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(54) Title: PROCESS FOR MANUFACTURE OF EXTENDED RELEASE PELLETS CONTAINING DILTIAZEM HCI

(57) Abstract: The present invention relates to process for the preparation of novel stable extended release pharmaceutical compositions comprising upto about 80%w/w of Diltiazem HCI suitable for once a day dosing, the pharmaceutical composition being exempt of wetting agent in mixture with Diltiazem HCI. The extended release pharmaceutical composition exhibits pH independent in-vitro release profile in 900ml of distilled water / pH 6.8 phosphate buffer / 0.1 N HCI / pH 4.5 acetate buffer at 100 rpm using USP type II apparatus. The preparation of the present invention is capable of being filled in capsule and comprise of pellets of single release profile.

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# Process For Manufacture Of Extended Release Pellets Containing Diltiazem HCl

## Field of the invention:

This invention relates to process for preparation of novel stable extended release pharmaceutical compositions comprising Diltiazem salt such as Diltiazem HCl.

## Background of the invention:

Diltiazem HCl, an anti-anginal agent blocks the influx of calcium ions in smooth and cardiac muscle, thus exhibiting potential cardiovascular activity. It also has negative chronotropic effect and negative ionotropic effect on heart muscles.

Diltiazem HCl, being an acidic salt of basic drug is more soluble in acidic media and is freely soluble in water. The half-life of Diltiazem HCl is of the order of about 4 hours and is therefore recommended to be taken 3 – 4 times a day for effective therapy. Various attempts have been made to provide Diltiazem HCl in extended release composition to reduce the frequency of administration making it suitable for once daily administration. Extended release compositions comprising Diltiazem HCl that are intended to be administered for once a day dosing should ideally exhibit an in-vitro drug release profile of

N.M.T 20% of Diltiazem HCl after 2 hours;
N.M.T 50% of Diltiazem HCl after 4 hours;
N.M.T 85% of Diltiazem HCl after 8 hours;
and N.L.T. 70% of Diltiazem HCl after 16 hours

Where "NMT" and "NLT" stands for "Not More Than" and "Not Less Than" respectively.

U.S. Patents 5529791, 5288505, Canadian Patent application CA 2307547 and CA 2292247 discloses an extended release galenical bead compositions wherein Diltiazem HCl is mixed with wetting agents that are essential to maintain the solubility of Diltiazem HCl and being unaffected by the pH and other adverse conditions in GI tract. The beads are coated with a microporous membrane comprising atleast a water-soluble or water dispersible polymer or copolymer and a water, acid and base insoluble polymer and pharmaceutically acceptable adjuvant.

U.S. Patent 4960596 and Canadian Patent CA 1331740 describe a slow release acid free galenical m icrogranules preparation comprising an inert central core. These inert cores were wetted with polyvinylpyrrolidone solution and active substance was deposited until the granules were dried. The operation was repeated several times till the quantity of active substance has been used up. Thereafter the microgranules were coated with an outer membrane comprising a mixture of shellac, ethylcellulose and talc or aqueous suspension of ethylcellulose and dibutylsebacate. However, it is essential

for formulations containing shellac, to eliminate all the traces of solvents at the end of the process, which otherwise would adversely affect the stability of the formulation.

U.S. Patent 5344657 and Canadian Patent CA 1336326 discloses sustained release microbeads comprising Diltiazem. Each microbeads comprises a core including an inert grain substrate coated with a layer(s) of Diltiazem combined with binder surrounded by a microporous membrane. Microporous membrane essentially consists of film forming polymer, plasticizer and filling material. Filling material represents 35 – 75%, preferably 50 – 70% by weight of the membrane. These formulations release about 60% of the drug at the end of 6 hours at a constant rate after a latent period of less than one hour. The formulation described in this patent is unsuitable for once a day dosing and is stable for 18 months at ambient temperature.

Canadian Patent Application CA 1327006 discloses an oral formulation comprising a mixture of 60 – 95% of delayed release pellets and 5 to 40% of fast release pellets. Diltiazem fast release pellets comprise of a central neutral microgranules covered with plurality of alternating Diltiazem and shellac (binder) layers. Fast release pellets are coated with a membrane, which comprises of a plurality of alternate layers of excipients in powder form and polymers in organic solvent. However It is essential for the formulations containing shellac to eliminate all the traces of solvents at the end of the process, which otherwise would adversely affect the stability of the formulation. Further, the formulation comprises mixtures of two different types of pellet thereby increasing processing steps and processing time resulting into expensive product.

U. S. Patents 5529790, 5376384 and Canadian Patent application CA 2110853 discloses delayed sustained release preparation comprising a mixture of short delay component and long delay component. These components comprises of core containing Diltiazem HCl and a hydratable diffusion barrier surrounding a core having a thickness of atleast 20 microns. The barrier comprises of film forming polymer such as fully esterified acrylic resins containing quaternary amine side chain and sufficient amount of additive such as lubricants, anionic surfactants, plasticizers, inert water soluble materials and mixtures to control the hydration rate and permeability so that less than 5% of the drug dissolves within 2 hours in 1 liter of 0.05M pH 6.8 phosphate buffer at 100rpm in U.S.P. basket dissolution apparatus. The said barrier is slowly hydrated to become permeable to dissolved drug within 2 – 12 hours after ingestion. The preparation comprises mixtures of two different components thereby increasing processing steps and processing time resulting into expensive product.

The prior art describe formulations that

- are unsuitable for once a day delivery especially for a dose of 120mg as it does not maintain desired blood levels suitable for once a day dosing;
- involves essential use of wetting agent in admixture with Diltiazem HCl that is essential to maintain the solubility of Diltiazem HCl in each bead unaffected by pH and other adverse conditions in GI tract;
- involves use of shellac that requires special precaution for elimination of traces of organic solvents, that is essential to obtain a stable formulation. This requires additional drying time and processing time, thereby making the product expensive;
- are stable only for 18 months at ambient temperature as against the desirable shelf life of atleast about 24 months;
- uses mixture of fast release pellets and delayed release pellets or mixture of long delay component and short delay component in the formulation, thereby increasing the processing step and processing time making the product expensive;
- contains polymer membrane having a thickness of atleast 20 microns;
- involves use of filling material preferably 50 – 70% by weight of the microporous membrane;

There is a long-standing need in the industry to provide "once a day", pH independent stable, extended release formulations comprising Diltiazem HCl, containing pellets of single release profile.

**Object of the Invention:**

The object of the invention is to provide a process for the preparation of novel stable extended release pharmaceutical compositions comprising Diltiazem salt such as Diltiazem HCl for once a day dosing exhibiting pH independent in-vitro release profile using pellets of single release profile.

Another object of the invention is to provide compositions exhibiting pH independent in-vitro release profile that is exempt of wetting agent in the layer comprising Diltiazem HCl, which is essential for the prior art to maintain the solubility of Diltiazem HCl in each bead unaffected by pH and other adverse conditions in GI tract.

It is yet another object of the invention to provide stable compositions that is exempt of shellac thereby avoiding unnecessary additional drying and processing time thereby making the product economical.

It is yet another object of the invention to provide compositions and preparations comprising Diltiazem HCl that are stable atleast for a period of 24 months.

It is yet another object of the invention to provide preparation comprising Diltiazem HCl that comprises pellets of single release profile only.

Further and other objects will be clear from the summary of the invention and detailed description of the invention thereof.

**Summary of the invention:**

The present invention relates to process for the preparation of novel stable extended release pharmaceutical compositions comprising Diltiazem salt such as Diltiazem HCl suitable for once a day dosing.

Extended release pharmaceutical composition of the present invention is prepared in the form of extended release pellets comprising Diltiazem HCl. Extended release pellet comprises of drug core that contains drug layer deposited on inert core that are further coated with a polymer membrane.

In contrast to the preparation disclosed in the prior art that comprises mixture of pellets to achieve the desired release profile for once a day dosing, the present invention discloses preparation of Diltiazem HCl containing pellets of single release profile and yet achieves the desired drug release profile that are suitable for once a day dosing.

The extended release pharmaceutical compositions containing Diltiazem HCl comprises drug layer that is exempt of wetting agent and yet achieves the desired pH independent in – vitro drug release profile. This is in contrast to the compositions disclosed in U.S. Patents 5529791, US 5288505, Canadian Patent application CA 2307547 and CA 2292247 where use of wetting agent is essential for maintaining the solubility of Diltiazem HCl that is unaffected by the pH and other adverse conditions in GI tract.

Further, the extended release pharmaceutical composition of the present invention is also exempt of shellac thereby avoiding unnecessary precaution and needless additional drying and processing time thus making the product economical.

Extended release pharmaceutical composition comprising Diltiazem HCl exhibits pH independent in-vitro drug release profile when analyzed in USP type II apparatus using 900ml of distilled water / 0.1N HCl / pH 4.5 acetate buffer / pH 6.8 phosphate buffer at 100 rpm.

An extended release pellet prepared by the process of the present invention is capable of being encapsulated in sized capsules and is stable atleast for a period of 2 years.

**Brief Description of Drawing:**

Figure 1 is the graphical representation of drug release profile of extended release pellets comprising Diltiazem HCl in different media.

**Description:**

In contrast to compositions disclosed in the prior art that are unsuitable for once a day dosing, the present invention relates to process for the preparation of novel stable extended release pharmaceutical compositions comprising Diltiazem salt such as Diltiazem HCl suitable for once a day dosing.

Extended release pharmaceutical composition is prepared in the form of pellets and is capable of being filled into sized capsule.

The preparation of the present invention contains pellets of single release profile. The preparation of the present invention achieves the desired pH independent in – vitro drug release profile suitable for once a day dosing. This is in particular contrast to the preparation disclosed in US Patent 5529790, US 5376384, Canadian Patent application CA 2110853 and CA 1327006 that requires mixture of pellets to achieve the desired in-vitro drug release profile.

Extended release pharmaceutical pellet compositions of the present invention essentially comprises of drug core that are coated with a polymer membrane. Each drug core comprises of drug layer deposited on inert core. Each drug layer comprises of Diltiazem HCl, binder and optionally other pharmaceutical ingredients. Deposition of drug layer on inert cores is accomplished by layering or coating.

Drug layer of the present invention is exempt of wetting agent and yet achieves the desired solubility thereby exhibiting pH independent in-vitro drug release profile which is in contrast to the prior art U.S. Patents 5529791, 5288505, Canadian Patent CA 2111085, Canadian Patent application CA 2307547 and CA 2292247 that essentially requires wetting agent in admixture with Diltiazem HCl to achieve the desired solubility unaffected by pH.

In an embodiment of the invention, drug core is prepared by layering Diltiazem HCl optionally with other pharmaceutical ingredient alternating with binder as multiple layers on inert core.

In another embodiment of the invention drug core is prepared by coating Diltiazem HCl, binder, antitack agent optionally with other pharmaceutical ingredient as single layer on inert core.

The drug core is optionally further coated with binder and antitack agent to obtain hardened drug core.

The drug core or the hardened drug core is further coated with a polymer membrane. The polymer membrane comprises of water insoluble polymer upto about 100% w/w of the polymer membrane, plasticizer from about 0% to about 30%w/w of the polymer membrane and pharmaceutically acceptable additive from about 0% to about 30%w/w

of the polymer membrane. The thickness of the polymer membrane coated on drug core or hardened drug core is less than 50 microns, preferably less than 20 microns, more preferably less than 15 microns.

Any equipment, suitable to the process described, for the preparation of extended release pellets comprising Diltiazem HCl can be utilized. Preferably the equipments are selected from coating pan, fluid bed processor preferably bottom spray, CF coater and the likes. The process can be carried out in single equipment or utilizes two or more equipments.

Extended release pellets of the present invention are capable of being filled into sized capsule that delivers therapeutic effective dose of Diltiazem HCl and are suitable for once a day dosing.

These extended release pellets filled in capsule exhibits pH independent in-vitro drug release profile in USP type II apparatus using 900ml of distilled water / pH 6.8 phosphate buffer / 0.1N HCl / pH 4.5 acetate buffer at 100 rpm.

Diltiazem HCl extended release pellets of the present invention is distinct from the prior art as it

- is suitable for once a day dosing;
- do not make use of wetting agent in admixture with Diltiazem HCl;
- do not use shellac in the composition;
- uses pellets of single release profile in the formulation;
- contains polymer membrane having a thickness of preferably less than 20 microns;
- is stable atleast for a period of two years;
- uses from about 0% to about 30%w/w of filling material (talc) in polymeric membrane.

**Detailed Description of the Invention:**

The present invention relates to process for the preparation of stable novel extended release pharmaceutical pellet compositions comprising Diltiazem HCl suitable for once a day dosing wherein,

a) the drug layer comprising Diltiazem HCl, binder and other pharmaceutical ingredient is deposited on inert core to obtain drug core, the drug layer being exempt of wetting agent;

b) coating drug core with a polymer membrane comprising water insoluble polymer to obtain extended release pellets exhibiting pH independent in-vitro release profile at 100 rpm using USP type II apparatus.

Extended release pellets of the present invention are capable of being filled into sized capsule and comprises pellets of single release profile. The pharmaceutical composition of the present invention is exempt of wetting agent in admixture with Diltiazem HCl and shellac. The process for preparing such compositions is described in the following two stages.

**Stage I:**

**Preparation of Drug Core:**

The first stage in the preparation of extended release pellets comprising Diltiazem HCl is the preparation of drug core. Drug core according to the present invention is prepared by depositing drug layer comprising Diltiazem HCl on inert core. Deposition of drug layer is accomplished by layering or coating drug layer on inert core to obtain layered drug core or coated drug core respectively.

Layered drug core comprise of alternate multiple layers of binder and drug blend comprising Diltiazem HCl and other pharmaceutical ingredients on inert core. This is achieved by spraying binder on inert core followed by layering drug blend of Diltiazem HCl and other pharmaceutical ingredients. This alternate process of spraying binder and layering drug blend is repeated several times till the drug blend is exhausted. The layered drug core is optionally further coated with binder and antitack agent to obtain hardened drug core. This is achieved by spraying suspension of binder and antitack agent in aqueous, alcoholic or hydroalcoholic media on drug core.

Coated drug core comprise of coating Diltiazem HCl, binder, antitack agent and optionally other pharmaceutical ingredient as single layer on inert core. This is achieved by spraying dispersion containing Diltiazem HCl, binder, antitack agent and other pharmaceutical ingredient from aqueous, alcoholic or hydroalcoholic media.

Drug core prepared by the present invention is in contrast to the prior art as it is exempt of wetting agent and shellac.

Preparation of layered drug core comprise steps of:

a) preparation of drug blend achieved by mixing Diltiazem HCl of particle size upto about 150 microns with other pharmaceutical ingredients other than wetting agent and shellac in a suitable mixer;

b) preparation of binder dispersion or solution which is accomplished by dispersing and / or dissolving binder in a suitable solvent;

c) spraying binder dispersion or solution on inert core followed by deposition of drug blend comprising Diltiazem HCl;

d) repeating step c) till the drug blend is exhausted to obtain drug core;

e) drying and sizing.

The drug core after sizing is optionally coated with binder dispersion to obtain hardened drug core. The processing steps for the preparation of hardened drug core comprise of:

a) preparation of binder dispersion or solution which is accomplished by dispersing and / or dissolving binder in a suitable solvent;
b) addition of antitack agent to step a);
c) spraying dispersion obtained in step b) on drug core to obtain hardened drug core:
d) drying and sizing.

Preparation of coated drug core comprise steps of:

a) preparation of binder dispersion or solution which is accomplished by dispersing and / or dissolving binder in a suitable solvent;
b) preparation of drug solution which is accomplished by dissolving Diltiazem HCl in a suitable solvent;
c) mixing of binder dispersion or solution with drug solution;
d) addition of other pharmaceutical ingredient preferably an antitack agent to the above mixture to obtain drug binder dispersion;
e) spraying drug binder dispersion on inert core to achieve drug core;
f) drying and sizing.

The inert core used in the preparation of drug core can be made up of any pharmaceutically acceptable inert excipient and has an average particle size of 1680 microns to 250 microns preferably between 1000 microns to 500 microns. Preferably inert core is made up of sugar and starch.

Other pharmaceutical ingredient used in the preparation of drug core is selected from diluents, antitack agents and their mixtures.

Diluent used for the preparation of drug core is selected from the group of starch, starch derivatives, cellulose derivatives such as microcrystalline cellulose, lactose, mannitol, glycols such as polyethylene glycol, cross linked povidone, crosslinked carboxymethyl cellulose and its sodium salt, natural gums and its derivatives such as sodium alginate, clays, alkali metal salts such as dibasic calcium phosphates, monobasic sodium phosphates, carbonates such as calcium carbonate and oxides of metal such as magnesium oxide and their mixtures, preferably starch.

Antitack agent used in the preparation of drug core is selected from talc, colloidal silicon dioxide, stearates such as calcium stearate, magnesium stearate, glyceryl monostearate and glyceryl behenate and their mixtures, preferably talc with or without colloidal silicon dioxide.

Binder used in the preparation of drug core is selected from the group of cellulose derivatives such as cellulose ethers selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, polymethacrylates natural gums, alginates and polyvinylpyrollidone, preferably hydroxypropylmethylcellulose.

Hydroxypropylmethylcellulose used as binder in the present invention has a nominal viscosity from about 3cps to about 18cps when measured at 2%w/w solution at 20 degree centigrade.

Solvent used for dispersing and / or dissolving binder and drug is selected from water, alcohol and their mixtures, preferably water.

The drug core or the hardened drug core so obtained are dried to achieve the moisture content of less than 5%w/w and preferably less than 3%w/w. Drying of drug core is accomplished in any suitable drier such as tray drier, fluid bed drier and the likes.

Drug core or hardened drug core after drying are sifted through desired mesh to obtain drug core or hardened drug core of desired particle size.

The drug core or the hardened drug core prepared by the process of the invention comprise of following ingredients, the percentage being expressed on weight basis of the final composition.

| Ingredients | % w/w |
|---|---|
| Inert core | Upto about 60% |
| Diltiazem HCl | Upto about 80% |
| Binder | Upto about 15% |
| Other Pharmaceutical Ingredient | Upto about 15 % |

Preferably, the drug core or the hardened drug core comprise of following ingredients, the percentage being expressed on weight basis of the final composition.

| Ingredients | % w/w |
|---|---|
| Inert core | About 10% to about 60% |
| Diltiazem HCl | About 30% to about 70% |
| Binder | About 2% to 12% |
| Other Pharmaceutical Ingredient | About 1.5% to 10% |

**Stage II**

**Preparation of Extended Release Pellets:**

The drug core or the hardened drug core prepared by the process of the invention is further processed to obtain extended release pellets comprising Diltiazem HCl. These

extended release pellets are achieved by coating drug core or hardened drug core with a polymer membrane. The polymer membrane that extends the release of Diltiazem HCl from the drug layer comprises of water insoluble polymer, from about 0% to about 30% w/w of pharmaceutically acceptable additive and from about 0% to about 30%w/w of plasticizer, relative to the total weight of the polymer membrane. The thickness of the polymer membrane coated on drug core or hardened drug core is less than 50 microns, preferably less than 20 microns, more preferably less than 15 microns. Extended release pellets comprising Diltiazem HCl are achieved by spraying a solution or dispersion of water insoluble polymer, plasticizer and pharmaceutically acceptable additive from a suitable solvent on drug core or hardened drug core.

Preparation of extended release pellets comprise steps of:

a) dispersing or dissolving water insoluble polymer in a suitable solvent to obtain coating dispersion or solution;
b) addition of plasticizer and / or pharmaceutically acceptable additive to step a);
c) spraying the dispersion obtained in step b) on drug core or hardened drug core to obtain extended release pellets;
d) drying and / or curing and sizing.

Water insoluble polymer present in the polymer membrane is selected from polymethacrylates, cellulose derivatives such as cellulose ethers as listed in Handbook of Pharmaceutical Excipients, 2nd Edition, The Pharmaceutical Press, London, 1994. In particular, water insoluble polymer is selected from Poly(ethyl acrylate, methylmethacrylate) 2:1 marketed under the trade name of Eudragit RTM NE30D of Rohm Pharma, Germany, Poly(ethyl acrylate methylmethacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 marketed under the trade name of Eudragit RTM RL of Rohm Pharma, Germany, Poly(ethyl acrylate methylmethacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1 marketed under the trade name of Eudragit RTM RS of Rohm Pharma, Germany, Poly(methacrylic acid, methyl methacrylate) 1:1 marketed under the trade name of Eudragit RTM L of Rohm Pharma, Germany, Poly(methacrylic acid, ethyl acrylate) 1:1 marketed under the trade name of Eudragit RTM L 30D – 55 and Eudragit RTM L100 – 55 of Rohm Pharma, Germany, Poly(methacrylic acid, methyl methacrylate) 1:2 marketed under the trade name of Eudragit RTM S of Rohm Pharma, Germany, and ethylcellulose marketed under the trade name of Ethocel RTM of Dow, U.S.A., Aquacoat RTM of FMC, USA and Surelease RTM of Colorcon, USA, polyvinyl alcohol, polyvinyl acetate and cellulose acetate. This water insoluble polymer is coated on drug core or hardened drug core as a single layer and is used alone or in a suitable mixture.

Alternatively, drug core or hardened drug core is coated with a water insoluble polymer/s in more than one layer wherein the polymer in different layers may be same or different.

Plasticizer used in the polymer membrane is commonly used pharmaceutically acceptable plasticizer such as triacetin, triethylcitrate, dibutylsebacate, polyethylene glycol, miglyol, cetyl alcohol and their mixtures thereof.

Pharmaceutical acceptable additive is preferably from one or more antitack agents and water soluble cellulose ether polymers. Antitack agents are selected from talc, colloidal silicon dioxide, stearates such as calcium stearate, magnesium stearate, glyceryl monostearate and glyceryl behenate and their mixtures preferably talc with or without colloidal silicon dioxide. Water soluble cellulose ethers polymers are selected from the hydroxyethylcellulose, carboxymethylcellulose and its pharmaceutically acceptable salts, hydroxypropylcellulose and hydroxypropylmethylcellulose preferably hydroxypropylmethylcellulose.

Water insoluble polymer is dispersed and / or dissolved in a suitable solvent selected from water, alcohol, organic solvent/s and their suitable mixtures.

In an embodiment of the invention the process for the preparation of extended release pellets comprising Diltiazem HCl is completely carried out using aqueous media.

Alternatively, a part or whole process is carried out using water and / or alcohol and / or organic solvent/s.

These extended release pellets comprising Diltiazem HCl are dried to achieve the moisture content of less than 5%w/w and preferably less than 3%w/w. Drying of these extended release pellets is accomplished in any suitable drier such as tray drier, fluid bed drier and the likes.

Extended released pellets obtained by the process of the invention are sifted through desired mesh to obtain pellets of desired particle size.

The polymer membrane of the extended release pellets comprising Diltiazem HCl prepared by the process of the invention comprise of following ingredients, the percentage being expressed on weight basis of the polymer membrane.

| **Ingredients** | **% w/w** |
|---|---|
| Water Insoluble Polymer | Upto about 100% |
| Plasticizer | 0% to about 30% |
| Pharmaceutical acceptable additive | 0% to about 30% |

Preferably, the polymer membrane comprise of following ingredients, the percentage being expressed on weight basis of the polymer membrane.

| Ingredients | % w/w |
|---|---|
| Water Insoluble Polymer | About 40% to about 95% |
| Plasticizer | 2.5% to about 30% |
| Pharmaceutical acceptable additive | 2.5% to about 25% |

The invention is now illustrated with a non-limiting example.

**Example 1**

**1.1 Preparation of drug binder dispersion:**

Water is poured into a stainless steel container and Diltiazem HCl (70%w/w) is added in small portion with stirring. Stirring is continued till a clear drug solution is obtained.

Water is poured into second stainless container and Hydroxypropylmethylcellulose (HPMC) (5.25%w/w) is added in small portion with stirring. Stirring is continued till HPMC is completely dispersed and dissolved in water.

The above two solution are mixed to obtain drug – binder solution and colloidal silicon dioxide (0.70%w/w) and talc (1.75%w/w) is added with stirring. The resulting dispersion is filtered through desired mesh.

**1.2 Preparation of Drug core:**

Inert core are introduced in fluid bed bottom spray processor. The drug core is obtained by continuous spraying of the drug – binder dispersion on inert core. The drug core obtained is dried in the same equipment till the moisture content of drug core is less than 3% w/w. Drug core so obtained are sifted through desired mesh to remove any undersize and oversize drug core.

**1.3 Preparation of Coating Solution or Dispersion:**

Methanol and Methylene chloride is poured in a stainless steel container and ethylcellulose (3.76%w/w) is added in small portions with stirring. Stirring is continued till a clear coating solution is obtained. Triacetin (0.37%w/w) is slowly added with stirring in the coating solution and the resulting solution is filtered to through desired mesh.

Alternatively, aqueous dispersion of ethylcellulose (3.76% w/w) can also be used for the preparation of extended release pellets comprising Diltiazem HCl. In that case aqueous dispersion of ethylcellulose is poured in stainless steel container and water is added in

small portions with stirring. Talc is added with stirring and the resulting dispersion is filtered through desired mesh.

**1.4 Preparation of Extended Release Pellets:**

Drug core obtained are introduced in fluid bed bottom spray processor and they are coated with the coating dispersion obtained above to obtain extended release pellets. These extended release pellets are dried in the same equipment till the moisture content of these pellets is less than 3% w/w. These pellets alternatively may be cured at about 40°C for about 12 – 24 hours. Extended release pellets so obtained are sifted through desired mesh to remove any undersize and oversize drug core.

Final composition of pellets comprising Diltiazem HCl expressed in percentage weight by weight of the final composition is listed below.

| Ingredients | Ex. 1 (%w/w) |
|---|---|
| Inert core (25 – 30# ASTM) | 18.17 |
| Diltiazem HCl | 70.00 |
| HPMC | 5.25 |
| Talc | 1.75 |
| Colloidal Silicon Dioxide | 0.70 |
| Ethylcellulose | 3.76 |
| Triacetin | 0.37 |
| Water * | QS |
| Methanol * | QS |
| Dichloromethane * | QS |

* Evaporated during the process

QS – Quantity Sufficient

**Example 2**

**2.1 Preparation Of Drug Blend:**

Diltiazem HCl (70%w/w) (200 mesh A.S.T.M.) and Talc (6.54%w/w) was passed through desired mesh and are placed in a planetary mixer. Mixing is carried out for 10 minutes with intermittent racking to obtain drug blend.

**2.2 Preparation of Binder Solution:**

Water is poured into a stainless steel container and Hydroxypropylmethylcellulose (HPMC) (4.10%w/w) is added in small portion with stirring. Stirring is continued till HPMC is completely dispersed and dissolved in water.

**2.3 Preparation of Drug Core:**

Inert core are introduced in coating pan. The drug core is obtained by alternate spraying of the binder solution on inert core followed by deposition of drug blend. This process of alternate spraying of binder solution and deposition of drug blend is repeated several times to completely deposit the drug blend. The drug core obtained is dried in tray drier to achieve moisture content of less than 3% w/w. Drug core so obtained are sifted through desired mesh to remove any undersize and oversize drug core.

**2.4 Preparation of Hardened Drug Core:**

Binder solution is prepared as described in 2.2. Talc is added to this solution. Resulting dispersion is filtered through desired mesh and is sprayed on drug core in coating pan to obtain hardened drug core. Hardened drug core so obtained are dried and sifted as described above.

**2.5 Preparation of Coating Solution or Dispersion:**

Coating solution or dispersion is prepared as described in 1.3

**2.6 Preparation of Extended Release Pellets:**

Extended release pellets comprising Diltiazem HCl is prepared as described in 1.4.

Final composition of pellets comprising Diltiazem HCl expressed in percentage weight by weight of the final composition is listed below.

| Ingredients | Ex. 2 (%w/w) |
|---|---|
| Inert core (25 – 30# ASTM) | 13.53 |
| Diltiazem HCl | 70.00 |
| HPMC | 4.10 |
| Talc | 6.54 |
| Ethylcellulose | 5.30 |
| Triacetin | 0.53 |
| Water * | QS |
| Methanol * | QS |
| Dichloromethane * | QS |

* Evaporated during the process

QS – Quantity Sufficient

**Example 3 – 4**

Extended release pellets comprising Diltiazem HCl is prepared as described in example 1.

| Ingredients | Ex. 3 (% w/w) | Ex. 4 (% w/w) |
|---|---|---|
| Inert core (25 – 30# ASTM) | 18.17 | 51.77 |
| Diltiazem HCl | 70.00 | 36.30 |
| HPMC E15 | 5.25 | 3.63 |
| Talc | 2.12 | 0.91 |
| Starch | - | 1.82 |
| Colloidal Silicon Dioxide | 0.70 | 0.36 |
| Ethylcellulose | - | 4.74 |
| Aqueous dispersion of Ethyl cellulose | 3.76 (solid content) | - |
| Triacetin | - | 0.47 |
| Water * | QS | QS |
| Methanol * | - | QS |
| Dichloromethane * | - | QS |

**Dissolution Studies:**

The extended release pellets comprising Diltiazem HCl is analyzed in-vitro at 100rpm in USP apparatus, Type I or Type II in 900 ml distilled water / pH 6.8 phosphate buffer / 0.1N HCl / pH 4.5 acetate buffer at 100 rpm. The specification of acceptable drug release profile of Diltiazem HCl extended release pellets is given below in table I.

Table I: Drug release profile of Diltiazem HCl extended release pellets

| Time (hours) | Mean % Drug Release |
|---|---|
| 2 | N.M.T. 20 |
| 4 | N.M.T. 50 |
| 8 | N.M.T. 85 |
| 16 | N.L.T. 70 |

Preferably the acceptable drug release profile of Diltiazem HCl extended release pellets is given in table II.

Table II: Preferable drug release profile of Diltiazem HCl extended release pellets

| Time (hours) | Mean % Drug Release |
|---|---|
| 2 | N.M.T. 15% |
| 4 | about 15% – about 45% |
| 8 | about 50% – about 85% |
| 16 | N.L.T. 75% |

The pellets prepared as per example 1 of the present invention is analyzed in-vitro in USP Type II apparatus using 900ml of distilled water / pH 6.8 phosphate buffer / 0.1N HCl / pH 4.5 acetate buffer at 100 rpm. The drug release profile of these pellets is different media is depicted in the figure I.

It is evident from the figure I that cumulative mean % drug release from the extended release pellets comprising Diltiazem HCl is substantially same irrespective of the pH of the media in which it is analyzed. In other words Diltiazem HCl extended release pellets exhibits pH independent in – vitro drug release profile with a maximum variation of less than 20% and preferably less than 15%.

If the extended release pellets comprising Diltiazem HCl releases drug too fast to comply the desired in-vitro dissolution profile, it may receive an additional coat to achieve the desired in-vitro dissolution profile. Extended release pellets comprising Diltiazem HCl complying with the desired dissolution profile is filled in capsule to deliver the therapeutic dose of Diltiazem HCl.

Extended release pellets comprising Diltiazem HCl are filled into sized capsule to deliver the therapeutic dose of about 90mg, 120mg, 180mg, 240mg, 300mg, 360mg and 420mg.

The extended release pellets filled in capsule are stable atleast for a period of 6months at 40 degree centigrade and 75% relative humidity indicating that the formulation can be assigned a shelf life of 24 months at room temperature.

A bioequivalent studies was carried out using Diltiazem HCl extended release capsule 120mg prepared by the process of the invention against Tizac extended release capsule RTM 120 mg of Biovail as reference product. Extended release capsule containing Diltiazem HCl 120 mg was found to be bioequivalent to reference product.

**Claims:**

**We claim**

1. A process for the preparation of novel, stable extended release pharmaceutical composition comprising Diltiazem salt such as Diltiazem HCl wherein, the extended release pharmaceutical composition comprises of drug core coated with a polymer membrane comprising water insoluble polymer, the said drug core comprises of drug layer comprising Diltiazem HCl, binder and other pharmaceutical ingredient layered or coated on inert core, said drug layer being exempt of wetting agent and shellac, the composition exhibiting pH independent in-vitro release profile for once a day dosing.

2. A process as claimed in claim 1, wherein the preparation of layered drug core comprise steps of:

a) preparation of drug blend by mixing Diltiazem HCl of upto about 150 microns with other pharmaceutical ingredients in a suitable mixer;
b) preparation of binder dispersion or solution which is accomplished by dispersing and / or dissolving binder in a suitable solvent or solvent mixture;
c) spraying binder dispersion or solution on inert core followed by deposition of drug blend comprising Diltiazem HCl;
d) repeating step c) till the drug blend is exhausted to obtain drug core;
e) drying and sizing.

3. A process as claimed in claim 1, wherein the preparation of coated drug core comprise steps of:

a) preparation of binder dispersion or solution which is accomplished by dispersing and / or dissolving binder in a suitable solvent or solvent mixture;
b) preparation of drug solution which is accomplished by dissolving Diltiazem HCl in a suitable solvent or solvent mixture;
c) mixing of binder dispersion or solution with drug solution;
d) addition of other pharmaceutical ingredient preferably an antitack agent(s) to the above mixture to obtain drug binder dispersion;
e) spraying drug binder dispersion on inert core to achieve drug core;
f) drying and sizing.

4. A process as claimed in claim 1, wherein the drug core is optionally further coated with binder to obtain hardened drug core which comprise steps of:

a) preparation of binder dispersion or solution which is accomplished by dispersing and / or dissolving binder in a suitable solvent or solvent mixture;
b) addition of antitack agent to step a);

c) spraying dispersion obtained in step b) on drug core to obtain hardened drug core;

d) drying and sizing.

5. A process as claimed in claim 1, wherein the preparation of extended release pellets comprising Diltiazem HCl comprises step of deposition of polymer membrane which comprise steps of:

a) dispersing or dissolving water insoluble polymer in a suitable solvent to obtain coating dispersion or solution;

b) addition of plasticizer from 0%w/w to about 30%w/w of the polymer membrane and / or pharmaceutically acceptable additive from 0%w/w to about 30%w/w of the polymer membrane to step a);

c) spraying the dispersion obtained in step b) on drug core or hardened drug core to obtain extended release pellets;

d) drying and / or curing and sizing.

6. A process as claimed in claims 1 – 4, wherein the drug core or hardened drug core comprises of Diltiazem HCl upto about 80%w/w of the composition;

binder selected from hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polymethacrylates natural gums, alginates and polyvinylpyrollidone and is hydroxypropylmethylcellulose upto about 15%w/w, preferably from about 2%w/w to about 12%w/w of the composition;

other pharmaceutical ingredients selected from diluents, antitack agents and their mixtures upto about 15%w/w, preferably from about 1.5 to about 10% w/w of the composition.

7. A process as claimed in claim 5, wherein the polymer membrane comprises of water insoluble polymer selected from group of cellulose derivatives, polymethacrylates and their mixtures and is ethylcellulose upto about 100%w/w, preferably from about 40%w/w to about 95%w/w of the polymer membrane, plasticizer selected from triacetin, triethylcitrate, dibutylsebacate, polyethylene glycol, miglyol, cetyl alcohol and their mixtures and is preferably triacetin, preferably from about 2.5%w/w to about 30%w/w of the polymer membrane.

8. A process as claimed in claims 1 – 6, wherein the other pharmaceutical ingredient and other pharmaceutical additive is antitack agent selected from talc, colloidal silicon dioxide, stearate such as calcium stearate, magnesium stearate, glyceryl monostearate and glyceryl behenate and their mixtures preferably talc with or without colloidal silicon dioxide.

9. A novel, stable extended release pharmaceutical composition comprising Diltiazem salt such as Diltiazem HCl wherein, the extended release pharmaceutical composition comprises of drug core coated with a polymer membrane comprising water insoluble polymer, the said drug core comprises of drug layer comprising Diltiazem HCl, binder and other pharmaceutical ingredient layered or coated on inert core, said drug layer being exempt of wetting agent and shellac, the composition exhibiting pH independent in-vitro release profile for once a day dosing.

10. A composition as claimed in claim 9, wherein the drug layer comprises of Diltiazem HCl upto about 80%w/w of the composition, binder and other pharmaceutical ingredient.

11. A composition as claimed in claim 10, wherein other pharmaceutical ingredient is selected from diluents, antitack agents and their mixtures.

12. A composition as claimed in claim 10, wherein binder is selected from hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polymethacrylates natural gums, alginates and polyvinylpyrollidone and is hydroxypropylmethylcellulose upto about 15%w/w, preferably from about 2%w/w to about 12%w/w of the composition.

13. A composition as claimed in claim 9, wherein the polymer membrane comprises water insoluble polymer, plasticizer from 0%w/w to about 30%w/w of the polymer membrane and / or pharmaceutically acceptable additive from 0%w/w to about 30%w/w of the polymer membrane.

14. A composition as claimed in claim 13, wherein plasticizer in polymer membrane is selected from triacetin, triethylcitrate, dibutylsebacate, polyethylene glycol, miglyol, cetyl alcohol from about 2.5%w/w to about 30%w/w of the polymer membrane.

15. A composition as claimed in claim 13, wherein pharmaceutically acceptable additive in polymer membrane is preferably from about 2.5%w/w to about 30%w/w of the polymer membrane.

16. A composition as claimed in claim 13, wherein the water insoluble polymer is selected from the group of cellulose derivatives, polymethacrylates and their mixtures upto about 100%w/w, preferably from about 40%w/w to about 95%w/w of the polymer membrane.

17. A composition as claimed in claim 16, wherein cellulose derivative is ethyl cellulose.

18. A composition as claimed in claims 11 and 15, wherein pharmaceutically acceptable additive and other pharmaceutical ingredient is an antitack agent selected from talc, colloidal silicon dioxide, stearate such as calcium stearate, magnesium stearate, glyceryl monostearate and glyceryl behenate and their mixtures preferably talc with or without colloidal silicon dioxide.

19. A novel, stable extended release pharmaceutical composition comprising Diltiazem salt such as Diltiazem HCl wherein, the extended release pharmaceutical composition comprises of drug core coated with a polymer membrane comprising ethylcellulose, the said drug core comprises of drug layer comprising Diltiazem HCl, hydroxypropylmethylcellulose and talc layered or coated on inert core, said drug layer being exempt of wetting agent and shellac, the composition exhibiting pH independent in-vitro release profile of

not more than 20% of Diltiazem HCl after 2 hours;
not more than 50% of Diltiazem HCl after 4 hours;
not more than 85% of Diltiazem HCl after 8 hours;
and not less than 70% of Diltiazem HCl after 16 hours
when analyzed in USP type II apparatus using 900ml of distilled water / pH 6.8 phosphate buffer / 0.1N HCl / pH 4.5 acetate buffer at 100 rpm.

20. A composition as claimed in claim 20 wherein the preferable in-vitro release profile of not more than 15% of Diltiazem HCl after 2 hours;
about 15 – about 45% of Diltiazem HCl after 4 hours;
about 50 – about 85% of Diltiazem HCl after 8 hours;
and not less than 75% of Diltiazem HCl after 16 hours
when analyzed in USP type II apparatus using distilled water / pH 6.8 phosphate buffer / 0.1N HCl / pH 4.5 acetate buffer at 100 rpm.

21. A composition as claimed in claims 9 and 19 wherein the composition comprising Diltiazem HCl is in the form of extended release pellets and is capable of being filled in sized capsule for a dose from about 90 mg to about 420 mg.

22. A composition as claimed claim 21, wherein the capsule preparation of Diltiazem HCl comprises of one type of pellets.

23. A composition as claimed in claims 1, 9 and 19, wherein the thickness of the polymer membrane is preferably less than 20 microns.

24. A composition and process as claimed in claims 1, 9 and 19, wherein Diltiazem HCl may be micronized.

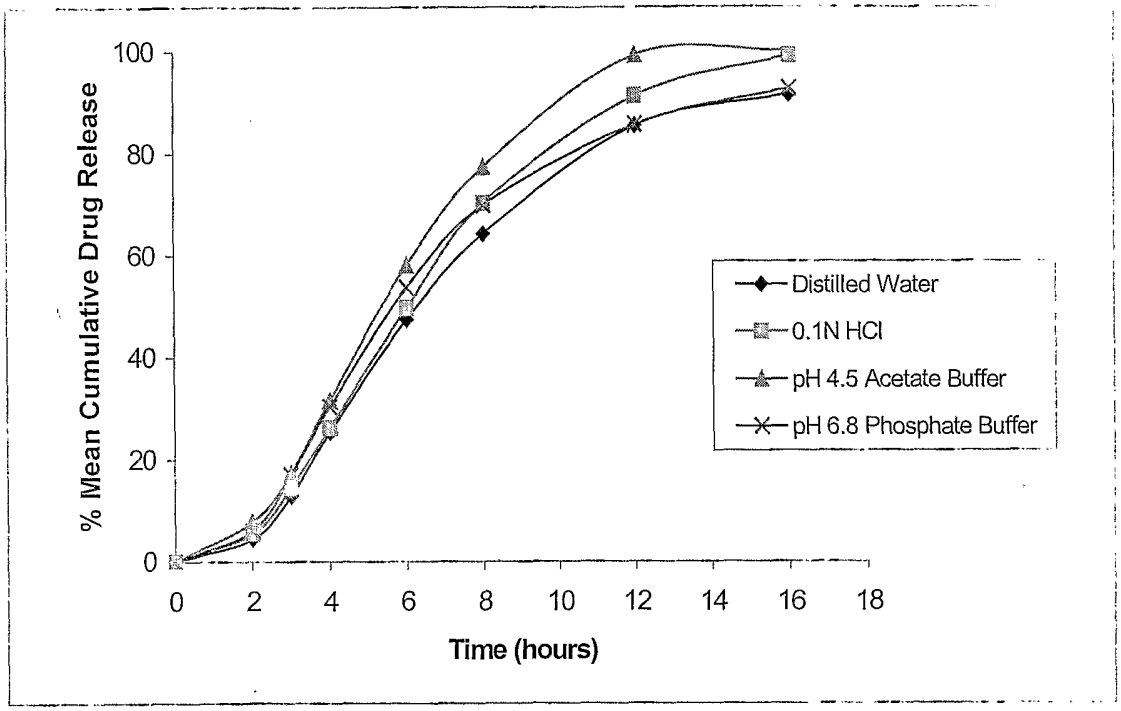
% Mean Cumulative Drug Release
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
Time (hours)
Distilled Water
0.1N HCl
pH 4.5 Acetate Buffer
pH 6.8 Phosphate Buffer

Fig. 1

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB04/02578

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 9/22
US CL : 424/468
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5,388,505 A (DEBOECK et al) 22 February 1994 (22.02.1994), abstract; column 2-4; column 5, lines 7-56. | 1-24 |
| X | US 5,133,974 A (PARADISSIS et al) 28 July 1992 (28.07.1992), abstract; column 1, lines 22 and 40-57; column 4, lines 1-7; column 8, line 29 to column 9 line 35. | 1-24 |
| A | US 6,228,398 A (DEVANE et al) 08 May 2001 (08.05.2001), see the whole document. | 1-24 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search
10 December 2004 (10.12.2004)

Date of mailing of the international search report
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