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(54) Title: LACIDIPINE PARTICLES

(57) Abstract: Lacidipine particles having small particle sizes and a narrow particle size distribution.

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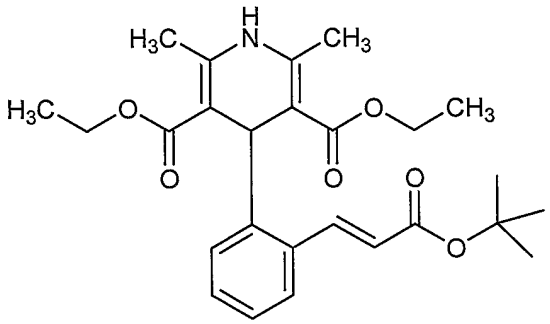
# LACIDIPINE PARTICLES

## INTRODUCTION TO THE INVENTION

The present invention relates to agglomerate free particles of lacidipine, processes to prepare the same, the pharmaceutical compositions comprising such agglomerate free particles and their use in the therapy of hypertension.

Lacidipine, chemically named (E)-4-[2-[3-(1,1-dimethylethoxy)-3-oxopropenyl]phenyl]-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester, is represented structurally by Formula I.



Formula I

Lacidipine is a dihydropyridine calcium antagonist, which is useful in the treatment of hypertension and is commercially available as MOTENS tablets (2, 4, and 6 mg). Lacidipine is a white to pale yellow crystalline powder, practically insoluble in water.

U.S. Patent Nos. 4,801,599 and 5,011,848 describe lacidipine and its related compounds, processes for the prepartion of crystalline lacidipine, pharmaceutical compositions containing them, and to their use in cardio vascular disorders.

PCT International Application Publication No. WO 2004/009057 describes a process to prepare dispersions of nano-crystalline particles in an aqueous medium.

There are an ever-increasing number of organic compounds being formulated for therapeutic or diagnostic effects that are poorly soluble or insoluble in aqueous environments. Such drugs provide challenges to their delivery *in vivo*

by an administrative route such as parenteral, oral, pulmonary, nasal, buccal, topical, ophthalmic, rectal, vaginal, transdermal and the like due to their poor solubility. Compounds that are insoluble in water can have significant benefits when formulated appropriately. Accurate control of particle size is essential for safe and efficacious use of these formulations. For example particles must be less than about 7 μm in diameter to safely pass through capillaries without causing emboli.

Preparations of small particles of water insoluble drugs can also be suitable for oral, pulmonary, topical, ophthalmic, nasal, buccal, rectal, vaginal, transdermal, or other routes of administration. The small size of the particles improves the dissolution rate of the drug, hence may improve its bioavailability and potentially its toxicity profiles. When administered by these routes, it may be desirable to have particle size in the range of 5 to 100 μm, depending on the route of administration, formulation, solubility, and bioavailability of the drug. For example, for oral administration, it is desirable to have a particle size of less than about 7 μm, and for pulmonary administration, the particles are preferably less than about 10 μm in size.

It would thus be a significant improvement in the art to provide agglomerate free particles of lacidipine of low particle size and a high specific surface area, pharmaceutical compositions comprising such particles and their use in the therapy of hypertension.

## SUMMARY OF THE INVENTION

The present invention relates to agglomerate free particles of lacidipine, processes to prepare the same, the pharmaceutical compositions comprising such agglomerate free particles and their use in the therapy of hypertension.

An embodiment of a process for preparing fine, uniform and agglomerate-free particles of crystalline lacidipine includes;

(a) dissolving lacidipine in an organic solvent or mixture of solvents to form a first solution;

(b) adding lacidipine solution to an anti solvent or mixture of anti solvents or adding anti solvent or mixture of anti solvents to lacidipine solution in the presence of ultrasound radiation;

(c) optionally cooling the mixture to get a slurry; and

(d) separating and drying the solid mass from slurry to recover fine, uniform and agglomerate free particles of lacidipine.

In another aspect the invention provides a premix composition having finely divided lacidipine, prepared by depositing a lacidipine solution onto a substrate material that is a pharmaceutical excipient or a mixture of pharmaceutical excipients, then removing at least a portion of the solvent.

An aspect of the invention comprises lacidipine particles having a particle size distribution with a span less than about 5.

Another aspect of the invention comprises lacidipine particles having a particle size distribution with a span less than about 3.

In a further aspect, the invention comprises a pharmaceutical composition comprising lacidipine particles having a span less than about 5, or less than about 3, and at least one pharmaceutically acceptable excipient.

## BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 shows an ultrasound flow cell that is useful in an aspect of the invention.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to agglomerate free particles of lacidipine, processes to prepare the same, pharmaceutical compositions comprising such agglomerate free particles and their use in the therapy of hypertension.

An embodiment of a process for preparing fine, uniform and agglomerate free particles of crystalline lacidipine includes;

(a) dissolving lacidipine in organic solvent to form a first solution;

(b) adding first solution to an anti solvent or mixture of anti solvents or adding anti solvent or mixture of anti solvents to first solution in the presence of controlled ultrasound radiations;

(c) optionally cooling the mixture to get slurry; and

(d) separating and drying the solid mass from slurry to recover fine, uniform and agglomerate free particles of lacidipine.

The organic solvents that can be used for the preparation of the first solution include various classes of solvents in which the lacidipine is soluble. Examples include but are not limited to alcohols, ketones, esters, ethers, halogenated solvents, hydrocarbons, nitriles, or mixtures thereof. Lower alkanols are useful and can be any alcohol such as for example one or more of the primary, secondary or tertiary alcohols having from one to about six carbon atoms. The lower alkanol can be for example one or more of methanol, ethanol, denatured spirits, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol and the like. The ketones can be any solvent from this class such as for example one or more of acetone, propanone, 2-butanone and the like. The halogenated solvent can be any solvent from this class such as for example one or more of chloroform, dichloromethane, 1,2-dichloroethane, carbon tetrachloride and the like. The ester can be any solvent from this class such as for example one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate and the like. The ether can be any solvent from this class such as for example one or more of dimethyl ether, diethyl ether, methyl tertiary-butyl ether ethyl methyl ether, diisopropyl ether, tetrahydrofuran, dioxane and the like.

Lacidipine can be first dissolved in the organic solvent to create a first solution. Lacidipine can be present at from about 5% (w/v) to about 30% (w/v) depending on the solubility of lacidipine in the first solvent. Heating lacidipine in a solvent or solvent mixture to temperatures about 30 °C to about 150 °C, or from about 10 °C to about 15 °C below the boiling point of the solvent or solvent mixture, will help to ensure dissolution.

The lacidipine solution is then mixed with an antisolvent to precipitate lacidipine. The anti solvent can be mixed into the lacidipine solution. The antisolvents that can be used for the preparation of second solution include polar solvents such as water, or non-polar organic solvents such as n-heptane, hexane or cyclohexane or combinations thereof.

The solution-antisolvent mixture can be subjected to ultrasound radiation. First solution can be mixed with antisolvent, or vice versa, and subjected to ultrasound, typically for about 15-20 minutes or up to about 1 hour. A power of 50-1000 watts has been found useful, but the power applied will depend upon the size and shape of the vessel that contains the mixture. The use of longer times or other ultrasonic energy levels is not detrimental.

If an ultrasonic bath having a different power is employed, the energy exposure time has to be altered correspondingly. Energy is continually applied to the antisolvent and lacidipine solution during mixing, both in the ultrasonic bath and the flow cell. The lacidipine particles precipitate out immediately when lacidipine solution comes in contact with antisolvent while being exposed to ultrasound. Although the ultrasound treatment can be carried out at any temperature or room temperature, it needs to be taken into account that, without any cooling, the ultrasonic energy radiated into the mixture will itself cause a rise in temperature. The treatment of the mixture with ultrasound therefore frequently will be carried out using external cooling to maintain a desired temperature.

The mixture can be optionally cooled to below 20 °C or below 10 °C for about 1 hour, or for about 40 minutes to form slurry. Solids are separated, such as using vacuum, a pressure filter, or a centrifuge, and the solids are dried, such as in a vacuum oven at about 120 °C, or at about 85 °C, for about 1 to 15 hours, or 11 to 13 hours, or in a fluid bed dryer at about 120 °C, or at about 60 °C for up to about 30 to 40 minutes or about 2 hours, to afford agglomerate free particles of lacidipine. Slurry or wet cake can also be dried using spin flash drying and other techniques known in art. The cooling typically increases yield of solids.

The present process can also use agitation to ensure uniform macro mixing. The obtained fine particles of lacidipine can further also be milled to get additional particle size reduction while retaining uniformity and the agglomerate free quality.

Fig. 1 is a cross-sectional diagram of an embodiment of an ultrasound flow cell 10. The flow cell comprises an inlet 12 and an outlet 14, for establishing a flow in the direction of the arrows through the cell of a first fluid that is introduced into inlet 12. The number, locations and dimensions of the inlets and outlets may vary according to the requirements of an application, and fluid flow for an embodiment can be opposite the direction shown, in which event the positions of inlet 12 and outlet 14 would be reversed. On the outer surface of flow cell 10 are mounted multiple ultrasonic transducers 16 that supply ultrasonic radiation into the contents of the flow cell, the transducers being electrically connected to a suitable external power source (not shown). The number and physical arrangement of the transducers around the flow cell can vary according to the process requirements. A temperature sensor 18 is optionally attached to outlet 14 to observe and control

the temperature of the removed product from the outlet. Similar sensors may also optionally be attached to the inlet system and at various locations in the flow cell, as desired. A dip tube 20 having an inlet 22 is used to supply a second fluid containing a reactant into the flow cell. The number, diameters and materials of construction of the dip tube may vary with the process requirements. Dip tube 20 may further be perforated at a point where it is desired to introduce reactant into the flow cell interior and therefore does not necessarily have an open lower end for delivery of the reactant. The flow cell optionally is provided with an outer cover 24, for protection from the environment or for provision of heating, cooling, or insulation to the cell.

In operation, a first fluid comprising a reactive substance is introduced into inlet 12 and flows toward outlet 14. A second fluid comprising a different reactive substance is introduced into inlet 22 of dip tube 20 and exits the dip tube into the flow of first reactive substance. Simultaneously, ultrasonic radiation having a desired frequency and power is being applied to flow cell 10 through transducers 16 to influence a reaction that takes place between the reactive substances.

In an embodiment, flow cell 10 has a height about 45 cm, a width about 15 cm and a depth about 15 cm, giving an enclosed flow cell volume about 10 liters. Flow rates into inlet 12 and through dip tube 20 can be established as required to provide a desired proportion of reactants and a desired residence time inside the flow cell. Of course, other dimensions and shapes can be used depending on specific process requirements.

Lacidipine of the present invention has a mean particle size less than about 50 μm, or about 30 μm, or about 10 μm. This mean is calculated as the sum of sizes of total particles divided by the number of the particles.

Lacidipine of the present invention has $D_{90}$ less than about 80 μm, or less than about 30 $\mu$m, or less than about 15 μm. The particle size mentioned herein refers to the diameter of the particles more commonly known as $D_{90}$ when measured by conventional particle size measuring instruments such as MALVERN, SEPTECH, PARTICLE SIZING SYSTEM and such other instruments. $D_{90}$ as used herein is defined as the size of particles where 90 volume percent of the particles have sizes less than the value given. The terms $D_{50}$ and $D_{10}$ similarly define sizes where either 50 or 10 volume percent of the particles have sizes less

than the value given. Lacidipine of the present invention is fine, uniform and agglomerate-free.

Agglomerate free lacidipine of present invention has a "span" of less than about 5 or less than about 3. The term "span" is used herein as a measure of the particle size distribution and refers to a dimensionless measure of the spread of particle sizes in the sample. The larger the value of span, the wider the range of particle sizes present in a sample. The lower the value of the span, the narrower the range of particle sizes present in a sample. A value of zero would indicate a monodisperse particle size distribution. The span is calculated using the formula:

$$\text{Span} = [(D_{90} - D_{10}) \div D_{50}].$$

In an embodiment of the present invention, agglomerate free lacidipine is prepared as follows:

a) dissolving lacidipine in isopropyl alcohol to form a first solution;

(b) adding lacidipine-isopropyl alcohol solution to an anti solvent water under continuous sonication;

(c) optionally cooling the mixture to about 5 °C to get slurry; and

(d) separating the solid mass from slurry by filtration and drying the wet mass under vacuum in a oven at about 80 °C to recover fine, uniform and agglomerate free particles of lacidipine.

In other embodiment of the present invention, agglomerate free lacidipine is prepared as follows:

a) dissolving lacidipine in isopropyl alcohol to form a first solution;

(b) pumping lacidipine-isopropyl alcohol solution and anti solvent water through separate inlets to a flow cell to which are attached ultrasound transducers that apply energy to the cell, and optionally circulating a cooling fluid about the cell;

(c) allowing lacidipine solution and anti solvent to stay in the flow cell for a predetermined time period; and

(d) removing and separating the solid mass from slurry by filtration and drying the wet mass under vacuum in a oven at about 85 °C to recover fine, uniform and agglomerate free particles of lacidipine.

In another aspect the present invention provides a pharmaceutical composition comprising lacidipine with an improved dissolution profile.

For lacidipine, which is a compound with poor aqueous solubility, this is achieved by providing the lacidipine in the composition in a finely divided form. The present invention provides two approaches towards achieving a finely divided lacidipine in a pharmaceutical composition:

1. Use of agglomerate-free lacidipine of a low particle size and a high surface area obtained by the above process in a pharmaceutical composition; or

2. Preparation of a high surface area premix of lacidipine by adsorption of an organic solution of lacidipine onto a substrate material that is a pharmaceutical excipient, or a mixture of pharmaceutical excipients, then removing at least a portion of the solvent.

Where the input material is agglomerate free finely divided lacidipine, a low particle size is desirable, such as obtained by the above process.

Agglomerate free material obtained from the process using the ultrasound techniques may further be subjected to milling using the techniques known in the art such as micronisation, air-jet milling, pulverization and the like.

Use of agglomerate free material aids in smooth handling of the material, eases in processing the material, processing the compositions, and tends to increase the dissolution and release profiles.

The agglomerate free material can be formulated into a suitable dosage form such as for example tablets, capsules, syrups, suspensions, soft gels and the like by procedures known to a person skilled in the art of preparation of pharmaceutical formulations. Such compositions could include other excipients as are required for the preparation of the compositions including but not limited to diluents, granulating agents, solvents, lubricants, wetting agents, disintegrating agents and the like.

In another embodiment of the invention, finely divided lacidipine is provided in the form of a premix of lacidipine. Such a premix of lacidipine is prepared by the adsorption of an organic solution of lacidipine onto a base material or onto a pharmaceutical excipient, or a mixture of pharmaceutical excipients, then removing at least a portion of the solvent.

The term "premix" as used in this invention refers to a blend or granules of lacidipine with a pharmaceutically acceptable excipient or a combination of excipients (that are compatible with lacidipine) in which the lacidipine is provided

in a finely divided state. Such a premix can be formulated with common carriers, diluents or excipients, and formed into tablets, capsules, and the like.

The lacidipine premix as defined above may be prepared by dissolving lacidipine in a suitable solvent or mixture of solvents. The solvents useful in the invention can be from any class such as for example, alcohols, ethers, halogenated organic solvents, water, esters and the like. There is no limitation on which organic solvent can be used as long as the solvent has a high enough solubility for the lacidipine for the practice of this invention and is compatible with lacidipine. Further, volatile organic solvents are used to facilitate the removal of the solvents after further processing.

The solution of lacidipine in the solvent or mixture of solvents may be prepared by any conventional means using mixing and other aids as required for enhancing solubility such as for example, heating or sonication, are within the scope of this invention. The solution of lacidipine may also contain optionally any stabilizers or solubilizers and the like. The concentration of lacidipine in the solvent or mixture of solvents is typically in the range of about 15% to about 25% w/v, although higher or lower concentrations can be used.

Such a solution of lacidipine is then dispersed onto a substrate material, which can comprise one or more pharmaceutically acceptable excipients, aided with continuous mixing to provide uniform distribution of the active onto the substrate material. The term "substrate material" as used herein is a pharmaceutically acceptable excipient, which is used as a carrier for the lacidipine in a finely divided state. Mixtures of such excipients also are considered as a substrate material. The pharmaceutically acceptable excipients include any excipients, which are compatible with lacidipine, such as but not limited to: microcrystalline cellulose, micro fine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

The wet mass thus produced is dried to remove solvent under controlled conditions to obtain an optimum loss on drying of less than 3.5% w/w. The blend thus obtained having the lacidipine in a finely divided state is further processed into various pharmaceutical dosage forms.

The pharmaceutical compositions of the present invention may contain one or more diluents added to increase mass and, hence, make a dosage form easier for the patient and caregiver to handle. Common diluents are microcrystalline cellulose, micro fine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Binders also can be included in the pharmaceutical compositions of the present invention to help hold a tablet together after compression. Some typical binders are acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The pharmaceutical compositions to be made into tablets can further include a disintegrant to accelerate disintegration of the tablet in the patient's stomach. Disintegrants include alginic acid, carboxymethyl cellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Pharmaceutical compositions for tabletting may further include glidants, lubricants, flavoring agents, colorants and other commonly used excipients.

In other embodiments, the pharmaceutical compositions of the present invention are filled into capsules (e.g., hard gelatin capsules). Pharmaceutical compositions to be filled into capsules can and preferably do include pharmaceutically acceptable excipients; for example diluents such as lactose, mannitol, calcium carbonate, or magnesium carbonate; or flow aids such as stearates.

Solid oral dosage forms of the present invention are formulated to provide a unit dose of lacidipine of about 0.1 to about 20 milligrams per individual dosage form.

The lacidipine premix thus prepared may be a part of a pharmaceutical composition such as for example tablets, capsules, sachets, suspensions and the like. Such compositions can include other excipients as are required for the preparation of the compositions including but not limited to diluents, granulating agents, solvents, lubricants, wetting agents, disintegrating agents and the like. The procedures to convert such a blend into one of the compositions mentioned above are well known to a person skilled in the art of pharmaceutical formulations.

The present invention is illustrated by the following examples describing certain specific aspects and embodiments of the invention, and which are not intended to limit the scope of the invention in any manner.

## COMPARATIVE EXAMPLE

Preparation of lacidipine particles by micronisation.

300 g of lacidipine was fed to an air jet mill (Midas Mikronizer M-50 sold by Micro Tech Engineering Company, India) at a rate of about 1 kg/hour, and material thus obtained was sifted through a 40 mesh ASTM sieve.

The resultant material yielded 262 g of particles having a size distribution of $D_{10} < 1.26$ µm, $D_{50} < 10.58$ µm, $D_{90} < 56.96$ µm, and a span of 5.3. Agglomeration of particles was observed by examination of the material using a microscope.

## EXAMPLE 1

Preparation of agglomerate free lacidipine by adding isopropanol-lacidipine solution to water in an ultrasound bath.

100 ml of water was taken in a beaker and placed in an ultrasound bath. Water was cooled to 10° C by circulating cooling water in the bath and sonication started. 10 g of lacidipine, was dissolved in 120 ml of isopropanol at 50 to 55 °C. The solution of lacidipine in isopropanol was added to the water with continuous sonication for 5 minutes, then the solution was cooled to 1 °C and maintained for

30 minutes. The slurry was filtered and the solid dried under vacuum at about 80 °C for 12 hours.

The resultant material yielded 3.12 g of agglomerate free particles of a size distribution of $D_{10}$ < 0.84 µm, $D_{50}$ < 5.28 µm, $D_{90}$ < 11.43 µm, and a span of 2.0.

The span value of the material prepared from this example, when compared with the span value of the material prepared from comparative example, indicates that the material obtained with the present invention process results in a more uniform particle size distribution than was obtained from the conventional method of producing particles.

## EXAMPLE 2

Preparation of agglomerate free lacidipine by adding water to isopropanol-lacidipine solution in an ultrasound bath.

10 g of lacidipine was dissolved in 120 ml isopropanol at 50 to 55 °C. This solution of lacidipine in isopropanol was placed in an ultrasound bath at 50 °C and sonication was started. Chilled water at 10 °C was added to this solution with sonication. After complete addition, solution was cooled to 2 °C and maintained for 30 minutes. The slurry was filtered and dried under vacuum at 75 to 80 °C for 12 hours.

The resultant material yielded 2.7 g of an agglomerate free particles of size distribution $D_{10}$ < 7.88 µm, $D_{50}$ < 19.53 µm, $D_{90}$ < 35.39 µm, and a span of 1.4.

## EXAMPLE 3

Preparation of agglomerate free lacidipine by slow cooling crystallization in an ultrasound bath.

15 g of lacidipine was dissolved in 135 ml of isopropanol at 50 to 55° C. This solution was cooled slowly to 5 °C for about 7 ½ hours while applying ultrasound. The slurry was filtered and dried under vacuum at 75 to 80 °C for about 12 hours.

The resultant material yielded 7.4 g of agglomerate free particles having a size distribution of $D_{10}$ < 8.95 µm, $D_{50}$ < 22.2 µm, $D_{90}$ < 41 µm, and a span of 1.4.

## EXAMPLE 4

Preparation of agglomerate free lacidipine by rapid cooling crystallization in an ultrasound bath.

15 g of lacidipine was dissolved in 135 ml isopropanol at 50 to 55 °C. This solution was cooled rapidly to 5 °C in about 35 minutes while applying ultrasound. The slurry was filtered and washed with 7.5 ml of chilled isopropanol. The solid was dried under vacuum at 75 to 80 °C for 12 hours.

The resultant material yielded 12.4 g of agglomerate-free particles of size distribution $D_{10} < 5.56$ µm, $D_{50} < 14.91$ µm, $D_{90} < 34.95$ µm, and a span of 1.9.

## EXAMPLE 5

Preparation of agglomerate free lacidipine by controlled addition of isopropanol-lacidipine solution to n-heptane in an ultrasound bath.

198 ml of n-heptane was taken in a beaker and placed in an ultrasound bath. This n-heptane was cooled to about 4 °C by circulating cooling water in the bath and sonication was started. 8.5 g of lacidipine was dissolved in 99 ml of isopropanol at 50 to 55 °C. The solution of lacidipine in isopropanol was added to n-heptane at a rate of 5 ml/minute with continuous sonication. The slurry was filtered and dried under vacuum at 75 to 80 °C for 12 hours.

The resultant material yielded 6.4 g of agglomerate-free particles of size distribution $D_{10} < 7.14$ µm, $D_{50} < 29.12$ µm, $D_{90} < 60.61$ µm, and a span of 1.8.

## EXAMPLE 6

Preparation of agglomerate free lacidipine by controlled addition of n-heptane to ethyl acetate-lacidipine solution in an ultrasound bath.

5 g of lacidipine was dissolved in 50 ml ethyl acetate at 50 to 55 °C. This solution of lacidipine in ethyl acetate was placed in an ultrasound bath at 50 °C and sonication was started. 60 ml of chilled n-heptane at 10 °C was added to this solution at a rate of 10 ml/minute with sonication. The slurry was filtered and dried under vacuum at 75 to 80 °C for 12 hours.

The resultant material yielded 3.4 g agglomerate-free particles of size distribution $D_{10}$ < 10.57 µm, $D_{50}$ < 27.85 µm, $D_{90}$ < 54.6 µm, and a span of 1.6.

## EXAMPLE 7

Preparation of agglomerate free lacidipine by controlled addition of ethyl acetate-lacidipine solution to n-heptane in an ultrasound bath.

60 ml of n-heptane was taken in a beaker and placed in an ultrasound bath. This n-heptane was cooled below 10 °C by circulating cooling water in the bath and sonication was started. 5 g of lacidipine was dissolved in 30 ml of ethyl acetate at 55 to 60 °C. The solution of lacidipine in ethyl acetate was added to the n-heptane with continuous sonication at rate of 5 ml/min. The slurry was filtered and the solid dried under vacuum at 75 to 80 °C for 12 hours.

The resultant material yielded 3.1 g of agglomerate-free particles of size distribution $D_{10}$ < 6.73 µm, $D_{50}$ < 18.63 µm, $D_{90}$ < 35.05 µm and a span of 1.5.

The ultrasonic wattage used for examples 1 through 7 was 250 W, at 20 KHz frequency. Either wattage or frequency is variable in the ultrasound bath used.

Span values of all the above examples indicate that the material prepared from the present invention process results in agglomerate free material compared to material obtained from conventional processes as discussed in the comparative example.

## EXAMPLE 8

Preparation of lacidipine of desired particle size.

Lacidipine of desired particle size was prepared using the ultrasound flow cell, by the following process:

1. 48 L of isopropanol was transferred into reactor (1).
2. Further, 1.9 Kg lacidipine was added to the reactor.

3. The contents of the reactor were heated to 62.5°C ± 2.5°C using a hot water circulation jacket.
4. The contents were maintained at the same temperature for 30 minutes to allow for dissolution of lacidipine in isopropanol.
5. Simultaneously, water is taken into another reactor (2) and cooled to 2±1°C.
6. Water from reactor (2) was passed through the flow cell at a rate of 60±2 L/hour for 30 minutes without applying ultrasound radiation to the flow cell.
7. At the end of 30 min, the ultrasound system of the flow cell was switched on and the water was continuously circulated through the flow cell for 1 hour at 60±2 L/hour to stabilize the system.
8. At the end of 1 hour, the lacidipine solution in the reactor (1) was fed into the flow cell through the perforated dip tube at 62.5±2.5°C at 10.5±0.5 L/hour while the water was being simultaneously fed at 60±2 L/hour.
9. The slurry coming out of the flow cell was continuously centrifuged to obtain a wet lacidipine material.
10. The wet lacidipine material was dried under vacuum.

## EXAMPLE 9

Pharmaceutical compositions comprising different particle size lacidipine.

Preparation of pharmaceutical composition using lacidipine of large particle size:

| Ingredients | Qty/batch (g) |
|---|---|
| Lacidipine | 12 |
| Isopropyl alcohol | 150 ml |
| Lactose monohydrate | 741.45 |
| Povidone (PVP K-30) | 36 |
| Croscarmellose sodium | 45 |
| Spray dried lactose (Flowlac 100) | 51 |

| | |
|---|---|
| Magnesium Stearate | 14.4 |
| Total: | 900 |

Dispersed and dissolved povidone (PVP K-30) in isopropyl alcohol (IPA). Sifted lactose monohydrate and lacidipine through a 40 mesh ASTM sieve. Mixed geometrically and granulated the lactose-lacidipine dry mixture with the PVP K-30/IPA solution as prepared above. Dried the granules in a fluid bed drier (Restch Rapidrier) at 60 °C till the loss on drying (LOD) by infrared moisture balance at 105 °C is about 1% w/w. Sifted the dried granules through a 24 mesh ASTM sieve. Milled the retained fraction in a comminuting mill, knives forward and medium speed and passed them through a 24 mesh ASTM sieve. Blended the granules with the sifted Flowlac 100, croscarmellose sodium and magnesium stearate. The blend was compressed using 12.8×7.2 mm oval shaped tooling.

Preparation of pharmaceutical composition using lacidipine of small particle size:

The compositions and the procedure used to prepare tablets with smaller particle size is the same as the procedure for preparation of tablets with larger particle size. Particle size of lacidipine larger particles size was $D_{90}$ < 32 µm and smaller size was $D_{90}$ < 7.6 µm.

In-vitro release profiles.

Dissolution Profile (in water + 1% polysorbate 20)

Dissolution conditions herein used were USP apparatus II, 50 rpm and 500 ml of dissolution medium at 37 °C.

| **Time (minutes)** | **Percent Drug Released** | |
|---|---|---|
| | Composition with higher particle size | Composition with smaller particle size |
| 10 | 48 | 85 |
| 20 | 54 | 91 |
| 30 | 57 | 92 |
| 45 | 60 | 92 |
| 60 | 62 | 92 |

| | | |
|---|---|---|
| 90 | 67 | 92 |

As can be seen from the data, finely divided lacidipine with a particle size $D_{90}$ < 7.6 μm has a much more rapid dissolution than the lacidipine with a larger particle size of $D_{90}$ < 32 μm.

## EXAMPLE 10

Pharmaceutical compositions comprising lacidipine premix with different particle size lacidipine.

Pharmaceutical composition of lacidipine through the use of a lacidipine premix prepared from large particle size lacidipine (particle size distribution of $D_{90}$ < 238 μm, $D_{50}$ < 120 μm, $D_{10}$ < 39 μm).

| Ingredients | Qty/tablet (mg) |
|---|---|
| Lacidipine | 8 |
| Ethyl acetate | 100 ml |
| Isopropyl alcohol | 30 ml |
| Lactose monohydrate | 494.4 |
| Povidone (PVP K-30) | 24 |
| Croscarmellose sodium | 30 |
| Flowlac 100 | 34 |
| Magnesium stearate | 9.6 |
| Total: | 600 |

Lacidipine and povidone were dissolved in a mixture of ethyl acetate and isopropyl alcohol. This solution was added to granulate 40 mesh ASTM sieve sifted lactose monohydrate, dried the granules in a fluid bed drier at 60 °C till the moisture content was less than 2.5% w/w when tested using an infrared moisture analyzer at 105 °C. Dried "premix" granules were sifted through a 24 mesh ASTM sieve and sieve retains were milled in a comminuting mill using a 1 mm screen, knives forward and medium speed. Sifted and milled granules were blended with 40 mesh ASTM sifted croscarmellose sodium and Flowlac 100 and then blended

with 60 mesh ASTM sifted magnesium stearate. Lubricated blend was compressed into tablets.

A pharmaceutical composition of lacidipine using a lacidipine premix prepared from small particle size lacidipine (particle size distribution of $D_{90}$ < 6.7 μm, $D_{50}$ < 3.17 μm, $D_{10}$ < 0.839 μm). Manufacturing process remained the same as above.

In-vitro release profiles of compositions using premixes.

Dissolution Profile (in water + 1% polysorbate 20)

Dissolution conditions herein used are USP apparatus II, 50 rpm and 500 ml of dissolution medium at 37 °C.

| **Time (minutes)** | **% Drug Released** | |
|---|---|---|
| | Compositions of premix prepared from large particle size | Compositions of premix prepared from small particle size |
| 10 | 73 | 91 |
| 20 | 83 | 99 |
| 30 | 85 | 100 |
| 45 | 85 | 100 |
| 60 | 84 | 101 |
| 90 | 84 | 94 |

As can be seen from these data, the availability of lacidipine in a finely divided state through the formation of a premix also helps in enhancing the dissolution profile of lacidipine.

## EXAMPLE 11

Composition comprising lacidipine having small particles.

| Ingredients | Qty/batch (g) |
|---|---|
| Lacidipine | 64 |
| Lactose monohydrate | 4227.2 |
| Sodium starch glycolate | 240 |
| Polyvinyl pyrrolidone (PVP K-30) | 192 |
| Ethyl acetate | 372 |
| Isopropyl alcohol | 327 |
| Magnesium stearate | 76.8 |

Manufacturing process:

Lacidipine was dissolved in a mixture of ethyl acetate and isopropyl alcohol. The solution was used to granulate 40 mesh ASTM sifted lactose and sodium starch glycolate, dried the granules in a fluid bed drier at 60 °C till the moisture content was less than 2.5% w/w when tested using an infrared moisture analyzer at 105 °C. Dried granules were sifted through a 24 mesh ASTM sieve and sieve retains were milled in a comminuting mill using a 1 mm screen, knives forward and medium speed. Sifted and milled granules were blended with 60 mesh ASTM sifted magnesium stearate. Lubricated blend was compressed into tablets.

Particle size distribution of lacidipine used was $D_{90}$ < 8 µm.

Dissolution data:

Medium: 500 ml of water + 1% polysorbate 20, USP apparatus type II, 50 rpm.

| Time (minutes) | % Drug released |
|---|---|
| 10 | 76 |
| 20 | 88 |
| 30 | 92 |
| 45 | 95 |
| 60 | 96 |

CLAIMS:

1. Lacidipine particles having a particle size distribution with a span less than about 5.

2. The lacidipine particles of claim 1, wherein the span is less than about 3.

3. The lacidipine particles of either of claims 1 or 2, wherein the particles have a $D_{90}$ less than about 80 $\mu$m.

4. The lacidipine particles of either of claims 1 or 2, wherein the particles have a $D_{90}$ less than about 30 $\mu$m.

5. The lacidipine particles of either of claims 1 or 2, wherein the particles have a $D_{90}$ less than about 15 $\mu$m.

6. The lacidipine particles of either of claims 1 or 2, wherein the particles have a mean particle size less than about 50 $\mu$m.

7. The lacidipine particles of either of claims 1 or 2, wherein the particles have a mean particle size less than about 30 $\mu$m.

8. The lacidipine particles of either of claims 1 or 2, wherein the particles have a mean particle size less than about 10 $\mu$m.

9. The lacidipine particles of either of claims 1 or 2, wherein the particles are produced by combining a solution of lacidipine in an organic solvent with an antisolvent for lacidipine, while applying ultrasound energy.

10. The lacidipine particles of claim 9, wherein an antisolvent comprises water or a hydrocarbon.

11. The lacidipine particles of claim 9, wherein an antisolvent comprises a hydrocarbon.

12. The lacidipine particles of claim 9, wherein ultrasound energy is applied continuously during combining and for a time thereafter.

13. The lacidipine particles of either of claims 1 or 2, wherein the particles are produced by cooling a lacidipine solution while applying ultrasound energy.

14. A pharmaceutical composition comprising the lacidipine particles of either of claims 1 or 2 and at least one pharmaceutically acceptable excipient.

15. A pharmaceutical composition comprising the lacidipine particles of claim 3 and at least one pharmaceutically acceptable excipient.

16. A pharmaceutical composition comprising the lacidipine particles of claim 4 and at least one pharmaceutically acceptable excipient.

17. A pharmaceutical composition comprising the lacidipine particles of claim 5 and at least one pharmaceutically acceptable excipient.

18. A process for preparing the lacidipine particles of either of claims 1 or 2, comprising combining a solution of lacidipine in an organic solvent with an antisolvent for lacidipine, while applying ultrasound energy.

19. A process for preparing the lacidipine particles of either of claims 1 or 2, comprising cooling a lacidipine solution while applying ultrasound energy.

20. A premix composition having lacidipine in finely divided form deposited onto a solid substrate.

21. The premix composition of claim 20, being prepared by dispersing a solution comprising lacidipine onto a solid substrate, and removing solvent.

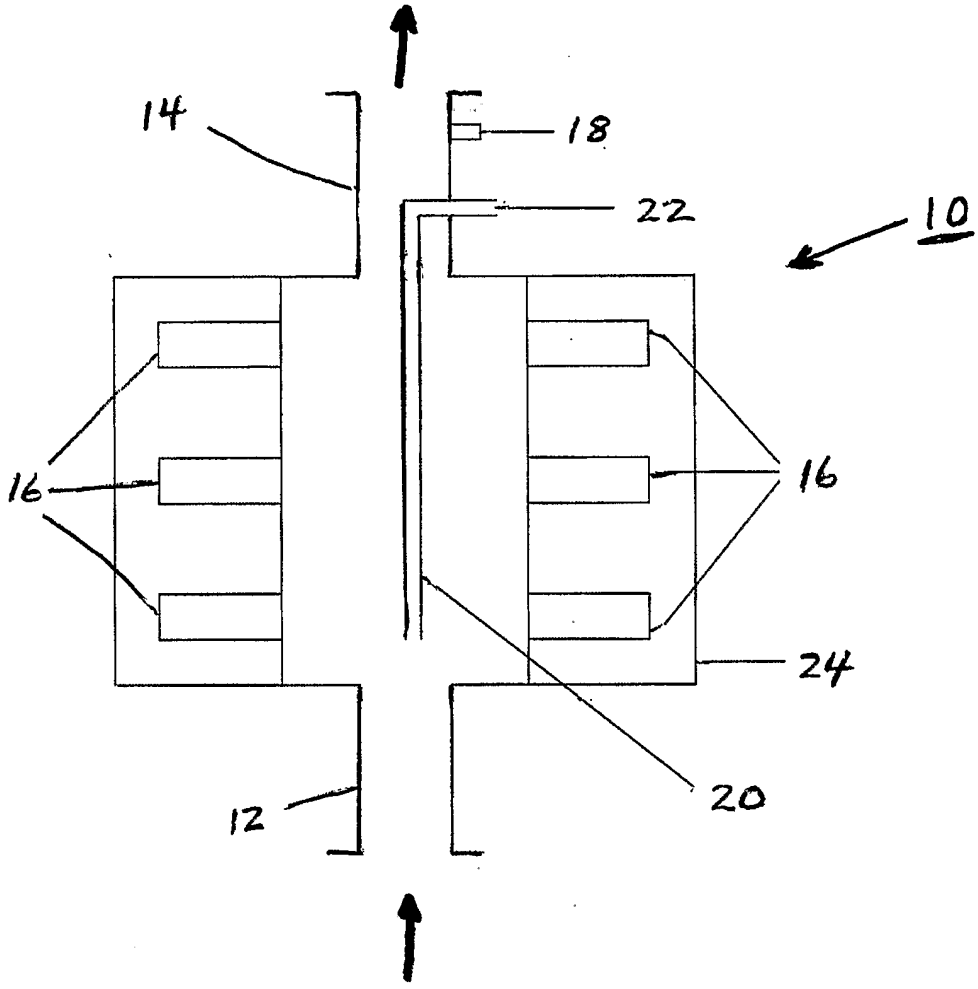



FIG. 1

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/13783

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A61K 9/14**( 2006.01)

USPC: 424/489

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. : 424/489

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)

PGPB,USPT,USOC,EPAB,JPAB,DWPI; lacidipine,span,particle,excipient,solvent,ultrasound

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,455,257 A (GAVIRAGHI) 03 October 1995 (03.10.1995), column 1, lines 51-60. | 1-8, 14-17, 20 and 21 |
| Y | US 2003/0075172 A1 (JOHNSON, et al) 24 April 2003 (24.04.2003), paragraph 0075. | 1-8, 14-17, 20 and 21 |
| Y,P | US 2005/0095267 A1 (CAMPBELL, et al) 05 May 2005 (05.05.2005), paragraphs 0044 and 0141. | 1-8, 14-17, 20 and 21 |

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

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