically effective amount of carvedilol free base or carvedilol salt thereof;
- (ii) about 20% to about 55 % by weight of a matrix forming polymer comprising one or more of the following: hydroxypropyl methylcellulose (HPMC), polyoxethylene oxide, alginate, methylcellulose, ethycellulose, a methacrylic

copolymer, or hydroethylmethylcellulose (HEMC);

(iii) about 1.0% to about 30 % by weight of a solubility enhancer comprising one or more of the following: hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), or sodium lauryl sulfate (SLS); and

(iv) about 0.01% to about 25 % by weight of an excipient.

According to one embodiment of the present invention, the ethycellulose contains about 20% to about 80% (w/w) of ethoxyl.

According to one embodiment of the present invention, the methoxyl content of the hydroethylmethylcellulose (HEMC) is from about 10% to about 60% (w/w).

According to one embodiment of the present invention, the excipient comprises one or more of the following: lactose, corn starch or magnesium stearate.

According to one embodiment of the present invention, the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed AUC_{0-∞} of the controlled release formulation to a geometric mean of logarithmic transformed AUC_{0-∞} of the reference drug (Coreg CRTM) of about 0.80 to about 1.20; or

the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed AUC_{0-t} of the controlled release formulation to a geometric mean of logarithmic transformed AUC_{0-t} of the reference drug (Coreg CRTM) of about 0.80 to about 1.20; or

the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed C_{max} of the controlled release formulation to a geometric mean of logarithmic transformed C_{max} of the reference drug (Coreg CRTM) of about 0.80 to about 1.20.

According to one embodiment of the present invention, the controlled release formulation exhibits a first peak plasma T_{max1} of about 4 hours, and a second peak plasma T_{max2} of about 24 hours after oral administration to a patient.

Further provided is a method of making a controlled release formulation, comprising:

A. Making an immediate release subunit, comprising the steps of:

i. Mixing and blending a therapeutically effective amount of carvedilol, about 4% to about 5 % by weight of a matrix-forming polymer to form a first mixture;

ii. Granulating said first mixture into first granules; and

B. Making a slow release subunit, comprising the steps of:

i. Mixing and blending a therapeutically effective amount of carvedilol, about 20% to about 55 % by weight of a matrix-forming polymer to form a

mixture;

ii. Adding about 1.0% to about 30 % by weight of a solubility enhancer to said mixture to form a second mixture;

iii. Granulating said second mixture into said second granules; and

C. Adding about 0.01% to about 25% by weight of an excipient to said first and second granules, and compressing said first and second granules into a tablet.

According to one embodiment of the present invention, the step of granulating said first mixture further comprises heating said first mixture at a temperature about 50°C to about 70°C. The step of granulating said first mixture can further comprises sieving said first mixture through a 20 mesh sieve

According to one embodiment of the present invention, the step of granulating said second mixture further comprises heating said second mixture at a temperature about 50°C to about 70°C. The step of granulating said second mixture can further comprises sieving said second mixture through a 20 mesh sieve.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the dissolution profile of the controlled release formulation in Table 1;

Figure 2 shows the dissolution profile of the controlled release formulation in Table 2;

Figure 3 shows the dissolution profile of the controlled release formulation in Table 3;

Figure 4 shows the dissolution profile of the controlled release formulation in Table 4;

Figure 5 shows the dissolution profile of the controlled release formulation in Table 5;

Figure 6 shows the dissolution profile of the controlled release formulation in Table 6;

Figure 7 shows the dissolution profile of the controlled release formulation in Table 7;

Figure 8 shows the dissolution profile of the T1 and T2 formulations in Tables 8 and 9, respectively;

Figure 9 shows the dissolution profile of the T4 formulation in Table 10;

Figure 10(A) shows the mean plasma concentration-time profile of carvedilol with the Linear

ordinate after subjects received the reference drug (Coreg CRTM) (● R-Mean) and the T4 formulation (△ T- Mean); and

Figure 10(B) shows the mean plasma concentration-time profile of carvedilol with the Log-Linear ordinate after subjects received the reference drug (CoregTM) (● R-Mean) and the T4 formulation (△ T- Mean).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a controlled release carvedilol formulation, comprising a therapeutically effective amount of carvedilol or a pharmaceutically acceptable salt thereof, a matrix forming polymer, a solubility enhancer, and a pharmaceutically acceptable carrier.

In another aspect of the present invention, the controlled release formulation includes two or more subunits, wherein at least one subunit is an "immediate release" subunit and wherein at least one subunit is a "slow-release" subunit. The controlled release formulation delivers the desired pharmacokinetic profile by releasing carvedilol at different rates: a slow-release subunit that releases carvedilol slowly, and an immediate-release subunit that releases carvedilol more rapidly to provide a loading dose of carvedilol. One example of a subunit configuration includes: a single layered immediate release subunit combined with a single layered slow release subunit to form a bi-layered formulation. A second example is configured such that a slow release subunit forms the core and is surrounded by an immediate release subunit.

An "immediate-release subunit" comprises a therapeutically effective amount of carvedilol or a pharmaceutically acceptable salt thereof, a matrix forming polymer, and a pharmaceutically acceptable carrier. The immediate-release subunit releases carvedilol in a conventional or non-modified way, which is greater than or equal to about 60% of carvedilol released within two hours of administration, and generally within one hour of administration.

A "slow-release subunit" comprises a therapeutically effective amount of carvedilol or a pharmaceutically acceptable salt thereof, a matrix forming polymer, a solubility enhancer, and a pharmaceutically acceptable carrier. It releases carvedilol in a controlled or modified way over

an extended period of time after administration, preferably over a period of about twenty-four hours. The solubility enhancer serves to increase the solubility of carvedilol in the proximal small intestine and extends the time of absorption.

A "subunit" includes a composition, mixture, particle, pellet, microcapsule, microtablet, or other pharmaceutically acceptable configuration that can deliver carvedilol alone or when combined with other subunits.

"The effective amount," as used herein, refers to an amount that alleviates or reduces one or more symptoms of cardiovascular diseases, such as high blood pressure, shortness of breath, and ankle swelling. The term "controlled release," as used herein, refers to the gradual release of carvedilol at a controlled rate over an extended period of time, preferably 24 hours, after the administration. The plasma concentration of carvedilol remains within the therapeutic range over an extended period of time, preferably 24 hours.

CARVEDILOL

The formulation of the present invention comprises a therapeutically effective amount of carvedilol, which can be prepared by known methods, for example, U.S. Patent No 4,503,067, which is incorporated herein by reference. In one embodiment, carvedilol is in the form of the free base.

"Pharmaceutically acceptable salts" include derivatives of carvedilol, wherein carvedilol is modified by making acidic salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, salts of mineral or organic acids, for example, hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, benzoic, citric, maleic, succinic or methanesulfonic. Exemplary carvedilol salts include carvedilol benzoate, carvedilol citrate, carvedilol glutarate, carvedilol hydrobromide, carvedilol hydrochloride, carvedilol hydrogen phosphate, carvedilol dihydrogen phosphate, carvedilol lactate, carvedilol mandelate, carvedilol maleate, carvedilol mesylate, carvedilol oxalate, carvedilol sulfate, or a hydrate or solvate of the foregoing salts

Carvedilol or a pharmaceutically acceptable salt thereof used in the present invention may be in crystalline, amorphous, polymorphic, anhydrous or hydrate form, or a combination of the forms thereof.

MATRIX-FORMING POLYMER

The controlled release formulation is a matrix formulation in which the active compound is homogeneously dispersed in a matrix by using a matrix-forming polymer. The matrix-forming polymer as used in the invention comprises hydroxypropyl methylcellulose (HPMC),
5 polyoxethylene oxide, alginate, methylcellulose, ethycellulose, a methacrylic copolymer, hydroethylmethylcellulose (HEMC), or any combination thereof.

In one embodiment, the HPMC has a molecular weight in the range from about 4,000 to about 220,000 Da. "About" as used herein, refers to $\pm 15\%$ of the recited value. A person skilled in the art will understand that different grades of HPMC can be used in the formulation according to the
10 present invention. For example, MethocelTM E4M Premium 2, MethocelTM E10M Premium CR, METHOCELTM F50 Premium, METHOCELTM F4M Premium, METHOCELTM K4M Premium2, METHOCELTM K15M Premium2, and METHOCELTM K100M 10 Premium2 (commercially available from Dow Chemical Company) can be used.

In another embodiment, the polyoxethylene oxide has a molecular weight in the range from
15 about 100,000 to about 7,000,000 Da. A person skilled in the art will understand that different grades of polyoxethylene oxide can be used in the formulation according to the present invention. For example, PolyoxTM WSR N-10 NF, PolyoxTM WSR N-12 NF, PolyoxTM WSR N-80 NF, PolyoxTM WSR N-750 NF, PolyoxTM WSR-205 NF, PolyoxTM WSR-1105 NF, PolyoxTM WSR N-12K NF, PolyoxTM WSR N-60K NF, PolyoxTM WSR-301 NF, PolyoxTM WSR Coagulant NF, and
20 PolyoxTM WSR-303 NF (commercially available from Dow Chemical Company) can be used.

In another embodiment, the alginate has a molecular weight in the range from about 10,000 to about 50,000 Da. A person skilled in the art will understand that different grades of alginate can be used in the formulation according to the present invention.

In one embodiment of the invention, the methylcellulose has a molecular weight in the range
25 from about 10,000 to about 250,000 Da. A person skilled in the art will understand that different grades of methylcellulose can be used in the formulation according to the present invention. Examples of methylcellulose include METHOCELTM A15 Premium LV, METHOCELTM A4C Premium, METHOCELTM A15C Premium, and METHOCELTM A4M Premium (commercially available from Dow Chemical Company).

30 In yet another embodiment, the ethycellulose contains about 20% to about 80% (w/w) of ethoxyl, preferably about 45% to 55% (w/w). Examples of ethycellulose include ETHOCEL

Standard 4 Premium, ETHOCEL Standard 7 Premium, ETHOCEL Standard 10 Premium, ETHOCEL Standard 14 Premium, ETHOCEL Standard 20 Premium, ETHOCEL Standard 45 Premium, and ETHOCEL Standard 100 Premium (commercially available from Dow Chemical Company).

5 In another embodiment, the methacrylic copolymer has a molecular weight in the range from about 10,000 to about 1,500,000 Da. Examples of methacrylic copolymer include EUDRAGIT® L, EUDRAGIT® S 100, EUDRAGIT® E 100, EUDRAGIT® E PO, EUDRAGIT® E 12.5, EUDRAGIT® L 100-55, EUDRAGIT® L 30 D-55, EUDRAGIT® NE 30 D, EUDRAGIT® RL 100, EUDRAGIT® RS 100, 10 EUDRAGIT® RL PO, EUDRAGIT® RS PO, EUDRAGIT® RL 10
10 12.5, EUDRAGIT® RS 12.5, EUDRAGIT® RL 30 D, EUDRAGIT® RS 30 D, EUDRAGIT® NM 30 D, and EUDRAGIT® FS 30 D (commercially available from Evonik Industries AG).

In another embodiment, the HEMC contains about 10 to about 60% (w/w) of methoxy content, preferably about 15% to about 45% (w/w). Example of HEMC includes CULMINAL®, which is commercially available from Ashland Inc.

SOLUBILITY ENHANCER

The solubility enhancer of the present invention comprises of hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), sodium lauryl sulfate (SLS), or any combination thereof.

20 In one embodiment, the HPC has a molecular weight of about 50,000 to about 1,250,000 Da. Examples of HPC include HPC-L, HPC-M, and HPC-SL (commercially available from Nisso America Inc.).

In one embodiment, the HEC has a molecular weight of about 80,000 to about 1,500,000 Da. Examples of HEC include Natrosol®, which is commercially available from Ashland Inc.

25 In another embodiment, the PVP has a molecular weight from about 2,500 to about 3,000,000 Da. Examples of PVP includes Kollidon®, which is commercially available from BASF.

In yet another embodiment, the PEG has a molecular weight from about 200 to about 35,000 Da. Examples of PEG include PEG200, PEG400, PEG600, PEG1000, PEG2000, PEG3000, PEG4000, PEG6000, and PEG8000.

PHARMACEUTICALLY ACCEPTABLE CARRIER

In one embodiment of the invention, a “pharmaceutically acceptable carrier” refers to a carrier that, after administration to or upon a subject, does not cause undesirable physiological effects. The carrier in a pharmaceutical composition must be “acceptable” also in the sense that it is compatible with the active ingredient and, preferably, capable of stabilizing it. One or more solubilizing agents can be used as pharmaceutical carriers for delivery of carvedilol. Pharmaceutically acceptable carriers can be selected by those skilled in the art using conventional criteria. Pharmaceutically acceptable carriers include, but are not limited to, sterile water or saline solution, aqueous electrolyte solutions, isotonicity modifiers, water polyethers such as polyethylene glycol, polyvinyls such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, polymers of acrylic acid such as carboxypolymethylene gel, polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate and salts such as sodium chloride and potassium chloride.

In another embodiment of the invention, a pharmaceutically acceptable carrier refers to one or more excipients that are normally employed in the oral formulations, such as fillers, extenders, binders, humectants, disintegrating agents, wetting agents, and/or lubricants. Examples of the excipients used in the invention include, but are not limited to cellulose, microcrystalline, starch, corn starch, lactose, sucrose, glucose, mannitol, silicic acid, citric acid, crospovidone, sodium chloride, cetyl alcohol, glycerol monostearate, kaolin, bentonite clay, talc, calcium stearate, magnesium stearate, and solid polyethylene glycols.

FORMULATION

In the present invention, carvedilol is present in an amount of about 1% to about 40 % by weight of the formulation, and preferably about 9% to about 25%, and more preferably about 9.5% to 10.5%. The matrix-forming polymer is present in an amount of about 10% to about 80% by weight of the formulation, and preferably about 2% to about 55%, and more preferably about 35% to 45%. The solubility enhancer is present in an amount of about 0.1% to about 60% by weight of the formulation, and preferably about 1.5% to 55%, and more preferably about 15% to 25%. The excipient is present in an amount of about 0.1% to about 75% by weight of the formulation, and preferably about 0.3% to about 35%.

In one embodiment, the controlled release formulation comprises a combination of about 15% to about 35% of HPMC and about 20% to about 55% of PVP. In another embodiment, the

controlled release formulation comprises a combination of about 25% to about 35% of HPMC and about 25% to about 35% of PEG. In another embodiment, the controlled release formulation comprises a combination of about 35% to about 45% of Eudragit and about 35% to about 45% of HPC. In another embodiment, the controlled release formulation comprises a combination of about 40% to about 50% of polyoxethylene oxide and about 25% to about 35% of PVP. In yet another embodiment, the controlled release formulation comprises a combination of about 35% to about 45% of polyoxethylene oxide and about 35% to about 45% of HPC.

The pharmaceutical composition of the present invention may be constituted into any form suitable for the mode of administration selected. For example, compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

The controlled release formulation of carvedilol can be prepared using any conventional methods such as dry granulation or wet granulation followed by compression or compaction. For example, the most common method of preparation involves mixing carvedilol with a matrix-forming polymer and the solubility enhancer, followed by granulating the mixture, sieving the granules formed through a 10 to 40 (preferably 20 to 30) mesh sieve, heating the granules at about 50°C to about 70°C (preferably at about 60°C) and compressing the granules into tablets. Details for the preparation are described in the following examples.

DISSOLUTION

A dissolution profile is a plot of the cumulative amount of active agent released as a function of time. A dissolution profile can be measured utilizing the Drug Release Test <724>, which incorporates standard test USP 26 (Test <711>). A profile is characterized by the test conditions selected such as, for example, apparatus type, shaft speed, temperature, volume, and pH of the dissolution medium. More than one dissolution profile can be measured. For example, a first dissolution profile can be measured at a pH level approximating that of stomach, and a second dissolution profile can be measured at a pH level approximating that of one point in the intestine or several pH levels approximating multiple points in the intestine.

A highly acidic pH may be employed to simulate the stomach and a less acidic to basic pH may be employed to simulate the intestine. By the term "highly acidic pH" is meant a pH of

about 1 to about 4.5. A pH of about 1.2, for example, can be used to simulate the pH of stomach. By the term “less acidic to basic pH” is meant a pH of greater than about 4 to about 7.5, specifically about 6 to about 7.5. A pH of about 6 to about 7.5, specifically about 6.8, can be used to simulate the pH of the intestine.

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PHARMACOKINETIC STUDY

Bioequivalence of carvedilol composition to a reference drug can be determined by an in vivo bioequivalence study to determine a pharmacokinetic parameter for the carvedilol composition. Specifically, bioequivalence can be determined by an in vivo bioequivalence study comparing a pharmacokinetic parameter for the two compositions. A pharmacokinetic parameter for the carvedilol composition or the reference drug can be measured in a single or multiple dose bioequivalence study using a replicate or a nonreplicate design. Single doses of the test composition and reference drug are administered and blood or plasma levels of the active agent are measured over time. Pharmacokinetic parameters characterizing rate and extent of active agent absorption are evaluated statistically.

The area under the plasma concentration-time curve from time zero to the time of measurement of the last quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$), C_{max} , and T_{max} can be determined according to standard techniques. Statistical analysis of pharmacokinetic data is performed on logarithmic transformed data (e.g., AUC_{0-t} , $AUC_{0-\infty}$, or C_{max} data) using analysis of variance (ANOVA).

In other embodiments, the single dose pharmacokinetic study is conducted between the controlled-release carvedilol composition and the reference listed drug using the strength specified by the FDA in APPROVE DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (ORANGE BOOK).

Under U.S. FDA guidelines, two products (e.g. an inventive composition and COREG CRTM) are bioequivalent if the 90% Confidence Interval (CI) limits for a ratio of geometric mean of logarithmic transformed AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} for the two products are about 0.80 to about 1.25.

In one embodiment, in a given experiment, a carvedilol composition is considered to be bioequivalent to COREG CRTM if both the Test/Reference ratio for the geometric mean of logarithmic transformed AUC_{0-t} , $AUC_{0-\infty}$, or C_{max} ratio along with its corresponding lower and

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upper 90% CI limits are within a lower limit of about 0.80 and an upper limit of about 1.25. Thus, for direct comparison between a carvedilol composition and Coreg CRTM, it is sometimes preferred to determine the pharmacokinetic parameters for the carvedilol composition and Coreg CRTM side-by side in the same pharmacokinetic study.

5 The controlled release formulation of the invention allows the release of carvedilol to be extended over at least 6 hours, and preferably at least 12 hours, and more preferably at least 24 hours, after administration even when the surrounding pH turns neutral (i.e. during passage through the small intestine *in vivo*).

10 Accordingly, the present invention further provides a method of delivering carvedilol to a subject in need thereof which comprises administering to the subject a controlled release carvedilol formulation, comprising one or more subunits disclosed and described herein.

The method of the invention is useful for the treatment of cardiovascular disorders, such as hypertension, angina, congestive heart failure, and left ventricular dysfunction following myocardial infarction.

15 The following examples further illustrate the present invention. These examples are intended merely to be illustrative of the present invention and are not to be construed as being limiting.

EXAMPLE

20 **Example 1: Preparation of Carvedilol Controlled Release Formulation**

The controlled release formulation of the present invention was prepared by wet granulations followed by compression, as illustrated below:

1. The exact amount of carvedilol and other ingredients (including a matrix-forming polymer and a solubility enhancer) were weighed, except for magnesium stearate, and
25 then transferred to a high shear granulation machine;
2. The ingredients in Step 1 were added to the blender and blended for 3 minutes with the appropriate impeller and chopper speed to form a mixture;
3. The mixture in Step 2 was dispersed in ethanol and water to start the granulation process;
- 30 4. The impeller and chopper settings and the characteristics of the granulation solution were monitored;

5. The granulation solution in Step 4 was granulated using a granulate machine and screened through a 20 to 30 mesh sieve when the granulation end-point was reached;
6. The granules in Step 5 were heated in an oven at 60°C and the moisture content of the granules was maintained at a range between 1.0% to 3.0 %;
7. An exact amount of magnesium stearate was weighed and mixed with the granules in Step 6;
8. The sample in Step 7 was compressed by a high speed rotary tabletting machine to form tablets.

Tables 1 to 7 show the contents of the controlled release formulation prepared in according to the steps described above.

Table 1

Ingredient	Weight (mg)	%
Carvedilol	63.46	12.69%
HPMC (Methocel K15M)	145.00	29.00%
Corn Starch	145.00	29.00%
Povidone (Kollidon®)	145.00	29.00%
Magnesium Stearate	1.50	0.30%
Total	499.96	100.00%

Table 2

Ingredient	Weight (mg)	%
Carvedilol	63.46	12.69%
HPMC (Methocel K15M)	155.00	31.00%
Corn Starch	155.02	31.01%
Povidone (Kollidon®)	125.00	25.00%
Magnesium Stearate	1.50	0.30%
Total	499.98	100.00%

Table 3

Ingredient	Weight (mg)	%
Carvedilol	63.46	12.69%
HPMC (Methocel K100M)	87.00	17.40%
Corn Starch	87.00	17.40%
Povidone (Kollidon®)	261.00	52.20%
Magnesium Stearate	1.50	0.30%
Total	499.96	100.00%

Table 4

Ingredient	Weight (mg)	%
Carvedilol	63.46	12.69%
HPMC (Methocel E4M)	145.00	29.00%
Corn Starch	145.00	29.00%
PEG 6000	145.00	29.00%
Magnesium Stearate	1.50	0.30%
Total	499.96	100.00%

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Table 5

Ingredient	Weight (mg)	%
Carvedilol	63.30	21.10%
Eudragit RSPO	117.60	39.20%
HPC-L	117.60	39.20%
Magnesium Stearate	1.50	0.50%
Total	300.00	100.00%

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Table 6

Ingredient	Weight (mg)	%
Carvedilol	63.30	21.10%
Polyox (WSR N12 NF)	141.12	47.04%
Povidone (Kollidon®)	94.08	31.36%
Magnesium Stearate	1.50	0.50%
Total	300	100.00%

Table 7

Ingredient	Weight (mg)	%
Carvedilol	63.30	21.10%
Polyox (WSR N12 NF)	117.60	39.20%
HPC-L	117.60	39.20%
Magnesium Stearate	1.50	0.50%
Total	300.00	100.00%

5 **Example 2: Dissolution Test of Carvedilol Controlled Release Formulation**

Dissolution was performed in accordance with the United States Pharmacopeia (USP 31-NF 26) 711, Dissolution, Apparatus II. Hydrochloric acid (0.1N) was used as the dissolution medium during the first 120 min. The pH of the dissolution medium was changed to pH 4.5 by adding a phosphate buffer. At 240 minutes, the dissolution medium was further changed to a pH of 6.8 by adding a phosphate buffer. Dissolution was performed in 900 ml dissolution medium with a paddle speed of 100 rpm over 24 hours. Samples were taken at suitable time intervals and analyzed for carvedilol content by means of high-pressure liquid chromatography (HPLC). Figures 1 to 7 show the dissolution profiles of Table 1 to Table 7 Formulations, respectively. These results show that the controlled release formulation prepared in accordance with Tables 1 to 7 extends the duration of release and maintains adequate dissolution for at least 24 hours.

Example 3: Preparation of the Controlled Release Formulation (T1 Formulation)

Immediate-Release Subunit

Immediate-release subunits were prepared by a granulation process followed by

compression into compressed subunits, as illustrated below:

1. 76.25 Grams of carvedilol, 296.25 grams of Flow Lac 100 (Lactose) and 125.60 grams of Methocel K100LV were weighed and blended for 5 minutes;
2. The mixture in Step 1 was screened through a 40 mesh sieve, and blended for another 10 minutes;
3. The mixture in Step 2 was transferred to a high shear granulator and mixed for 1 minute;
4. The mixture in Step 3 was dispersed in 200 ml of 95% ethanol and 55ml of water to start the granulation process;
5. The granules in Step 4 were heated in an oven at 60°C for 8 hours, and the moisture content of the granules was maintained at a range between 1.0% to 3.0 %;
6. The granulation solution was further screened through a 20 mesh sieve;
7. 1.5 Grams of magnesium stearate was added to said immediate release granules in the first cell of a rotatory double-deck tabletting machine.

Slow-Release Subunit

Slow-release subunits were prepared by a granulation process followed by compression into compressed subunits, as illustrated below:

1A. 240.0 Grams of carvedilol, 600 grams of corn starch and 600 grams of Methocel K15M were weighed and blended for 5 minutes;

2A The mixture in Step 1A was screened through a 40 mesh sieve, and blended for another 10 minutes;

3A. The mixture in step 2A was transferred to a to a high shear granulation machine and mixed for 1 minute;

4A. The mixture in Step 3A was dispersed in 638.5ml of 95% ethanol and mixed for 5 minutes;

5A. 187.5 Grams of Povidone K30 was added and mixed for 1 minute, a further 250 grams of Povidone K30 was added and mixed for 1 minute, and another 250 grams of Povidone K30 was added and mixed for 3 minutes.

6A. The granules in Step 5A were heated in an oven at 60°C for 8 hours, and the moisture content of the granules was maintained at a range between 1.0% to 3.0 %;

7A. The granulation solution was further screened through a 20 mesh sieve;

8A. 6.0 Grams of magnesium stearate was added to said slow release granules in the second cell of a rotatory double-deck tabletting machine.

Formation of Controlled Release Formulation

The bi-layered controlled release formulation was formed by compressing the slow release granules in Step 8A and immediate release granules in Step 7 in the rotating double-deck tabletting machine. The resulting controlled release carvedilol formulation contained a total of about 63.46 mg of carvedilol. Table 8 shows the ingredients of the controlled release formulation (T1 formulation), manufactured by the process described above.

Table 8

Ingredient	Weight (mg)	
<u>Immediate-Release Subunit:</u>		
Carvedilol	15.46	2.9%
HPMC(Methocel K100LV)	25.04	4.8%
Lactose	59.20	11.3%
Magnesium Stearate	0.30	0.0%
<u>Slow-Release Subunit:</u>		
Carvedilol	48.00	9.1%
HPMC (Methocel K15M)	120.00	22.8%
Corn starch	120.00	22.8%
PVP	137.50	26.2%
Magnesium Stearate	1.20	0.0%
Total	526.7	

Example 4: Preparation of the Controlled Release Formulation (T2 Formulation)

Immediate-Release Subunit

Immediate-release subunits were prepared by a granulation process followed by compression into compressed subunits, as illustrated below:

1. 76.25 Grams of carvedilol, 296.25 grams of Flow Lac 100 (Lactose) and 125.60 grams of Methocel K100LV were weighed and blended for 5 minutes
2. The mixture in Step 1 was screened through a 40 mesh sieve, and blended for another 10 minutes;
3. The mixture in Step 2 was transferred to a high shear granulation machine and mixed for 1 minute;

4. The mixture in Step 3 was dispersed in 200 ml of 95% ethanol and 55ml of water to start the granulation process;
5. The granules in Step 4 were heated in an oven at 60°C for 8 hours, and the moisture content of the granules was maintained at a range between 1.0% to 3.0 %;
- 5 6. The granulation solution was further screened through a 20 mesh sieve;
7. 1.5 Grams of magnesium stearate was added to said immediate release granules in the first cell of a rotatory double-deck tabletting machine.

Slow-Release Subunit

10 Slow-release subunits were prepared by a granulation process followed by compression into compressed subunits, as illustrated below:

1A. 240.0 Grams of carvedilol, 500 grams of corn starch, 1500 grams of Methocel K15M and 50 grams of Sodium Lauryl Sulfate were weighed and the mixture was blended for 5 minutes;

15 2A. The mixture in Step 1A was screened through a 40 mesh sieve, and blended for another 10 minutes;

3A. The mixture in Step 2A was transferred to a to a high shear granulator and mixed for 1 minute;

4A. The mixture in Step 3A was dispersed in 1374ml of 95% ethanol and 1832ml of water and mixed for 3 minutes;

20 5A. The granules in Step 4A were heated in an oven at 60°C for 8 hours, and the moisture content of the granules was maintained at a range between 1.0% to 3.0 %;

6A. The granulation solution was further screened through a 20 mesh seive;

7A. 6.0 Grams of magnesium stearate was added to said slow release granules in the second cell of a rotatory double-deck tabletting machine.

Formation of Controlled Release Formulation

The bi-layered controlled release formulation was formed by compressing the slow release granules in Step 7A and immediate release granules in Step 7 in the rotating double-deck tabletting machine. The resulting controlled release carvedilol formulation contained a total of
 30 about 63.46 mg of carvedilol. Table 9 shows the ingredients of the controlled release formulation (T2 formulation) manufactured by the above process.

Table 9

Ingredient	Weight (mg)	
<u>Immediate-Release Subunit:</u>		
Carvedilol	15.46	2.7%
HPMC(K100LV)	25.04	4.5%
Lactose	59.20	10.6%
Magnesium Stearate	0.30	0.0%
<u>Slow-Release Subunit:</u>		
Carvedilol	48.00	8.6%
HPMC (Methocel K15M)	300.00	53.6%
Corn starch	100.00	17.9%
Sodium lauryl sulfate	10.00	1.8%
Magnesium Stearate	1.20	0.0%
Total	559.2	

Example 5: Dissolution Test of Carvedilol Controlled Release Formulation (T1/T2 Formulations)

5 Dissolution was performed in accordance with the United States Pharmacopeia (USP 31-NF 26) 711, Dissolution, Apparatus II. Hydrochloric acid (0.1N) was used as the dissolution medium during the first 120 min. The pH of the dissolution medium was changed to pH 4.5 by adding a phosphate buffer. At 240 minutes, the dissolution medium was further changed to a pH of 6.8 by adding a phosphate buffer. Dissolution was performed in 900 ml dissolution medium with a
10 paddle speed of 100 rpm over 24 hours. Samples were taken at suitable time intervals and analyzed for carvedilol content by means of high pressure liquid chromatography (HPLC).

Figure 8 shows the dissolution profiles of T1/T2 Formulations and reference drug, Coreg CRTM (commercially available from GSK). The result shows that the controlled release formulations prepared in accordance with Tables 8 and 9 extends the duration of release and
15 maintains adequate dissolution for at least 24 hours.

Example 6: Preparation of the Controlled Release Formulation (T4 Formulation)

Immediate-Release Subunit

Immediate-release subunits were prepared by a granulation process followed by
20 compression into compressed subunits, as illustrated below:

1. 4 Grams of carvedilol, 32.5 grams of Granulac 200 and 13.5 grams of Methocel K100LV were weighed and blended for 5 minutes;

2. The ingredients in Step 1 were transferred to a high shear granulation machine and mixed for 1 minute;
3. The mixture in Step 2 in was dispersed in 20 ml of 95% ethanol and 5.5ml of water to start the granulation process;
- 5 4. The granules in Step 3 were heated in an oven at 60°C for 8 hours, and the moisture content of the granules was maintained at a range between 1.0% to 3.0 %;
5. The granulation solution was screened through a 20 mesh sieve;
6. 0.15 Gram of magnesium stearate was added to said immediate release granules in the first cell of a rotatory double-deck tabletting machine.

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Slow-Release Subunit

Slow-release subunits were prepared by a granulation process followed by compression into compressed subunits, as illustrated below:

- 15 1A. 27.7 Grams of carvedilol, 60 grams of corn starch and 115 grams of Methocel K15M were weighed and blended for 5 minutes;
- 2A. The mixture in Step 1A was transferred to a high shear granulation machine and mixed for 1 minute;
- 3A. The mixture in Step 2A was dispersed in 63.9ml of 95% ethanol and mixed for 5 minutes;
- 20 4A. 18.8 Grams of Povidone K30 was added and mixed for 1 minute, a further 15.0 grams of Povidone K30 was added and mixed for 1 minute, and another 15.0 grams of Povidone K30 was added and mixed for 3 minutes.
- 5A. The granules in Step 4A were heated in an oven at 60°C for 8 hours, and the moisture content of the granules was maintained at a range between 1.0% to 3.0 %;
- 25 6A. The granulation solution was screened through a 20 mesh sieve;
- 7A. 0.8 Gram of magnesium stearate was added to said slow release granules in the second cell of a rotatory double-deck tabletting machine.

Formation of Controlled Release Formulation

- 30 The bi-layered controlled release formulation was formed by compressing the slow release granules in Step 7A and immediate release granules in Step 6 in the rotating double-deck

tableting machine. The resulting controlled release carvedilol formulation contained a total of about 63.3 mg of carvedilol. Table 10 shows the ingredients of the controlled release formulation (T4 formulation), manufactured by the process described above.

5

Table 10

Ingredient	Weight (mg)	
<u>Immediate-Release Subunit:</u>		
Carvedilol	8.0	1.2%
Granulac 200 (Lactose)	65.0	10.1%
Methocel (K100LV)	27.0	4.2%
Magnesium Stearate	0.30	0.0%
<u>Slow-Release Subunit:</u>		
Carvedilol	55.3	8.6%
Corn starch	120.0	18.6%
Methocel K15M	230.0	35.7%
Povidone K30	137.5	21.3%
Magnesium Stearate	1.6	0.2%
Total	644.70	

Example 7: Dissolution Test of Carvedilol Controlled Release Formulation (T4 Formulation)

Dissolution was performed in accordance with the United States Pharmacopeia (USP 31-NF 26) 711, Dissolution, Apparatus II. Hydrochloric acid (0.1N) was used as the dissolution medium during the first 120 min. The pH of the dissolution medium was changed to pH 4.5 by adding a phosphate buffer. At 240 minutes, the dissolution medium was further changed to a pH of 6.8 by adding a phosphate buffer. Dissolution was performed in 900 ml dissolution medium with a paddle speed of 100 rpm over 24 hours. Samples were taken at suitable time intervals and analyzed for carvedilol content by means of high pressure liquid chromatography (HPLC).

Figure 9 shows the dissolution profile of T4 Formulation and reference Drug (Coreg CRTM). The result shows that the controlled release formulation prepared in accordance with Table 10 extends the duration of release and maintains adequate dissolution for at least 24 hours.

Example 8: PK Data of the T4 Formulation An open-label, two-way, crossover study of the T4 Formulation versus Coreg CRTM was performed in normal healthy subjects. This study addresses the bioequivalence of carvedilol from the T4 Formulation under relevant clinical

20

conditions.

Study Design:

Twelve healthy subjects with stable vital signs, a body weight above 50kg and ability to communicate with the investigators were included in this study. The two dosing periods were separated by a washout period of at least three days. The two dosing regimens were as follows: 25mg of T4 Formulation and 25mg of Coreg CRTM, administered 30 minutes after the initiation of a standardized breakfast preceded by an overnight fasting. Blood samples were taken 30 minutes before dosing (0 h) and 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16 and 24 hours post dose for the T4 formulation and Coreg CRTM.

Results:

Table 11 summarizes the mean pharmacokinetic parameters of carvedilol after subjects received Coreg CRTM (Reference drug) and T4 formulation.

Table 11

Parameters	AUC _{0-t} (ng/mLxhr)	AUC _{0-∞} (ng/mLxhr)	AUC _{0-t} / AUC _{0-∞}	C _{max} (ng/mL)	T _{max} (hr)	MRT (hr)	T _{1/2} (hr)	RSQ
Reference drug								
Mean	864.4	976.3	89.7	115.229	6.83	12.34	7.25	0.9730
SD	501.7	596.8	4.2	44.350	3.54	2.43	2.33	0.0176
CV(%)	58.0	61.1	4.7	38.5	51.8	19.7	32.2	1.8
Test drug (T4)								
Mean	779.4	950.0	83.7	116.783	5.21	14.98	10.98	0.9638
SD	452.6	527.2	14.0	93.013	3.88	8.60	7.30	0.0562
CV(%)	58.1	55.5	16.8	79.6	74.4	57.4	67.0	5.8

Table 12 shows a summary of pharmacokinetic ratio of CoregTM (Reference drug) and T4 Formulation.

Table 12

		<u>PK Value</u>		
5	Comparison	AUC _{0-t} Ratio	AUC _{0-∞} Ratio	C _{max} Ratio
	T4/R			
	Geometric Mean ratio	0.8962	0.9749	0.8632
10	T4/R			
	Mean ratio	0.9017	0.9730	1.0135

15 Figures 10(A) and 10(B) show the mean plasma concentration-time profiles of carvedilol after subjects received CoregTM and the T4 formulation. These results show that the T4 Formulation provides an immediate loading dose of carvedilol, extends the duration of carvedilol release and maintains an adequate plasma concentration for at least 24 hours.

WHAT IS CLAIMED IS:

1. A controlled release formulation, comprising:

(a) a therapeutically effective amount of carvedilol free base or carvedilol salt thereof;

(b) a matrix forming polymer comprising one or more of the following: about 20% to about 60% by weight of Methocel K15M, about 15% to about 20% by weight of Methocel K100M, about 25% to about 35% by weight of Methocel E4M, about 35% to about 45% by weight of Eudragit RSPO, or about 35% to about 55% by weight of WSR N12NF;

(c) a solubility enhancer comprising one or more of the following: about 25% to about 55% by weight of Povidone, about 25% to about 35% by weight of PEG6000, or about 35% to about 45% by weight of HPC-L; and

(d) an excipient comprising one or more of the following: about 15% to about 35% by weight of corn starch, or about 0.1% to about 2% by weight of magnesium stearate.

2. The controlled release formulation of claim 1 wherein the carvedilol is carvedilol free base.

3. A controlled release formulation comprising, two or more subunits wherein at least one of said subunits is an immediate release carvedilol subunit comprising a therapeutically effective amount of carvedilol free base or carvedilol salt thereof, a matrix forming polymer, a solubility enhancer and a pharmaceutically acceptable carrier, and wherein at least one of said subunits is a slow release carvedilol subunit comprising a therapeutically effective amount of carvedilol free base or carvedilol salt thereof, a matrix forming polymer and a pharmaceutically acceptable carrier.

4. The controlled release formulation of claim 3 wherein the carvedilol is carvedilol free base.

5. The controlled release formulation according to claim 3, wherein the matrix forming polymer comprises one or more of the following: hydroxypropyl methylcellulose (HPMC), polyoxethylene oxide, alginate, methylcellulose, ethycellulose, methacrylic copolymer, or hydroethylmethylcellulose (HEMC).

6. The controlled release formulation according to claim 3, wherein the solubility enhancer comprises one or more of the following: hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), or sodium lauryl sulfate (SLS).

7. The controlled release formulation of Claim 5, wherein ethycellulose contains about 20% to about 80% (w/w) of ethoxyl.

8. The controlled release formulation of Claim 5, wherein the methoxyl content of the

hydroethylmethylcellulose (HEMC) is from about 10% to about 60% (w/w).

9. The controlled release formulation according to claim 3, wherein the pharmaceutically acceptable carrier comprises one or more of the following: lactose, corn starch or magnesium stearate.

5 10. The controlled release formulation according to claim 3,
 wherein the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed $AUC_{0-\infty}$ of the controlled release formulation to a geometric mean of logarithmic transformed $AUC_{0-\infty}$ of the reference drug (Coreg CRTM) of about 0.80 to about 1.20;

10 wherein the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed AUC_{0-t} of the controlled release formulation to a geometric mean of logarithmic transformed AUC_{0-t} of the reference drug (Coreg CRTM) of about 0.80 to about 1.20; or

15 wherein the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed C_{max} of the controlled release formulation to a geometric mean of logarithmic transformed C_{max} of the reference drug (Coreg CRTM) of about 0.80 to about 1.20.

11. The controlled release formulation according to claim 3, wherein the controlled release formulation exhibits a first peak plasma T_{max1} of about 4 hours, and a second peak plasma T_{max2} of about 24 hours after oral administration to a patient.

20 12. A controlled release formulation, comprising:
 A. One or more immediate release subunits, comprising;
 (i) a therapeutically effective amount of carvedilol free base or carvedilol salt thereof;
 (ii) about 4% to about 5 % by weight of a matrix forming polymer comprising one or more of
 25 the following: hydroxypropyl methylcellulose (HPMC), polyoxethylene oxide, alginate, methylcellulose, ethylcellulose, a methacrylic copolymer, or hydroethylmethylcellulose (HEMC); and
 (iii) about 0.01% to about 0.1% by weight of an excipient; and
 B. one or more slow release subunits, comprising;
 (i) a therapeutically effective amount of carvedilol free base or carvedilol salt thereof;
 30 (ii) about 20% to about 55 % by weight of a matrix forming polymer comprising one or more

of the following: hydroxypropyl methylcellulose (HPMC), polyoxethylene oxide, alginate, methylcellulose, ethycellulose, a methacrylic copolymer, or hydroethylmethylcellulose (HEMC);

(iii) about 1.0% to about 30 % by weight of a solubility enhancer comprising one or more of the following: hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), or sodium lauryl sulfate (SLS); and

(iv) about 0.01% to about 25 % by weight of an excipient.

13. The controlled release formulation according to claim 12, wherein carvedilol is carvedilol free base.

14. The controlled release formulation of Claim 12, wherein ethycellulose contains about 20% to about 80% (w/w) of ethoxyl.

15. The controlled release formulation of Claim 12, wherein the methoxyl content of the hydroethylmethylcellulose (HEMC) is from about 10% to about 60% (w/w).

16. The controlled release formulation according to claim 12, wherein the excipient comprises one or more of the following: lactose, corn starch, or magnesium stearate.

17. The controlled release formulation according to claim 12, wherein the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed $AUC_{0-\infty}$ of the controlled release formulation to a geometric mean of logarithmic transformed $AUC_{0-\infty}$ of the reference drug (Coreg CRTM) of about 0.80 to about 1.20;

wherein the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed AUC_{0-t} of the controlled release formulation to a geometric mean of logarithmic transformed AUC_{0-t} of the reference drug (Coreg CRTM) of about 0.80 to about 1.20; or

wherein the controlled release formulation exhibits a ratio of a geometric mean of logarithmic transformed C_{max} of the controlled release formulation to a geometric mean of logarithmic transformed C_{max} of the reference drug (Coreg CRTM) of about 0.80 to about 1.20.

18. The controlled release formulation according to claim 12, wherein the controlled release formulation exhibits a first peak plasma T_{max1} of about 4 hours, and a second peak plasma T_{max2} of about 24 hours after oral administration to a patient.

19. A method of making a controlled release formulation, comprising:

A. Making an immediate release subunit, comprising the steps of:

- i. Mixing and blending a therapeutically effective amount of carvedilol, about 4% to about 5 % by weight of a matrix-forming polymer to form a first mixture;
- ii. Granulating said first mixture into first granules; and

B. Making a slow release subunit, comprising the steps of:

- i. Mixing and blending a therapeutically effective amount of carvedilol, about 20% to about 55 % by weight of a matrix-forming polymer to form a mixture;
- ii. Adding about 1.0% to about 30 % by weight of a solubility enhancer to said mixture to form a second mixture;
- iii. Granulating said second mixture into said second granules; and

C. Adding about 0.01% to about 25% by weight of an excipient to said first and second granules, and compressing said first and second granules into a tablet.

20. The method according to Claim 19, wherein the step of granulating said first mixture further comprises heating said first mixture at a temperature about 50°C to about 70°C.

21. The method according to Claim 20, wherein the step of granulating said first mixture further comprises sieving said first mixture through a 20 mesh sieve.

22. The method according to Claim 19, wherein the step of granulating said second mixture comprises heating said second mixture at a temperature about 50°C to about 70°C.

23. The method according to Claim 22, wherein the step of granulating said second mixture further comprises sieving said second mixture through a 20 mesh sieve.