(54) Title: EXTENDED RELEASE FORMULATION OF GLICLIZIDE

(57) Abstract: The present invention relates to a dry ready to use modified release dosage formulation for Gliclazide dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTAMODEL (A43 D00048) manufactured by Ideal Cures Private Limited Mumbai India thereof also use thereof as additive to animal feeds, foods and food supplements and also cosmetic and pharmaceutical compositions. Invention also relates to ready-to-use modified release compositions capable of regulating release of glazide at various dosage strengths, a process for production thereof and also use thereof as formulated pharmaceutical compositions.
Description

EXTENDED RELEASE FORMULATION OF GLICLAZIDE

Technical Field

[1] The present invention relates to a dry ready to use modified release dosage formulation for Glliclazide dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTAMODEL (A43D00048) manufactured by Ideal Cures Private Limited Mumbai India thereof also use thereof as additive to animal feeds, foods and food supplements and also cosmetic and pharmaceutical compositions. Invention also relates to ready-to-use modified release compositions capable of regulating release of glliclazide at various dosage strengths. a process for production thereof and also use thereof as formulated pharmaceutical compositions.

Background Art

[2] In general Gliclazide are indicated for use as a hypo-glycaemic drug or commonly known as anti-diabetic drug. In state of art it is classified as a sulfonylurea. Gliclazide is a white or almost white powder which is practically insoluble in water. The solubility in water increases with increase in pH. It belongs to class II of the biopharmaceutical classification (BCS) in which dissolution rate is the controlling step in drug absorption. In general minor changes within a pH range of from 5.8 to 8 can alter the solubility of Gliclazide. The characteristic of pH dependent solubility causes the absorption problems for the active ingredient. Gliclazide between pH 6.2 and 7.4 has been controlled by the characteristic combination of polymer and glucose syrup in tablet composition.

[3] Gliclazide is administered through solid dosage ranges from 80 mg to 320 mg daily. In standard doses of 160 mg and above should be taken at two equally divided doses. Prescription of gliclazide recommends that it should be taken with meals if possible and daily. Dosage generally should not exceed 320 mg daily.

[4] One tablet of Gliclazide 80 mg Tablets is comparable to one tablet of Gliclazide Modified release 30 mg prolonged-release tablets. Consequently the switch can be performed provided a careful blood monitoring. For a modified release formulation the daily dose may vary from 1 to 4 tablets per day, i.e. from 30 to 120 mg taken orally in a single intake at breakfast time. If a dose is forgotten, there must be no increase in the dose taken the next day.

[5] It's well known in the art that Gliclazide is poorly soluble in water leading to erratic dissolution, oral absorption and therefore poor bioavailability (less than 70%) is also observed. Gliclazide is a BCS Class-II drug (Biopharmaceutical Classification System) i.e. Low solubility and High permeability. Further as Gliclazide has poor solubility in water, this leads to its erratic dissolution, oral absorption and therefore poor bioavailability.

[6] In state of the art modified release compositions are developed to provide relatively
constant drug plasma levels and sustained efficacy for longer period of time. Some prior art that disclose compositions for slow release of drug comprise, WO 2009098195, WO 2008062470, WO 2005105109. In principle aim of extended and modified release composition is to get required therapeutic concentration of the active in the blood stream and maintain its therapeutic concentration without deviation from strength during specified period.

[7] In state of art various grades of cellulosic polymers are used in the modified release compositions e.g. HPMC polymer. These polymers extend the release of drug by showing osmosis nature in aqueous conditions. Cellulosic matrix based system work by the swelling and gelling function i.e. these polymer swell through influx of liquids and a gel like physical structure is formed which provides extended release effect facilitated by diffusion of the Gliclazide. Prior art disclosing matrix based systems comprise US 6056977, US 2003219481 and US 2003113371.

[8] In theory it is known that with high viscosity grade polymer after attaining gelling effect drug release is lower but as time progresses drug release is increased. On the contrary with low viscosity grade polymer after attaining gelling effect drug is released at faster speed due to larger pore sized and concentration of drug decreases as time progresses.

[9] In order to minimize difficulties associated in ratios of polymers, batch to batch variations, formulating, storing and preserving many loose components of differently textured and sized ingredients means have been desired in industry to make ready to use extended release or modified release composition which are convenient to handle.

[10] The object of the present invention is to provide a ready-to-use matrix system and method of preparation for Gliclazide extended release or modified release formulation.

**Disclosure of Invention**

**Summary of Invention**

Accordingly, the present invention provides hydrophilic matrix system based ready to use technology for Modified or Extended Release Formulation of Gliclazide Hydrochloride using INSTAMODEL (A43D00048) manufactured by Ideal Cures Private Limited Mumbai India.

[11] Accordingly, the present invention also provides method for making ready to use Gliclazide modified or extended release formulation, involving steps of aqueous granulation, drying, lubrication and punching of tablets.

[12] In another aspect, present invention also provides once and twice a day Gliclazide table dosage form.

[13] Extended release or modified release tablet formulation can be in the form of single or multilayer tablets, capsule shaped oral dosage form, caplet, granules, disc, pellets, granules in capsule, mini-tablets in oral dosage form and other possible oral dosage form mean thereof.

[14] In yet another embodiment, the solid oral dosage form can optionally include one
or more pharmaceutically acceptable excipients.

[16] The details of one or more embodiments in the practice of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the appended examples and claims.

**Detailed Discription**

[17] Below description specify various scientific terms unless stated with context, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

[18] Unless stated to the contrary, The feature 'ready-to-use', in the context of the present invention, is taken to mean the property that the composition according to the invention can be used directly for its purposes by the user by simply dispersing it in required quantity of water.

[19] The term 'modified release' is in context of the invention as a way of active drug delivery where the rate of release of the active drug from the composition is not exclusively dependent on the concentration of active drug remaining in the dosage form and / or the solubility of the active drug in the liquid surrounding the composition, and where the time course with or without respective location of release of active drug from an oral dosage form are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. For the purpose of invention active drug is selected from Glipizide, its intermediates and derivatives thereof.

[20] The term 'Gliclazide' is in context of the invention includes its polymorphic forms, the pharmaceutically acceptable salts, including salts esters and other chemical derivatives or intermediates etc. The solid pharmaceutical composition comprises Gliclazide from 1 to 50 w/w % of dosage form.

[21] The term 'dosage', 'solid pharmaceutical composition' may include one or more of tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitablets, miniblets in capsule, pellets in capsule, sachet and the like. The solid pharmaceutical composition also includes multilayer tablets. The solid pharmaceutical compositions are meant for oral administration.

[22] The term 'tablet' includes pharmaceutical compositions of all shapes and sizes, whether coated or uncoated.

[23] The term 'Lubricant' in the context of the present invention, is taken to mean that an ingredient added to prevent the adhesion of tablet material to the punches and dies, reduce inter-particle friction and facilitate the ejection of oral dosage forms from the die cavity. Lubricant of present invention includes but not limited to talc, magnesium stearate, stearic acid, sodium stearyl fumarate and there derivatives thereof.

[24] The term 'Glidant' in the context of the present invention, is taken to mean that an
ingredient which enhance product flow by reducing inter-particulate friction. Glidant can be used in present invention includes but not limited to silicon di-oxide, colloidal silicon dioxide and there derivatives thereof. It is available under several brand names like AEROSIL® and CAB-O-SIL®.

The term 'Solvent' in the context of the present invention, is taken to mean ingredient that facilitate mixing of components in wet granulation process. Solvent can be used in present invention includes but not limited to Acetone, ethanol, methylene di chloride, isopropyl alcohol, water or their mixture thereof.

The term 'Binder' or 'Binding agent' in the context of the present invention, is taken to mean ingredient that facilitate binding of components in wet granulation process. Solvent can be used in present invention includes but not limited to dextrin and their derivatives, maltodextrin, polyvinyl polymers, Polyvinyl pyrrolidone K30 (PVP K30) and there derivatives thereof.

The ready to use polymeric composition Instamodel A43D00048 for extended and modified release formulation was supplied by Ideal Cures Private Limited, Mumbai, www.idealcures.co.in . This product was used to create inventive dosage form having ideal modified release profile for twice a day administration.

According to inventors it was surprisingly found that extended release solid oral dosage form for Gliclazide can be created with ready to use Instamodel (A43D00048) system and dosage form have advantageous modified release properties. The ready to use composition in accordance with present invention comprise INSTAMODEL (A43D00048). In one of the embodiment of present invention Gliclazide is formulated with ready to use composition to prepare modified release dosage form. In accordance with present invention different salts, derivatives, polymorphs of Gliclazide could be combined to achieve ready-to-use composition to achieve extended or modified release dosage form.

In a dosage form according to the invention Gliclazide is blended with the ready to use polymer and aqueous granulated further the granulated mixture is compressed to produce a solid formulation. The ingredients are blended to form a uniform powder and then compressed with means generally known to skilled in the art.

In yet another embodiment of present invention Gliclazide and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and finally coated.

In yet another embodiment of present invention Gliclazide and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and optionally coated.

This system of formulation uses simple and economic polymers hence cost effective to the customer. Another advantage of the present formulation is its robust
and reproducible results for extended release dose form without batch to batch variations. Further by using aqueous solvent system for granulation dosage form does not have any residual solvent or hazardous effect found in many organic solvent based formulations.

Inventive dosage form may be prepared by blending Gliclazide, their derivatives or combination thereof along with ready to use composition. Therefore inventive formulation preparation comprise steps as:-

1. Blending of ready to use formulation Instamode (A43D00048) with Gliclazide.
2. Thorough mixing to form dry powder
3. Wet granulation with active drug and solvent
4. Sieving through appropriate size
5. Tray drying or fluidized bed drying
6. Optionally addition of lubricant
7. Final tablet compression

According to one of the embodiment inventive dosage form is prepared by blending ready to use composition (Instamode A43D00048), process blending is performed by conventional dry blender or a food processor or 'V-blender' or a similar function device. Further Gliclazide are processed using aqueous solvent with binder through wet granulation or a similar wet mixing method to generate dosage formulation. Dosage formulation is further dried, sieved and compressed optionally with addition of lubricant, binder, glidant to form modified release oral dosage form.

In one of the embodiment of present invention, inventive dosage formulations are prepared by blending Gliclazide along with Instamode (A43D00048). Initially all components are blended by conventional dry blending in a food processor or 'V-blender' or a similar function device. Other solid oral dosage formulation components like binders, lubricants, glidants, detackifier, excipients can be added to create inventive formulation. Further mixture is then processed with appropriate quantity of aqueous solvent with binder and wet granulated. Obtained sieved granulated is then uniformly mixed with premeasured amount of the lubricant to improve industrial acceptability and oral dosage compression quality. Subsequently uniform mixed inventive formulation is compressed in standard pharmacopoeial equipment to get a controlled release oral dosage formulation of the correct desired weight and strength.

According to one of the main embodiment wherein hardness of tablets produced is in range of 7 Kg/cm² to 15 Kg/cm². In one of the embodiment oral dosage forms produced by inventive composition having human administrable active ingredient is suitable for human use. Alternatively drug suitable for veterinary purpose formulated in accordance with present composition will be suitable for veterinary use.

According to the objective of present invention Gliclazide is formulated in oral
dosage form for modified or extended release delivery. Inventive composition comprising 10 to 30 mg or 50 mg of Gliclazide in plurality of dosage formulations. Controlled release formulation can have combination of one or more additional drugs.

[39] Suitable APIs that can be used with the present invention include, but are not limited to: andrenergic blocking agent; acetyl-cholin-esterase inhibitor; analgesic or antipyretics; angiotensin modulator; anthelmintic agents; anti anxiety agent; antibacterial; antibiotic; anticoagulant; anticonvulsant; antidepressant; antifungal; antihistamine; antimalarial; antimicrobial agent; antipsychotic agent; Antiviral agents; blood glucose lowering drug; calcium channel modulator; diuretic; erectile dysfunction; gastric acid secretion inhibitor; histamine H2-receptor antagonist; inhibitor of steroid Type II 5[alpha]- reductase including; lipid regulating agents; selective H1-receptor antagonist; vasodilator; vitamins.

[40] Following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof.

Mode for Invention

[41] Example 1

[42] Preparation of Gliclazide modified release tablets (30 mg)

[43] The dosage formulation for 100,000 (20.00 kg) Tablets of Gliclazide is prepared using composition as stated in table: 1 wherein Gliclazide is 3.0 kg, 6.8 kg of Dicalcium phosphate dihydrate and 2.0 kg of Maltodextrin are weighed, sifted in rapid mixture granulated accordingly, subsequently sieved to get uniformly granulated powder through 40 mesh screen. It is noted that other size screen could be used to get similar results. Sieved Gliclazide with above ingredient is granulated using water as granulating solvent in rapid mixture granulator (RMG). It is recommended that RMG should be at slow speed for 10 min followed by high speed for 2 - 3 mins (Total qty of water used approx. 0.80 - 0.90 kg). Granulation step requires proper optimization of water quantity and continuous monitoring to avoid heavy granulation. If required extra water can be added gradually under continuous observation (to avoid heavy wet mass). Generated wet mass is sieved using #20 mesh screen (Multi-mill/ Fitzmill) dried in tray drier (or Fluidized bed dryer) at temperature not more than 50°C-55°C keeping loss on drying at 1-2%.

[44] Subsequently sift the dried granule using #30 mesh sieve on vibratory sifter and again sift on 1.0 mm screen at slow speed. Blend the dried granule with 8.0 kg of ready to use Instamold (A43D00048) in blender for 20 minutes (e.g. RMG granulator). Solvent system for wet granulation is prepared by taking 1.2 kg PVP K -30 in 5 kg of water, in RMG granulator in low to medium speed in the duration of 10 minutes followed by 5 minutes of high speed with chopper.

[45] Table 1

[46]
<table>
<thead>
<tr>
<th>Formulation ingredients</th>
<th>Composition</th>
<th>Quantity for Batch size of 100,000 Tabs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% w/w</td>
<td>mg/tablet</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>15.00%</td>
<td>30.00</td>
</tr>
<tr>
<td>Instamol (A42D000048) IH</td>
<td>40.00%</td>
<td>80.00</td>
</tr>
<tr>
<td>Malodextrin</td>
<td>10.00%</td>
<td>20.00</td>
</tr>
<tr>
<td>Dicalcium Phosphate Dihydrate</td>
<td>34.00%</td>
<td>68.00</td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Magnesium Stearate, USP/EP/Ph</td>
<td>0.50%</td>
<td>1.00</td>
</tr>
<tr>
<td>Colloidal silicon dioxide (Aerosil 200)</td>
<td>0.50%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100.00</td>
<td>200.00</td>
</tr>
</tbody>
</table>

To promote efficient tablet punching further 0.1 kg of Colloidal silicon dioxide and 0.1 kg of magnesium stearate sieved through 40 mesh screen is added to above dried blended formulation in blender for subsequent 5 minutes. Final screened granules are compressed using 10.0 mm (for 200 mg strength at 200 mg average weight) circular standard concave circular punches using Karnavati Tablet Compression M/C-17 Stn. GMP machine at hardness not less than 6-10 kg/cm².

**Example 2**

**Dissolution Profile Evaluation of Gliclazide tablet**

Gliclazide dose form dissolution study was performed. Drug dissolution profiles of tablet prepared are measured by USP 35 dissolution test of rotating basket method <711>. It is evident from standard state of the art that active ingredient may have its own dissolution testing parameters which can be found in their respective monographs. The active ingredient content for present invention is standardized for sustained release profile is as per table 2:-

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 20%</td>
</tr>
<tr>
<td>4</td>
<td>20% - 50%</td>
</tr>
<tr>
<td>8</td>
<td>60% - 85%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>
It was observed that it shows maximum absorbance at 284 nm on Double Beam UV-VIS Spectrophotometer (UV 2700- Thermo Fisher Scientific).

**GLICLAZIDE IN VITRO % DRUG RELEASE USING INSTAMODEL**

<table>
<thead>
<tr>
<th>(A43D00048) DISSOLUTION COMPARISON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Intervals</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

**Gliclazide Dissolution Comparison**

Diamicron MR v/s Gliclazide ER Tablets 30 mg using Instamodel

The drug dissolved profile of the Reference products and Gliclazide having dose strength of 30 mg using Instamodel (A43D00048) formulations are compared. The release exponents for the Reference and formulated Gliclazide is found to be having similar modified release profile indicating a predominantly diffusion based drug release mechanism.
Claims


[2] The solid pharmaceutical composition of claim 1, wherein Gliclazide can be in form of salt, polymorphic form, its derivatives or mixture thereof.

[3] The solid pharmaceutical composition of claim 1, wherein binder is selected from polyvinyl polymers. Polyvinyl pyrrolidone K30 (PVP K30) and like.

[4] The solid pharmaceutical composition of claim 1, wherein lubricant is selected from talc, magnesium stearate, stearic acid, sodium stearyl fumarate and combination thereof.

[5] The solid pharmaceutical composition of claim 1, wherein glidant is selected from silicon di-oxide, colloidal silicon dioxide and there derivatives thereof.

[6] A process for preparing Gliclazide tablet according to claim 1 comprising
   a. Blending Instamodel (A43D00048) with Gliclazide.
   b. Thorough mixing and Wet granulation with binder and solvent
   c. Sieving and drying
   d. Addition of lubricant and glidant
   e. Final tablet compression.

[7] The solid pharmaceutical composition prepare using process for preparing Gliclazide tablet according to claim 1 comprising
   a. Blending Instamodel (A43D00048) with Gliclazide.
   b. Thorough mixing and Wet granulation with binder and solvent
   c. Sieving and drying
   d. Addition of lubricant and glidant
   e. Final tablet compression.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K09/22 Version=2014.01

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)
A61K

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)
Orbit, IPO Internal database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>WO 2008/062470A2 Pub Date 2008-05-29 Claims, Table 2, Examples</td>
<td>1-7</td>
</tr>
<tr>
<td>Y</td>
<td>890/MUM/2004 A Pub. Date 2007-01-26 Claims, Page 6-7</td>
<td>1-7</td>
</tr>
<tr>
<td>A</td>
<td>US2004081697 A1 Pub. Date 2004-04-29 Examples and claims</td>
<td>1-7</td>
</tr>
<tr>
<td>Y</td>
<td>EP2181705 A1 Pub Date 2010-05-05 Page 3, Examples, Claims</td>
<td>1-7</td>
</tr>
<tr>
<td>Y</td>
<td>WO200018373 A1Pub. Date 2000-04-06 Examples</td>
<td>1-7</td>
</tr>
<tr>
<td>Y</td>
<td>WO2009082359A1 Pub Date 2009-07-02 Table 1,</td>
<td>1-7</td>
</tr>
</tbody>
</table>

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

* Special categories of cited documents:
“A” document defining the general state of the art which is not considered to be of particular relevance
“E” earlier application or patent but published on or after the international filing date
“L” document which may throw doubts on priority claims(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
“O” document referring to an oral disclosure, use, exhibition or other means
“P” document published prior to the international filing date but later than the priority date claimed

“T” inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“&” document member of the same patent family

Date of the actual completion of the international search: 24-02-2015

Date of mailing of the international search report: 24-02-2015

Name and mailing address of the ISA/Indian Patent Office
Plot No.32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer
Dr. A. P. Singh
Telephone No. +91-11253000200

Form PCT/ISA/210 (second sheet) (January 2015)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>claims</td>
<td>1-7</td>
</tr>
<tr>
<td></td>
<td>WO2006061697 A1 Pub Date 2006-06-15 Claims, Examples 2-5</td>
<td>1-7</td>
</tr>
<tr>
<td>Citation</td>
<td>Pub.Date</td>
<td>Family</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 4716465 B2</td>
</tr>
</tbody>
</table>