The present invention provides a novel amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier, process for its preparation and pharmaceutical compositions comprising it.
CARVEDILOL PHOSPHATE SOLID DISPERSION

This application claims the benefit of Indian Provisional Patent Application No. 159/CHE/2013, filed on January 10, 2013, which is incorporated herein by reference.

Filed of the Invention

The present invention provides a novel amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier, process for its preparation and pharmaceutical compositions comprising it.

Background of the Invention

Carvedilol and its phosphate salt are antihypertensive agents, which were disclosed in U.S. Patent No. 4,503,067. Carvedilol is known by the chemical name 1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethyl]amino]propanol and has the structural formula:

![Structural formula of carvedilol phosphate](image)

Carvedilol phosphate is a nonselective beta blocker/alpha-1 blocker indicated in the treatment of mild to severe congestive heart failure (CHF). The generic name carvedilol phosphate is marketed by SB PHARMCO under the brand name COREG CR®.

Polymorphism is defined as "the ability of a substance to exist as two or more crystalline phases that have different arrangement and/or conformations of the molecules in the crystal Lattice. Thus, in the strict sense, polymorphs are different crystalline structures of the same pure substance in which the molecules have different arrangements and/or different configurations of the molecules". Different polymorphs may differ in their physical properties such as melting point, solubility, X-ray diffraction patterns, etc.
Although those differences disappear once the compound is dissolved, they can appreciably influence pharmaceutically relevant properties of the solid form, such as handling properties, dissolution rate and stability. Such properties can significantly influence the processing, shelf life, and commercial acceptance of a polymorph. It is therefore important to investigate all solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in the laboratory by analytical methods such as X-ray diffraction (XRD), Differential Scanning Calorimetry (DSC) and Infrared spectrometry (IR).

Solvent medium and mode of crystallization play very important role in obtaining one polymorphic Form over the other.

Carvedilol and its phosphate salt can exist in different polymorphic Forms, which may differ from each other in terms of stability, physical properties, spectral data and methods of preparation.

U.S. patent no. 7,268,156 disclosed crystalline Form I of carvedilol dihydrogen phosphate hemihydrate.

U.S. patent no. 7,626,041 disclosed Form II and Form IV of carvedilol dihydrogen phosphate dihydrate.

Crystalline Form III of carvedilol dihydrogen phosphate methanol solvate was disclosed in U.S. patent no. 7,893,100.

Crystalline Form V of carvedilol dihydrogen phosphate was disclosed in U.S. patent no. 7,759,384.

U.S. patent no. 7,902,378 disclosed crystalline Form VI of carvedilol dihydrogen phosphate.


Indian patent application no. IN 362/KOL/2007 disclosed crystalline Form B of carvedilol dihydrogen phosphate.

International patent application publication no. WO 2008/002683 (‘683 patent) disclosed amorphous carvedilol phosphate, pure amorphous carvedilol, amorphous carvedilol hydrogen phosphate, pure amorphous carvedilol hydrogen phosphate,
amorphous carvedilol dihydrogen phosphate and pure amorphous carvedilol dihydrogen phosphate.

According to the '683 patent also disclosed crystalline Form G, Form H, Form K and Form Q of carvedilol hydrogen phosphate.

According to the '683 patent also disclosed Crystalline Form I, Form L, Form LI, Form N, Form O, Form P, Form F, Form Fl, Form R, Form Y, Form W and Form F2 of carvedilol dihydrogen phosphate.

Indian patent application no. IN 621/MUM/2007 disclosed crystalline polymorph Form VII of carvedilol dihydrogen phosphate.

Crystalline Form of carvedilol dihydrogen phosphate monohydrate was disclosed in U.S. patent no. 7,763,645.

It was observed that the crystalline Forms and amorphous Form of carvedilol phosphate either not reproducible or not stable.

We have also found a novel amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier. The amorphous solid dispersion of carvedilol phosphate is stable, reproducible and so, the amorphous solid dispersion of carvedilol phosphate is suitable for formulating carvedilol phosphate. Normally amorphous Forms are hygroscopic. Amorphous solid dispersion of carvedilol phosphate is found to be non-hygroscopic.

Thus, an object of the present invention is to provide a novel amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier, process for its preparation and pharmaceutical compositions comprising it.

Summary of the Invention

In one aspect, the present invention provides amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention there is provided a process for the preparation of amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier, which comprises:

- preparing a solution comprising a mixture of carvedilol phosphate and one or more pharmaceutically acceptable carriers selected from copovidone, ethyl
cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus in a solvent; and

b) removing the solvent to obtain amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier.

Yet in another aspect, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of amorphous solid dispersion of carvedilol phosphate along with a pharmaceutically acceptable carrier, and at least one pharmaceutically acceptable excipient.

**Brief Description of the Drawing**

Figure 1 is a powder X-ray diffractogram patterns of amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier.

Powder X-ray diffraction spectrum was measured on a bruker AXS D8 advance powder X-ray diffractometer having a copper-Kα radiation. Approximately 500 mg of sample was gently flattered on a sample holder and scanned from 2 to 50 degrees two-theta, at 0.020 degrees two theta per step and a step time of 1 second. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 kV and current 35 mA.

**Detailed Description of the Invention**

The term "room temperature" refers to temperature at about 25 to 35°C.

According to one aspect of the present invention, there is provided amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier.

The powdered x-ray diffractogram (PXRD) of amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier is shown in figure 1.

Amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier obtained according to the present invention typically has the water content of less than 10 % by weight of the product obtained, preferably the water content of less than 5 % by weight as determined by Karl fisher method.
Amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier having enhanced stability, dissolution properties that can be easily formulated into pharmaceutical compositions.

Preferably the pharmaceutically acceptable carriers may be one or more of copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus. The said pharmaceutically acceptable carriers are used to facilitate the presence of an amorphous carvedilol phosphate.

The term "solid dispersion" herein refers to a composition prepared by dissolving or dispersing a substituted carvedilol phosphate in an organic solvent or mixture of organic solvents with one or more pharmaceutically acceptable carriers and converting the solution or dispersion to a solid form.

According to another aspect of the present invention, there is provided a process for the preparation of amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier, which comprises:

a) preparing a solution comprising a mixture of carvedilol phosphate and one or more pharmaceutically acceptable carriers selected from copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus in a solvent; and

b) removing the solvent to obtain amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier.

Carvedilol phosphate used in step (a) may preferably be carvedilol phosphate obtained by the known process.

The solvent used in step (a) may preferably be a solvent or a mixture of solvents selected from dimethyl sulfoxide, dimethylacetamide, dimethylformamide, methanol, ethanol, isopropanol, n-butanol, n-pentanol, methylene chloride, chloroform, carbon tetrachloride and ethylene dichloride. More preferably the solvents are methylene chloride, dimethyl sulfoxide, dimethylacetamide, dimethylformamide and methanol.

Preferably the pharmaceutically acceptable carriers used in step (a) may be selected from copovidone, soluplus or hydroxypropyl methylcellulose.

The solvent may be removed from the solution in step (b) by known methods, for example, distillation or spray drying.
The distillation of the solvent may be carried out at atmospheric pressure or at reduced pressure. The distillation may preferably be carried out until the solvent is almost completely distilled off.

As used herein, "reduced pressure" refers to a pressure of less than 100 mmHg.

The term "spray drying" refers to a method of producing a dry powder from a liquid or slurry by rapidly drying with a hot gas.

According to another aspect of the present invention, there is provided pharmaceutical compositions comprising a therapeutically effective amount of amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier and along with at least one pharmaceutically acceptable excipient. The amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier may preferably be formulated into tablets, capsules, suspensions, dispersions, injectables or other pharmaceutical forms.

Preferably the present invention provides a pharmaceutical composition containing said solid dispersion along with the pharmaceutically acceptable excipients such as diluents, chelating agents, disintegrant, glidant, binders, surfactants, coloring agents and/or lubricants.

Specific examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Specific examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, cellulose powdered, dextrans, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like and mixtures thereof.

Surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and its derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol-20 dioleate, polyethylene glycol 4-150 mono dilaurate,
and polyethylene glycol - 20 glyceryl stearate; alcohol - oil transesterification products, for example, polyethylene glycol - 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl - 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monocaprylate; mono and diglycerides, for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example, polyethylene glycol - 20 sorbitan monooleate and sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol - 20 cetyl ether and polyethylene glycol - 10 - 100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene - polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine; and the like and mixtures thereof.

Specific examples of disintegrants include low-substituted hydroxypropylcellulose (L-HPC), sodium starch glycollate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium A-type (Ac-di-sol), starch, crystalline cellulose, hydroxypropyl starch, pregelatinized starch, and the like and mixtures thereof.

Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like and mixtures thereof.

Coloring agents include any FDA approved colors for oral use.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

Examples

Example 1:

Preparation of carvedilol phosphate

4-(Oxiranylmethoxy)-9H-carbazole (75 gm) was added to 2-(2-methoxyphenoxy)ethylamine (140 gm) at room temperature, followed by stirring the reaction mixture for 37 hours at room temperature. Ethyl acetate (385 ml) was added to
the reaction mass, followed by maintaining the resulting mass at room temperature for 1 hour 30 minutes. The resulting mass was cooled to 0 to 5°C and then maintained at the same temperature for 1 hour 30 minutes. The separated solid was filtered, washed with chilled ethyl acetate and then dried to obtain carvedilol. To the carvedilol obtained was added acetone (300 ml) and water (100 ml) at room temperature. To the reaction mixture was added phosphoric acid (5 ml), followed by stirring the reaction mixture at room temperature. The separated solid was filtered and then dried to obtain 90 gm of carvedilol phosphate.

Example 2:
Preparation of amorphous carvedilol phosphate solid dispersion with copovidone
A mixture of carvedilol phosphate (50 gm) as obtained in example 1 and copovidone (25 gm) was dissolved in a mixture of methanol (1000 ml) and methylene chloride (100 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 73 gm of amorphous carvedilol phosphate solid dispersion with copovidone. The amorphous carvedilol phosphate solid dispersion with copovidone obtained was stabilized in stability chamber at the temperature of 40°C under relative humidity of 75%.

Water content: 3.87%.

Example 3:
Preparation of amorphous carvedilol phosphate solid dispersion with copovidone
A mixture of carvedilol phosphate (50 gm) and copovidone (50 gm) was dissolved in a mixture of methanol (1200 ml) and methylene chloride (120 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 96 gm of amorphous carvedilol phosphate solid dispersion with copovidone.

Example 4:
Preparation of amorphous carvedilol phosphate solid dispersion with copovidone
A mixture of carvedilol phosphate (25 gm) and copovidone (25 gm) was dissolved in a mixture of methanol (1000 ml) and methylene chloride (100 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The resulting filtrate was subjected to spray drying at 60 to 65°C to obtain 73 gm of amorphous carvedilol phosphate solid dispersion with copovidone.

Example 5:

Preparation of amorphous carvedilol phosphate solid dispersion with copovidone

Example 2 was repeated using dimethylformamide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with copovidone.

Example 6:

Preparation of amorphous carvedilol phosphate solid dispersion with copovidone

Example 2 was repeated using dimethylacetamide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with copovidone.

Example 7:

Preparation of amorphous carvedilol phosphate solid dispersion with copovidone

Example 2 was repeated using dimethyl sulfoxide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with copovidone.

Example 8:

Preparation of amorphous carvedilol phosphate solid dispersion with copovidone

Example 2 was repeated using ethanol solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with copovidone.

Example 9:

Preparation of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose

A mixture of carvedilol phosphate (50 gm) and hydroxypropyl methylcellulose (25 gm) was dissolved in a mixture of methanol (1000 ml) and methylene chloride (100
ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 71 gm of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose. The amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose obtained was stabilized in stability chamber at the temperature of 40°C under relative humidity of 75%.

Example 10:

Preparation of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose

Example 9 was repeated using dimethylformamide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose.

Example 11:

Preparation of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose

Example 9 was repeated using dimethylacetamide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose.

Example 12:

Preparation of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose

Example 9 was repeated using dimethyl sulfoxide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose.

Example 13:

Example 13:
Preparation of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose

Example 9 was repeated using ethanol solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose.

Example 14:
Preparation of amorphous carvedilol phosphate solid dispersion with soluplus

A mixture of carvedilol phosphate (10 gm) and soluplus (10 gm) was dissolved in a mixture of methanol (1200 ml) and methylene chloride (120 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 18 gm of amorphous carvedilol phosphate solid dispersion with soluplus. The amorphous carvedilol phosphate solid dispersion with soluplus obtained was stabilized in stability chamber at the temperature of 40°C under relative humidity of 75%.

Water content: 3.86%.

Example 15:
Preparation of amorphous carvedilol phosphate solid dispersion with soluplus

Example 14 was repeated using dimethylformamide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with soluplus.

Example 16:
Preparation of amorphous carvedilol phosphate solid dispersion with soluplus

Example 14 was repeated using dimethylacetamide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with soluplus.

Example 17:
Preparation of amorphous carvedilol phosphate solid dispersion with soluplus

Example 14 was repeated using dimethyl sulfoxide solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with soluplus.
Example 18:
Preparation of amorphous carvedilol phosphate solid dispersion with soluplus

Example 14 was repeated using ethanol solvent instead of methanol solvent to obtain amorphous carvedilol phosphate solid dispersion with soluplus.

Example 19:
Preparation of amorphous carvedilol phosphate solid dispersion with polyethylene glycol

A mixture of carvedilol phosphate (10 gm) and polyethylene glycol (5 gm) was dissolved in a mixture of methanol (1000 ml) and methylene chloride (100 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 13 gm of amorphous carvedilol phosphate solid dispersion with polyethylene glycol.

Example 20:
Preparation of amorphous carvedilol phosphate solid dispersion with ethyl cellulose

A mixture of carvedilol phosphate (5 gm) and ethyl cellulose (5 gm) was dissolved in a mixture of methanol (1000 ml) and methylene chloride (100 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 8 gm of amorphous carvedilol phosphate solid dispersion with ethyl cellulose.

Example 21:
Preparation of amorphous carvedilol phosphate solid dispersion with copovidone

4-(Oxiranylmethoxy)-9H-carbazole (75 gm) was added to 2-(2-methoxyphenoxy)ethylamine (140 gm) at room temperature, followed by stirring the reaction mixture for 37 hours at room temperature. Ethyl acetate (385 ml) was added to the reaction mass, followed by maintaining the resulting mass at room temperature for 1 hour 30 minutes. The resulting mass was cooled to 0 to 5°C and then maintained at the same temperature for 1 hour 30 minutes. The separated solid was filtered, washed with
chilled ethyl acetate and then dried to obtain carvedilol. To the carvedilol obtained was added acetone (300 ml) and water (100 ml) at room temperature. To the reaction mixture was added phosphoric acid (5 ml), followed by stirring the reaction mixture at room temperature. To the reaction mass was added copovidone (45 gm) and a mixture of methanol (1800 ml) and methylene chloride (180 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 131 gm of amorphous carvedilol phosphate solid dispersion with copovidone.

Example 22:

Preparation of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose

4-(Oxiranylmethoxy)-9H-carbazole (75 gm) was added to 2-(2-methoxyphenoxy)ethyamine (140 gm) at room temperature, followed by stirring the reaction mixture for 37 hours at room temperature. Ethyl acetate (385 ml) was added to the reaction mass, followed by maintaining the resulting mass at room temperature for 1 hour 30 minutes. The resulting mass was cooled to 0 to 5°C and then maintained at the same temperature for 1 hour 30 minutes. The separated solid was filtered, washed with chilled ethyl acetate and then dried to obtain carvedilol. To the carvedilol obtained was added acetone (300 ml) and water (100 ml) at room temperature. To the reaction mixture was added phosphoric acid (5 ml), followed by stirring the reaction mixture at room temperature. To the reaction mass was added hydroxypropyl methylcellulose (90 gm) and a mixture of methanol (2000 ml) and methylene chloride (200 ml) at room temperature. The contents were heated to 35 to 40°C for 20 minutes and filtered through celite bed. The solvent was distilled off under reduced pressure at below 50°C to obtain 165 gm of amorphous carvedilol phosphate solid dispersion with hydroxypropyl methylcellulose.
We claim:

1. Amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier.

2. The amorphous solid dispersion of claim 1, wherein the pharmaceutically acceptable carriers may be one or more of copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus.

3. The amorphous solid dispersion of claim 1, having powdered X-ray diffractogram as shown in figure 1.

4. A process for the preparation of amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier, which comprises:
   a) preparing a solution comprising a mixture of carvedilol phosphate and one or more pharmaceutically acceptable carriers selected from copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus in a solvent; and
   b) removing the solvent to obtain amorphous solid dispersion of carvedilol phosphate in combination with a pharmaceutically acceptable carrier.

5. The process as claimed in claim 4, wherein the solvent used in step (a) is a solvent or a mixture of solvents selected from dimethyl sulfoxide, dimethylacetamide, dimethylformamide, methanol, ethanol, isopropanol, n-butanol, n-pentanol, methylene chloride, chloroform, carbontetrachloride and ethylene dichloride.

6. The process as claimed in claim 5, wherein the solvents are methylene chloride, dimethyl sulfoxide, dimethylacetamide, dimethylformamide and methanol.

7. The process as claimed in claim 4, wherein the pharmaceutically acceptable carriers used in step (a) is selected from copovidone, soluplus or hydroxypropyl methylcellulose.

8. Pharmaceutical compositions comprising a therapeutically effective amount of amorphous solid dispersion of carvedilol phosphate along with pharmaceutically acceptable excipients, and at least one pharmaceutically acceptable excipient.

9. The pharmaceutical composition as claimed in claim 8, wherein the amorphous solid dispersion of carvedilol phosphate is formulated into tablets, capsules, suspensions, dispersions or injectables.