A sustained release dosage form comprising a sulfonlurea compound, preferably, gliclazide, or pharmaceutically acceptable salt thereof as active ingredient. The dosage form comprises water-swellable polymer, a pH modifier selected from sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, and calcium carbonate, a diluent modifier selected from mannitol and microcrystallised cellulose, and preferably as well a sparingly soluble or non-soluble diluent such as calcium hydrogen phosphate.

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**Title:** MODIFIED RELEASE DOSAGE FORM OF SULFONYLUREA COMPOUND

**Abstract:** A sustained release dosage form comprising a sulfonlurea compound, preferably, gliclazide, or pharmaceutically acceptable salt thereof as active ingredient. The dosage form comprises water-swellable polymer, a pH modifier selected from sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, and calcium carbonate, a diluent modifier selected from mannitol and microcrystallised cellulose, and preferably as well a sparingly soluble or non-soluble diluent such as calcium hydrogen phosphate.
Modified release dosage form of sulfonylurea compound

FIELD OF INVENTION

The present invention relates to suitable release dosage forms of sulfonylurea compounds.

TECHNICAL BACKGROUND AND PRIOR ART

Sulfonylurea derivatives are a class of antidiabetic drugs that are used in the management of diabetes mellitus type 2 ("adult-onset"). They act by increasing insulin release from the beta cells in the pancreas. Various sulfonylureas have different pharmacokinetics. The choice depends on the propensity of the patient to develop hypoglycemia - long-acting sulfonylureas with active metabolites can induce hypoglycemia. First generation sulfonylurea compounds include acetohexamide, chlorpropamide, tolbutamide, and tolazamide. Newer derivatives include glipizide (Formula I), gliclazide (Formula II), glibenclamide (Formula III, also known as glyburide), gliquidone (Formula IV), and glimepiride (Formula V). Gliclazide has been administered orally in the form of tablets and is marketed under the trade names Diamicron and Diabeton. The conventional prescription regimen is two tablets per day but varies from 1 to 4 tablets per day in several administrations depending on the severity of the diabetes.

![Formula I](image1)

![Formula II](image2)

![Formula III](image3)
US 4,696,815 discloses immediate release tablets of sulfonylurea drugs based on acidified and/or alkalized excipient and an inert polar solvent such as polyethylene glycol.

US 6,056,977 discloses a sustained release oral dosage form of sulfonylurea or a salt or derivative thereof in a polysaccharide matrix comprising a heteropolysaccharide and a homopolysaccharide, which in the examples is a mixture of xanthan gum, locust bean gum, dextrose and Surelease® (plasticised ethylcellulose dispersion). The document further teaches the use of an alkalizing agent to obtain complete bioavailability of the drug from the matrix. Suggested alkalizing agents include sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, N-methylglucamine and L-lysine. Sodium hydroxide is the agent used in the examples.

US 6,733,782 discloses a table matrix for prolonged release of gliclazide, which matrix comprises a cellulose polymer, e.g. HPMC and a glucose syrup.

WO 2006/123213 discloses modified release formulations of gliclazide comprising a controlled release polymer and one or more binder; hydroxypropyl methylcellulose is used as the controlled release polymer the preferred binder is vinylpyrrolidone. Dibasic calcium phosphate dihydrate is used as excipient.

WO 2006/061697 provides modified release formulations suitable for once daily administration; the formulation comprising a sulfonylurea compound as active ingredient, polymer and disaccharide and/or monosaccharide. Hydroxypropyl methylcellulose is used as the polymer, and the exemplified mono- and/or disaccharide is lactose or dextrose. Dibasic calcium phosphate is used in some examples as excipient. Sodium carboxymethylcellulose is used as binder.

New alternative modified release formulations would be appreciated that do not rely on saccharide compounds, which are generally undesirable in formulations for diabetic patients.
SUMMARY OF THE INVENTION

The present invention provides a sustained release dosage form which has a suitable in-vitro release profile and excellent stability. The dosage form of the invention comprises a sulfonylurea compound or pharmaceutically acceptable salt thereof as active ingredient, a water-swellable polymer, a pH modifier selected from sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, and calcium carbonate, and a diluent selected from mannitol and microcrystallised cellulose. The dosage forms preferably also have a substantial amount of a sparingly soluble or non-soluble diluent such as calcium hydrogen phosphate dihydrate.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned, the invention provides in a first aspect a sustained release dosage form comprising a sulfonylurea compound or pharmaceutically acceptable salt thereof as active ingredient. The term extended release (ER) is interchangeable with the term sustained release (SR) and generally refer to in the context of this invention compositions which preferably have a release profile such that 50% of the active agent has been released at a timepoint between about 4 to about 6 hours from administration. Sustained release dosage forms of the type provided by the invention make possible once-daily dosing of the active compounds being administered by the inventive formulations, simplifying medication and enhancing patient compliance.

Water-swellable polymers which may be utilised in the formulation of the invention may suitably be selected from the group including one or more of hydroxypropylmethylcellulose (HPMC, also referred to as hypromellose), hydroxypropylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, generally those having a number average molecular weight in the range 10,000 to 250,000. Suitable cellulose ethers are sold by Dow Chemicals under the trade names "Methocel" (HPMC and methylcellulose) and "Opadry" (sold by Colorcon). Preferably the water-swellable polymer is HPMC, optionally in combination with methylcellulose. Among commercially available are "Methocel" E5, E6, E15, E50-LV, K4M, K15M, KIOOM, KIOOLV and E4M, and "Opadry" OY-S-7251. The water swellable polymer is preferably present in the composition in amounts ranging from 10 to 35 wt%, preferably in the range 10-30 wt%, including the range 15-25%, such as about 15 wt%, about 18 wt% or about 20 wt%.

Suitable water-soluble polymers (e.g. with varying viscosity characteristics) can be selected based on the desired dissolution rate. In the examples included herein illustrating the invention, two types of HPMC polymer are used, Methocel KM4 and Methocel KIOO LV CR, separately or in mixture, to obtain desired formulation characteristics.

As mentioned, the dosage form of the invention comprises a diluent selected from mannitol, microcrystallised cellulose or a mixture of both. Both of these have been found by the inventor to
provide formulations with highly desirable characteristics. Of these two compounds, mannitol is presently preferred.

Mannitol (hexan-1,2,3,4,5,6-hexol) is a polyol, with a much lower caloric content than sugar, and is therefore often used as a sweetener for people with diabetes. It is slightly acidic when dissolved in water. It has a negative heat of solution, and is therefore used as a sweetener in "breath-freshening" candies. It is sold under the trade names Pearlitol, Mannidex, Sorbex, and more. It can be obtained from Roquette Pharma under the tradename of Pearlitol® 160 C, 50 C and 25 C having the mean diameters of 160, 50 and 25 micron, respectively.

Microcrystallised cellulose (MCC) forms with shear in water a three-dimensional matrix comprised of insoluble microcrystals that form a stable, thixotropic gel. MCC products from FMC Corp. are preferred. FMC Corp. offers different commercially available forms under the trade name of Avicel® pH-101, Avicel® pH-102 and Avicel® pH-103, having the mean particle size of 50, 100 and 50 micron, respectively.

The main function in the inventive compositions of said mannitol or MCC diluent is as a release modifier, dissolving from the matrix or the gel layer. Mannitol also provides some binding action dissolving during granulation and creating solid bridges on drying.

Another feature of the invention is the inclusion of a pH modifier, preferably selected from sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, and calcium carbonate. Sodium hydrogen carbonate is particularly preferred.

When employing such carbonate compound as pH modifier, the formulation is not sensitive to acidic environment, and will consequently substantially pass through the gastric environment to the intestines where it is slowly dissolved and absorbed. This may result from an advantageous interaction between the microcrystalline cellulose and/or mannitol diluent with the carbonate compound during the gel-forming dissolution process.

The pH-modifier further affects favorably the local pH in the microenvironment within and in the immediate vicinity of the gelled tablet while being eroded, increasing the local solubility of the active compound and advantageously affecting the full release of the active ingredient. The solubility of Gliclazide is pH-dependent increasing almost 3-fold from pH 7 to pH 8.3 (A 0.1 M solution of NaHCO₃ has pH 8.3, and calcium hydrogen phosphate is also basic with a pH of 7.4.) The water-based granulation of the formulation is also easier with a pH modifier such as sodium bicarbonate added; less water is needed and the granulation is denser with increased binding.

The amount of the pH modifier can in some embodiments be in the range of 1.0-5.0 wt%, such as about 2, about 3, about 3.25, about 3.5, about 3.75, about 4 or about 4.5 wt%.
The sulfonylurea compound or salt thereof is preferably selected from the group consisting of gliclazide, glibenclamide, glimepiride, glipizide, and glipizide or a pharmaceutically acceptable salt thereof.

In preferred embodiments the dosage form comprises a sparingly soluble or non-soluble further diluent is included in the formulation, preferably selected from calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, monobasic sodium phosphate, dibasic sodium phosphate, and tribasic sodium phosphate, preferably calcium hydrogen phosphate dihydrate. The amount of said sparingly soluble or non-soluble diluent is preferably in the range of about 25-65 wt%, such as in the range of about 40-60 wt%, including the range of about 50-60 wt%, such as for example, about 50 wt%, about 55 wt% or about 60 wt%. Such sparingly soluble or non-soluble diluent such as calcium hydrogen phosphate dihydrate provides a water insoluble skeleton/matrix from which the active is slowly and gradually released at a desired rate.

A lubricant may suitably be included in the dosage form, preferably one or more of magnesium stearate, sodium stearyl fumarate, sodium lauryl sulfate, stearic acid, colloidal anhydrous silica, synthetic aluminum silicate, magnesium oxide, calcium stearate, talc, glyceryl monostearate, glyceryl behenate, hydrogenated castor oil, and mixtures thereof. The amount of lubricant can vary lubricant from about 0.1% to about 4% by weight, preferably from about 0.5 % to about 2% by weight, relative to the total weight of the said oral dosage form, may be used. According to the most preferred embodiments, magnesium stearate is selected as the preferred lubricant.

Other conventional excipients may as well be comprised in the formulations of the invention such as binder, filler, diluent, and stabilizer. In certain embodiments, polyvinylpyrrolidone (PVP) is included in the formulations as a binder. PVP is used to enhance the solubility and bioavailability of poorly soluble drugs through the formation of solid solutions and dispersions. ISP Corp. Inc. manufactures several different forms of the povidone under the trade name of Plasdone® which are compatible with a wide range of materials as demonstrated by their tolerance to pH changes and salts. Plasdone® K-29/32 polymer is generally regarded as the universal binder for wet granulation process as its intermediate molecular weight results in high binding capacity and low solution viscosity for ease of processing. Average molecular weights of typical Plasdones, i.e., K-12, C-15, K-25, K-29/32, K90D are 4,000; 10,000; 34,000; 58,000; 1,300,000, respectively. A binder may be employed in a total amount of about 0.5 to 10 wt%, preferably from about 1 to about 5 wt%, relative to the total weight of the said oral dosage form.

Optionally, disintegrants such as sodium starch glycolate, crospovidone, low-substituted HPC, and others in a small amount to affect the internal disintegration and dissolution, within the eroding gel matrix; glidants such as silicon oxide and others can also be employed in the formulation.

In one aspect the present invention provides a solid pharmaceutical composition for release of active substance into a desired aqueous environment, which contains an outer layer (coating) surrounding a core, wherein the core generally comprises the active ingredient. The coating layer
will generally comprise from about 1% to 10% by weight, relative to the total weight of the said oral dosage form. Said coating layer preferably includes one or more of the following excipients; plasticizer, water swellable polymer, and color agent.

In the Examples shown herein, the sulfonylurea compound is prepared as micronised material which is found useful in some embodiments of the invention. Micronised material in this context refers generally to material with an average particle size of less than about 20 µm, preferably less than about 10 µm, such as less than about 5 µm, e.g. about 1 µm, about 2 µm or about 3 µm or 5 µm. The micronised material preferably has a $d_{50}$ value of less than 20 µm, and more preferably less than 10 µm.

However, non-micronised material has also been tested and found to provide satisfactory formulations. Such non-micronised material preferably though has a relatively fine grain size, such as an average particle size in the range of about 20 to about 50 µm and preferably in the range of about 20 to about 40 µm, such as about 20, 25, 30 or 40 µm average particle size.

EXAMPLES

The following examples are illustrative of the present invention and should not be considered as limiting the scope of the invention.

Example 1: Tablet formulations

In all cases, tablets are prepared by wet granulation.

Table 1: Tablet formulation A

<table>
<thead>
<tr>
<th>Component</th>
<th>wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliclazide (micronised)</td>
<td>18.5%</td>
</tr>
<tr>
<td>Calcium hydrogen phosphate dihydrate, (DI-TAB®)</td>
<td>52.5%</td>
</tr>
<tr>
<td>Mannitol (Pearlitol C160)</td>
<td>6.2%</td>
</tr>
<tr>
<td>Sodium hydrogen carbonate</td>
<td>1.25%</td>
</tr>
<tr>
<td>Water purified</td>
<td>-</td>
</tr>
<tr>
<td>HPMC (Methocel K4M CR premium®)</td>
<td>9.9%</td>
</tr>
<tr>
<td>HPMC (Methocel K100 LV CR premium®)</td>
<td>11.1%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.049%</td>
</tr>
<tr>
<td>Total:</td>
<td>698 g</td>
</tr>
</tbody>
</table>

Ingredient 4 is sieved and mixed with ingredient 2, ingredients 1 and 3 are mixed together and subsequently, the two mixtures are mixed together, screened and remixed, wetted with ingredient
4, a granulation mass is formed, wet screened and dried. The dried granules are blended with the polymer components 6 and 7 in a blender after which ingredient 8 is added and the blend is stirred further. 160 mg tablets (target weight 162.0 mg) are compressed from the granulate. Tablet hardness 6 N, oval shape with thickness approx. 2.5 mm.

The average particle size of the gliclazide material was 5 \( \mu \)m, \( d_{90} = 9.5 \mu m \).

Table 2: Tablet formulation B

<table>
<thead>
<tr>
<th>Component</th>
<th>Wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Gliclazide (micronised)</td>
<td>120.0 g</td>
</tr>
<tr>
<td>2 Calcium hydrogen phosphate dihydrate, (DI-TAB®)</td>
<td>340.0 g</td>
</tr>
<tr>
<td>3 Microcrystalline cellulose (Avicel pH 101)</td>
<td>40.00 mg</td>
</tr>
<tr>
<td>4 Water purified</td>
<td>q.s. (80.0 g)</td>
</tr>
<tr>
<td>5 Sodium hydrogen carbonate</td>
<td>8.80 g</td>
</tr>
<tr>
<td>6 HPMC (Methocel K100 LV CR premium®)</td>
<td>64.0 g</td>
</tr>
<tr>
<td>7 HPMC (Methocel K4M)</td>
<td>72.0 g</td>
</tr>
<tr>
<td>8 Magnesium stearate</td>
<td>3.20 g</td>
</tr>
<tr>
<td>9 Total:</td>
<td>728 g</td>
</tr>
</tbody>
</table>

Ingredient 4 is sieved and mixed with ingredient 2, ingredients 1 and 3 are mixed together and subsequently, the two mixtures are mixed together, screened and remixed, wetted with ingredient 4, a granulation mass is formed, wet screened and dried. The dried granules are blended with the polymer components 6 and 7 in a blender after which ingredient 8 is added and the blend is stirred further. 160 mg tablets (target weight 162.0 mg) are compressed from the granulate. Tablet hardness 64-69 N, oval shape with thickness approx. 2.5 mm.

The average particle size of the gliclazide material was 5 \( \mu \)m, \( d_{90} = 9.5 \mu m \)

Example 2: Dissolution characteristics of Tablet formulations A and B

<table>
<thead>
<tr>
<th>Formulation</th>
<th>60 min</th>
<th>240 min</th>
<th>360 min</th>
<th>480 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>11.4%</td>
<td>43.0%</td>
<td>64.3%</td>
<td>79.5%</td>
</tr>
<tr>
<td>B</td>
<td>12.2%</td>
<td>46.3%</td>
<td>68.3%</td>
<td>83.5%</td>
</tr>
<tr>
<td>Diamicron tablets</td>
<td>10.1%</td>
<td>49.8%</td>
<td>70.5%</td>
<td>85.2%</td>
</tr>
</tbody>
</table>

The Example shows that the exemplified formulations of the invention give very satisfactory dissolution profiles, e.g. as compared to the marketed formulation Diamicron, which formulation, however, contains maltodextrin.
Example 3: Tablet formulation C

<table>
<thead>
<tr>
<th>Materials</th>
<th>mg per tablet</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Purified water*</td>
<td>14.0 (q.s.)</td>
<td>*</td>
</tr>
<tr>
<td>2 Magnesium stearate</td>
<td>1.28 mg</td>
<td>0.75%</td>
</tr>
<tr>
<td>3 Aerosil 200</td>
<td>0.320 mg</td>
<td>0.19%</td>
</tr>
<tr>
<td>4 Sodium hydrogen carbonate</td>
<td>5.50 mg</td>
<td>3.24%</td>
</tr>
<tr>
<td>5 Mannitol (Peritol C160®)</td>
<td>5.00 mg</td>
<td>2.94%</td>
</tr>
<tr>
<td>6 HPMC (Methocel K100 LV CR premium®)</td>
<td>32.0 mg</td>
<td>18.8%</td>
</tr>
<tr>
<td>7 Calcium hydrogen phosphate dihydrate</td>
<td>95.9 mg</td>
<td>56.4%</td>
</tr>
<tr>
<td>(DI-CAFOS C 92-14 H®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Gliclazide</td>
<td>30.0 mg</td>
<td>17.6%</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>170.0 mg</strong></td>
<td><strong>100.0 %</strong></td>
</tr>
</tbody>
</table>

Dissolution test
Method: USP Apparatus i used, speed 100 rpm, temperature 37°C, initial volume 900 mL, set pH 7.4.

<table>
<thead>
<tr>
<th></th>
<th>Batch 31521</th>
<th>Batch 31520</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 min</td>
<td>18.6%</td>
<td>16.6%</td>
</tr>
<tr>
<td>240 min</td>
<td>45.3%</td>
<td>44.1%</td>
</tr>
<tr>
<td>360 min</td>
<td>58.2%</td>
<td>58.2%</td>
</tr>
<tr>
<td>480 min</td>
<td>68.0%</td>
<td>68.7%</td>
</tr>
<tr>
<td>720 min</td>
<td>83.5%</td>
<td>84.9%</td>
</tr>
</tbody>
</table>

The tablets of formulation C give a more extended dissolution profile than formulations A and B.
CLAIMS

1. A sustained release dosage form comprising a sulfonylurea compound or pharmaceutically acceptable salt thereof as active ingredient, comprising a water-swellable polymer, a pH modifier selected from sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, and calcium carbonate, and a diluent selected from mannitol and microcrystallised cellulose.

2. The dosage form of claim 1 wherein said sulfonylurea compound or salt thereof is selected from gliclazide, glibenclamide, glimepiride, glipizide, and gliquidone or a pharmaceutically acceptable salt thereof.

3. The dosage form of claim 2 wherein said sulfonylurea compound is gliclazide.

4. The dosage form of any of claims 1 to 3 wherein said diluent is mannitol.

5. The dosage form of any of claims 1 to 3, wherein said water-soluble polymer is selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylcellulose, ethylcellulose, and carboxymethylcellulose.

6. The dosage form of claim 5, wherein said water-swellable polymer is hydroxypropylmethylcellulose (HPMC) or mixture of hydroxypropylmethylcellulose and methylcellulose.

7. The dosage form of claim 6 comprising in the range of about 10-35 wt% of water-swellable polymer.

8. The dosage form of any of the aforementioned claims wherein said pH modifier is sodium hydrogen carbonate.

9. The dosage form of any of the aforementioned claims comprising a sparingly soluble or non-soluble diluent selected from calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, monobasic sodium phosphate, dibasic sodium phosphate, and tribasic sodium phosphate.

10. The dosage form of claim 9, comprising in the range of about 25-65 wt% calcium hydrogen phosphate dihydrate.

11. The dosage form of claim 10, comprising in the range of about 40-60 wt% calcium hydrogen phosphate dihydrate.
12. The dosage form of any of the aforementioned claims comprising a lubricant selected from glyceryl monostearate, glycercy1 behenate, magnesium stearate, calcium stearate, and sodium lauryl sulfate.

13. The dosage form of any of the aforementioned claims comprising in the range of 10 to 50 mg of gliclazide.

14. The dosage form of any of the preceding claims comprising colloidal anhydrous silica as glidant.

15. The dosage form of claim 1 comprising:
   - in the range of 10-25 wt% gliclazide,
   - in the range of 40-60 wt% calcium hydrogen phosphate dihydrate,
   - in the range of 15-25 wt% HPMC,
   - in the range of 1.0-4.5 wt% of a pH modifier selected from sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, and calcium carbonate, and
   - in the range of 2-8 wt% mannitol.

16. The dosage form of claim 15, further comprising in the range of 0.1-lwt% colloidal anhydrous silica.