

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number  
**WO 2005/107717 A2**

(51) International Patent Classification<sup>7</sup>: **A61K 9/22**,  
9/24, 45/06, 31/64, 31/155, A61P 3/10

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(21) International Application Number:  
PCT/IB2005/001281

(81) Designated States (*unless otherwise indicated, for every  
kind of national protection available*): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ,  
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL,  
SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,  
VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 11 May 2005 (11.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
860/DEL/2004 11 May 2004 (11.05.2004) IN

(84) Designated States (*unless otherwise indicated, for every  
kind of regional protection available*): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,  
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,  
GQ, GW, ML, MR, NE, SN, TD, TG).

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**Published:**

— *without international search report and to be republished  
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: ORAL DOSAGE FORM FOR THE EXTENDED RELEASE OF BIGUANIDE AND SULFONYLUREA

(57) Abstract: The present invention relates to a solid dosage form comprising a combination of a biguanide and a sulfonylurea. The dosage form provides an extended-release phase of a biguanide and an extended release phase of a sulfonylurea. Also provided are processes for the preparation thereof.



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## PHARMACEUTICAL FORMULATIONS OF BIGUANIDES AND SULFONYLUREAS

### Technical field of the Invention

The present invention relates to a solid dosage form comprising a combination of a  
5 biguanide and a sulfonylurea. The dosage form provides an extended-release phase of a  
biguanide and an extended release phase of a sulfonylurea. Also provided are processes  
for the preparation thereof.

### Background of the Invention

Type 2 diabetes mellitus is becoming an increasingly prevalent disease  
10 worldwide. Although the circulating levels of insulin in a type 2 diabetic patient are  
generally higher than in someone without the disease, the levels are insufficient to  
overcome a defect in insulin action. Hence, type 2 diabetes is generally characterized by  
insulin resistance rather than an absolute insulin deficiency. Diet and exercise remain  
the mainstays of therapy, but lifestyle changes are difficult, and frequently  
15 pharmacotherapy is required to treat elevated blood glucose concentrations and reduce  
the risk of complications. Until as recently as a decade ago, the only pharmacological  
treatments were oral sulfonylureas or insulin by injection, both of which act to heighten  
the patient's already elevated but insufficient insulin levels.

With the availability of more oral agents for type 2 diabetes, it is now possible to  
20 combine agents that have different mechanisms of action in order to achieve a more  
potent reduction in hyperglycemia. This strategy also reduces the number of daily  
doses, the side effects of individual drugs, and delays the institution of insulin therapy in  
some patients.

Studies show that combining two or more antidiabetic drugs each with different  
25 mechanisms of action can be very effective due to the complementary and additive effects  
of these combinations. A combination therapy of a biguanide and a sulfonylurea has a  
synergistic effect on glucose control, since both agents act by different but complementary  
mechanisms.

Combination therapy plays an important therapeutic role since it allows obtaining  
30 an effective metabolic control in patients in whom monotherapy with only sulfonylureas

or biguanides becomes ineffective with time. Apart from this, another advantage of the combination therapy is to provide a simpler therapeutic regimen. Further, the overall cost of the fixed dose combination is also less as compared to the individual administration of dosage forms.

5           The use of sulfonylureas and biguanides in monotherapy, in most cases, allows patients to obtain an effective glycometabolic control for some years, if an appropriate diet and behavioural regimen are kept. Nevertheless, the efficacy of the therapy with oral hypoglycemic agents can decrease with time. Since sulfonylureas are capable of stimulating insulin release, but are not capable of acting on insulin resistance, and  
10   biguanides are able to act on insulin resistance, but not able to stimulate insulin secretion, the use of a combined formulation of both medicaments is useful in correcting both the deficiency in insulin secretion and the insulin-resistance condition.

          Bristol Myers Squibb is currently marketing a combination of glipizide and metformin HCl tablets under the brand name Metaglip<sup>TM</sup>. Metaglip<sup>TM</sup> was shown to be  
15   more effective in lowering blood sugar levels than either glipizide or metformin when used alone in patients with type 2 diabetes. Further, both metformin hydrochloride and glipizide are individually commercially available as extended release dosage forms. Extended release glipizide formulations are commercially available as osmotic dosage forms (Glucotrol XL<sup>TM</sup>), which are complex and costly to prepare. Similarly, a number of  
20   extended release metformin formulations are commercially available. However, there are no formulations available that contain both an extended release phase of metformin in combination with an extended release phase of glipizide in a once a day single dosage form.

          Formulating a metformin and glipizide extended release combination in a single  
25   tablet poses many challenges. First, the therapeutic dose for each agent varies greatly. Metformin is commercially available in tablet form with a dose range of 500-1000 mg. Glipizide is commercially available as 5 mg and 10 mg tablets. Moreover, glipizide, due to its poor solubility, is used in a micronized form. On the other hand, Metformin is freely soluble. Given the disparity in the doses of the two actives and the differences in their  
30   particle sizes, content uniformity poses significant problems. Further, the selection of one

or more rate-controlling polymers is also difficult due to the difference in the solubility of glipizide and metformin.

Hydrophobic therapeutic agents, such as glipizide, present difficulty when being formulated into a dosage form. A well-designed formulation must, at a minimum, be capable of presenting a therapeutically effective amount of the hydrophobic compound to the desired absorption site, in an absorbable form. Even this minimal functionality is difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with an aqueous physiological environment, such as with gastric and intestinal fluids.

A similar problem is faced on formulating extended release dosage forms for highly soluble therapeutic agents, such as metformin. The high solubility of the therapeutic agent requires the incorporation of a high percentage of polymers to achieve a desired release profile and a prolonged effect. This increases the size of the dosage form when the dose of the therapeutic agent is high and presents problem when attempting to control the initial burst of the drug upon administration.

Apart from the major difference in the dose size of the two therapeutic agents, viz. glipizide and metformin, dissimilarity in their physical properties also makes it difficult to combine these in a single dosage form.

Therefore, there is a need for pharmaceutical compositions for oral administration which include a combination of a hydrophobic, water-insoluble, low-dose therapeutic agent, such as glipizide and a highly water-soluble, high dose therapeutic agent, such as metformin, in an once daily, extended-release form. The dosage form must also possess content uniformity.

### Summary of the Invention

In one general aspect there is provided a solid dosage form that includes a biguanide and a sulfonylurea, wherein the dosage form provides extended release of the biguanide and the sulfonylurea.

5        Embodiments of the solid dosage form may include one or more of the following features. For example, the biguanide comprises metformin, phenformin or buformin. The biguanide may be present at a concentration of from about 25% to about 80% by weight of the dosage form.

10        The sulfonylurea may be glipizide, glimepiride, glibornuride, glyburide, glisoxepide, gliclazide, acetohexamide, chlorpropamide, tolazamide or tolbutamide.

The sulfonylurea may be present at a concentration of from about 0.05% to about 10% by weight of the dosage form. The particle size of the sulfonylurea may be equal to or less than about 10 microns.

15        The biguanide may be incorporated into a solid matrix and the sulfonylurea is dispersed in one or more inert carriers to make a dispersion. The inert carriers may be one or more of polyvinylpyrrolidone, polyethylene glycol, urea, citric acid, vinyl acetate copolymer, methacrylic and acrylic polymers, succinic acid, sugars and mixtures thereof. The dispersion may include the sulfonylurea and the one or more inert carriers in a ratio ranging from about 1:1 to about 1:20. In addition, the dispersion may further include one  
20        or more of tableting aids, alkalizing agents, surfactants, water-soluble polymers, pH modifiers, fillers, binders, colorants, disintegrants, lubricants and flavorants.

25        The dispersion may be incorporated into a solid matrix and may also include one or more rate controlling polymers and one or more pharmaceutically acceptable excipients. The rate controlling polymers may be one or more of hydrophilic polymers, hydrophobic polymers and combinations thereof. The pharmaceutically acceptable excipients may include one or more of diluents, binders, lubricants, glidants, colorants and flavoring agents.

The solid matrix may further include one or more alkalizing agents. The alkalizing agent may be one or more of sodium hydroxide, potassium hydroxide, calcium hydroxide,

magnesium hydroxide, magnesium oxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, N-methylglucamine, 6 N-methyl-glucamine, L-lysine and mixtures thereof.

5 The dosage form is a single matrix, bilayered or multilayered tablet. The dosage form may also be in the form of a capsule.

In another general aspect there is provided a bilayered tablet which includes a first layer comprising metformin and one or more rate controlling polymers; and a second layer comprising glipizide, one or more rate controlling polymers and optionally one or more alkalizing agents, wherein the glipizide is dispersed in one or more inert carriers.

10 Embodiments of the dosage form may include one or more of the following features. For example, the dosage form may further include a separating layer in between the first and the second layers.

In another general aspect there is provided a process for preparing a bilayered tablet of metformin and glipizide. The process includes dispersing metformin in a solid  
15 matrix to form a first blend; dispersing glipizide in a solid matrix to form a second blend; and compressing the first and second blends to form bilayered tablet.

Embodiments of the process may include one or more of the following features. For example, the first and the second blend may be in the form of granules. The glipizide matrix blend may further include one or more alkalizing agents. The glipizide may be  
20 dispersed in one or more inert carriers prior to dispersing in a solid matrix.

In another general aspect there is provided a method for the treatment of non-insulin dependent diabetes mellitus in a patient in need thereof. The method includes administering a solid dosage form comprising a biguanide and a sulfonylurea, wherein the dosage form provides extended release of the biguanide and the sulfonylurea.

25 Embodiments of the method may include one or more of the following features. For example, the solid dosage form may further include one or more of glitazones, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene synthesis inhibitors and angiotensin-converting enzyme inhibitors.

### Detailed Description of the Invention

The inventors have now developed an oral solid dosage form which includes a combination of biguanide and sulfonylurea wherein the dosage form provides a combination of a highly water-soluble, high dose active and a water-insoluble, low-dose active and releases both the actives on a prolonged basis.

The pharmaceutical compositions of the present invention can be administered orally in the form of tablets, such as monolithic tablets, tablet in a tablet, bilayered or multilayered tablets. The composition may also be in the form of capsules containing pellets, beads, granules, multiparticulates, tablets or powder.

Suitable biguanides include metformin, phenformin and buformin including their salts, solvates, hydrates and polymorphs. Particularly, the biguanide may be metformin. Different salts of metformin may be used including hydrochloride, acetate, maleate, fumarate, succinate and other salts. The daily effective dose of metformin may range from about 500 mg to about 2550 mg, and particularly the dose may be a single dose of about 500 mg to about 1000 mg. The biguanide may be present in an amount from about 25% to about 80% by weight of the total composition.

Suitable sulfonylureas include glipizide, glimepiride, glibornuride, glyburide, glisoxepide, gliclazide, acetohexamide, chlorpropamide, tolazamide, tolbutamide and other medicinally active and pharmaceutically acceptable forms of the sulfonylurea class of compounds; including their salts, solvates, hydrates, polymorphs, and complexes. Particularly, the sulfonylurea may be glipizide. The daily effective dose of glipizide may range from about 2.5 mg to about 20 mg, particularly the dose may be from about 5.0 mg to about 10 mg, twice a day. The sulfonylurea may be present in an amount from about 0.05% to about 10% by weight of the total composition. The particle size of the sulfonylurea is equal to or less than about 10 microns in diameter.

The biguanide may be incorporated into an extended release carrier base by dispersing in a solid matrix, as described in our pending application, published as WO 03/028704, which is incorporated herein in entirety. Alternatively, the biguanide may be layered onto pharmaceutically acceptable inert cores or seeds in admixture with one or more rate controlling polymers or surrounded by one or more rate controlling polymers.

The term matrix, as used herein, refers to a uniform mixture of a biguanide, one or more rate-controlling polymers and optionally one or more excipients.

In order to achieve content uniformity and to increase the wetting and dissolution rate of the low-dose, water-insoluble sulfonylurea (glipizide), a homogeneous dispersion  
5 of the sulfonylurea is prepared in one or more inert carriers. Suitable carriers include one or more of polyvinylpyrrolidone, polyethylene glycol, urea, citric acid, vinyl acetate copolymer, methacrylic and acrylic polymers, succinic acid, sugars and mixtures thereof. The choice of the carrier is dependent upon the drug to be dispersed but generally the  
10 chosen carrier must be pharmacologically inert and chemically compatible with the drug in the solid state. They should not form highly bonded complexes with a strong association constant and should be freely water soluble with intrinsic rapid dissolution properties.

The dispersion may be formed by one or more of solvent evaporation, spray drying, spray coating, spraying drug solution onto the carrier in a fluidized bed granulator,  
15 twin screw extrusion, melt fusion, mechanical admixture, such as ball milling and by preparing mechanical admixture at an elevated but non-melting temperature.

The dispersion may include the drug and carrier in a ratio ranging from about 1:1 to about 1:20, particularly from about 1:2 to about 1:10.

The dispersion may include one or more additives or excipients that promote  
20 stability, tableting or processing of the dispersion. Suitable additives or excipients include one or more of tableting aids, surfactants, water-soluble polymers, pH modifiers, fillers, binders, pigments, disintegrants, lubricants and flavorants. For example, the dispersion may include one or more of microcrystalline cellulose; metallic salts of acids, such as aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, and  
25 zinc stearate; fatty acids, hydrocarbons and fatty alcohols, such as stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol; fatty acid esters, such as glyceryl (mono- and di-) stearates, triglycerides, glyceryl (palmitic stearic) ester, sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, and sodium stearyl fumarate; alkyl sulfates, such as sodium lauryl sulfate and magnesium lauryl sulfate; and  
30 inorganic materials, such as talc and dicalcium phosphate.

The polymeric matrix into which the dispersion is incorporated may generally be described as a set of excipients that are mixed with the dispersion following its formation. When in contact with the aqueous environment it imbibes water and forms a water-swollen gel or "matrix" that entraps the dispersion. Drug release may occur by a variety of mechanisms: the matrix may disintegrate or dissolve from around the dispersion particles or granules; or the drug may dissolve in the imbibed aqueous solution and diffuse from the tablet, beads or granules of the dosage form.

Suitable rate-controlling polymers may be hydrophilic polymers, hydrophobic polymers or a combination thereof. The rate-controlling polymers are uniformly dispersed throughout the matrix to achieve uniform drug release. Suitable hydrophilic polymers include one or more cellulose derivatives, such as hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose and combinations thereof; polyvinyl pyrrolidone, polysaccharides, polyalkylene glycols, starch and derivatives thereof. Suitable hydrophobic polymers include one or more of ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, poly (alkyl) methacrylate, and copolymers of acrylic or methacrylic acid esters, waxes, shellac and hydrogenated vegetable oils.

The matrix may be made by any pharmaceutically acceptable technique that achieves uniform blending including dry blending, wet granulation, compaction and fluid bed granulation.

In addition to the active and rate-controlling polymers, the matrix of the present invention may contain one or more additional pharmaceutically acceptable excipients. Suitable additional excipients include one or more of diluents, binders, lubricants, glidants, colorants and flavoring agents.

Suitable diluents include one or more of microcrystalline cellulose, lactose, dibasic calcium phosphate, mannitol, starch, sorbitol, sucrose, dextrose, maltodextrin and mixtures thereof.

Suitable binders include one or more of polyvinyl pyrrolidone, lactose, starches, gums, waxes, gelatin, polymers and mixtures thereof.

Suitable lubricants include one or more of colloidal silicon dioxide, talc, stearic acid, magnesium stearate, magnesium silicate, sodium benzoate, sodium lauryl sulphate, fumaric acid, zinc stearate, paraffin, glyceryl behenate and mixtures thereof.

Suitable glidants include one or both of talc and colloidal silicon dioxide.

- 5        One or more alkalizing agents may be provided as part of the sulfonylurea matrix so that the incorporated active agent attains optimal dissolution and release from the matrix. It ensures substantially complete bioavailability of the sulfonylurea from the matrix.

- 10       Suitable alkalizing excipients include one or more of sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, magnesium oxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, N-methylglucamine, 6 N-methyl-glucamine, L-lysine and mixtures thereof. The alkalizing agent may be added to the sulfonylurea before dispersing it into the inert carrier or to the matrix.

- 15       The first and second granules/blends, which include the biguanide and the sulfonylurea, respectively, may then be compressed and combined to form a bilayered tablet by employing conventional bilayer tableting equipment. An inert/seal-coat layer may be incorporated between the two granules/blends to form a multilayered tablet.

Alternatively, the first and second granules/blend may be blended together and compressed into a single monolithic matrix.

- 20       The first and second granules/blends, which include the biguanide and the sulfonylurea respectively, may also then be compressed in such a manner that the biguanide granules/blend envelope the sulfonylurea granules/blend on all the sides except the top surface, which remains uncovered, and the level of the two blends is the same.

- 25       Other conventional ingredients which may optionally be present in either of the two layers include one or more of preservatives, stabilizers, colorants, anti-adherents and antioxidants.

- 30       The solid dosage form may also include an outer protective coating layer which may comprise any conventional coating formulations. Suitable conventional coating formulations include one or more film-formers and binders, such as a hydrophilic polymer like hydroxypropyl methyl cellulose and a hydrophobic polymer like ethyl cellulose,

cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, acrylic copolymers, glyceryl esters of wood resins or mixtures thereof, and one or more plasticizers, such as polyethylene glycol, triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate and castor oil.

- 5           The film formers are applied from a solvent system containing one or more solvents including water; alcohols, such as methyl alcohol, ethyl alcohol and isopropyl alcohol; ketones, such as acetone and ethylmethyl ketone; and chlorinated hydrocarbons, such as methylene chloride, dichloroethane, and 1,1,1-trichloroethane.

- 10           The matrix may be formulated as a plurality of discrete or aggregated particles, pellets, beads or granules. Separate beads, pellets, particles or granules may be prepared for both the therapeutic agents. Beads or pellets can be prepared using techniques including extrusion-spheronization and drug layering onto inert cores or seeds.

- 15           The inert core or seeds may be hydrosoluble, such as sucrose, lactose, and maltodextrin or hydroinsoluble such as microcrystalline cellulose, partially pregelatinized starch, and dicalcium phosphate. The therapeutic agent and one or more rate controlling polymers may be coated as a single layer or as separate layers on to these inert cores; granulated with the inert cores; or mixed with inert cores and extruded and spheronized to form the pellets.

- 20           The coating may be applied to the inert/active core using a conventional coating pan, a spray coater, a rotating perforated pan, or an automated system, such as centrifugal fluidizing granulator, a fluidized bed process or any other suitably automated coating equipment.

- 25           The extended-release cores may optionally be coated to seal the cores. The coated active cores may be dried under conditions effective for drying, such as in an oven or by means of fluidized bed dryer.

Finally the two separate beads/pellets, one including the biguanide and the other the sulfonylurea, may be filled into capsules or compressed to form tablets. The capsule dosage form may include a plurality of pellets, granules and beads or may be a compressed tablet, which release the therapeutic agents over an extended period of time.

In those embodiments where the solid dosage form is in the form of spherical pellets or beads, such dosage forms may be produced by the known techniques of extrusion and spheronization, and techniques based on high shear granulation or fluidized bed techniques.

- 5           The following examples illustrate various aspects of the present invention. These examples are for illustration only and should not be construed as limiting the scope of the invention.

**EXAMPLE 1****Bilayered tablet**

|                               | <b>INGREDIENTS</b>            | <b>Percent w/w of the tablet</b> |
|-------------------------------|-------------------------------|----------------------------------|
| <b><u>Glipizide layer</u></b> | Glipizide                     | 0.44                             |
|                               | Polyethylene glycol           | 2.22                             |
|                               | Hydroxypropyl methylcellulose | 7.10                             |
|                               | Carbopol                      | 0.02                             |
|                               | Microcrystalline Cellulose    | 4.82                             |
|                               | Lactose                       | 4.44                             |
|                               | Magnesium oxide               | 0.22                             |
|                               | Talc                          | 0.09                             |
|                               | Magnesium Stearate            | 0.09                             |
|                               | Colloidal silicon dioxide     | 0.09                             |
|                               | Purified Water                | qs                               |
|                               | Isopropyl alcohol             | qs                               |
| <b><u>Metformin layer</u></b> | Metformin hydrochloride       | 44.39                            |
|                               | Hydroxypropyl methylcellulose | 31.07                            |
|                               | Polyvinylpyrrolidone          | 1.77                             |
|                               | Magnesium stearate            | 0.44                             |
|                               | Talc                          | 0.44                             |
|                               | Purified Water                | 2.34                             |

Procedure:

5 **Glipizide layer**

1. Polyethylene glycol was melted and glipizide was homogeneously dispersed in the melt. The dispersion was allowed to cool to room temperature.
2. The cooled dispersion was milled and sized.
3. The dispersion of step 2 was blended with carbopol, lactose, a part of hydroxy propyl methylcellulose and microcrystalline cellulose and granulated with a solution of hydroxy propyl methylcellulose in a mixture of isopropyl alcohol/water.
4. The wet mass of step 3 was dried and milled to obtain the granules of desired size.
5. Sized granules were blended with magnesium oxide, talc and magnesium stearate.

Metformin layer

1. Metformin hydrochloride was blended with hydroxy propyl methylcellulose and granulated with an aqueous solution of polyvinyl pyrrolidone.
2. The wet mass was dried and milled to size.
- 5 3. The milled granules were lubricated with magnesium stearate and talc.

The two layers, metformin layer and glipizide layer, were compressed over each other to form a bilayered tablet.

- Tables 1 and 2 provide the in-vitro release profiles of metformin and glipizide, respectively, from bilayered tablets prepared by the composition and process of Example 1
- 10 in phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.

**Table 1: Release profile of metformin from bilayered tablets prepared as per Example 1 in Phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.**

| Time (hrs) | Percent release of metformin from tablets of Example 1 (%) |
|------------|------------------------------------------------------------|
| 1.0        | 27                                                         |
| 2.0        | 37                                                         |
| 4.0        | 55                                                         |
| 6.0        | 72                                                         |
| 8.0        | 85                                                         |
| 12.0       | 101                                                        |

- 15 **Table 2: Release profile of glipizide from bilayered tablets prepared as per Example 1 in Phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.**

| Time (hrs) | Percent release of glipizide from tablets of Example 1 (%) |
|------------|------------------------------------------------------------|
| 1.0        | 11                                                         |
| 2.0        | 22                                                         |
| 4.0        | 41                                                         |
| 6.0        | 55                                                         |
| 8.0        | 67                                                         |
| 12.0       | 83                                                         |
| 16.0       | 91                                                         |
| 20.0       | 98                                                         |

**EXAMPLE 2****Single matrix tablet**

| <b>S.no.</b> | <b>Ingredients</b>              | <b>Percent w/w of the tablet</b> |
|--------------|---------------------------------|----------------------------------|
| 1.           | Metformin hydrochloride         | 48.08                            |
| 2.           | Hydroxypropyl methylcellulose   | 35.09                            |
| 3.           | Sodium carboxy methyl cellulose | 3.46                             |
| 4.           | Microcrystalline cellulose      | 6.63                             |
| 5.           | Polyvinyl pyrrolidone           | 1.92                             |
| 6.           | Magnesium stearate              | 0.48                             |
| 7.           | Talc                            | 0.48                             |
| 8.           | Glipizide                       | 0.48                             |
| 9.           | Polyethylene glycol             | 2.40                             |
| 10.          | Magnesium oxide                 | 0.96                             |

**Procedure:**

- 5    1. Polyethylene glycol was melted and glipizide and magnesium oxide were dispersed into the melt.
2. The melt was stirred and cooled to obtain the dispersion.
3. The dispersion was milled to desired size.
4. Metformin, hydroxypropyl methylcellulose and microcrystalline cellulose were
- 10    blended and granulated using polyvinyl pyrrolidone solution in water.
5. The granules of step 4 were dried. Magnesium stearate, talc and the dispersion of step 3 were added to the dried granules and mixed.
6. The blend of step 5 was compressed into tablets.

15    Table 3 provides the in-vitro release profile of glipizide from the single matrix tablets prepared by the composition and process of example 2 in phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.

**Table 3: Release profile of glipizide from single matrix tablets prepared as per Example 2 in Phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.**

| Time (hrs) | Percent release of glipizide from tablets of Example 2 (%) |
|------------|------------------------------------------------------------|
| 1.0        | 4                                                          |
| 2.0        | 8                                                          |
| 4.0        | 14                                                         |
| 6.0        | 22                                                         |
| 8.0        | 27                                                         |
| 12.0       | 39                                                         |
| 16.0       | 50                                                         |
| 20         | 59                                                         |
| 24         | 68                                                         |

### EXAMPLE 3

5

#### Bilayered tablet

|                               | INGREDIENTS                   | Percent w/w of the tablet |
|-------------------------------|-------------------------------|---------------------------|
| <b><u>Glipizide layer</u></b> | Glipizide                     | 0.46                      |
|                               | Hydroxypropyl methylcellulose | 0.28                      |
|                               | Poly vinylpyrrolidone         | 9.26                      |
|                               | Microcrystalline Cellulose    | 3.47                      |
|                               | Magnesium oxide               | 0.23                      |
|                               | Talc                          | 0.09                      |
|                               | Magnesium Stearate            | 0.09                      |
|                               | Purified Water                | Qs                        |
| <b><u>Metformin layer</u></b> | Metformin hydrochloride       | 46.29                     |
|                               | Hydroxypropyl methylcellulose | 32.41                     |
|                               | Polyvinylpyrrolidone          | 1.85                      |
|                               | Magnesium stearate            | 0.46                      |
|                               | Talc                          | 0.46                      |
|                               | Purified Water                | qs                        |

Procedure:

#### Glipizide layer

1. Glipizide, hydroxy propyl methylcellulose, magnesium oxide and a part of microcrystalline cellulose were blended and granulated with a solution of polyvinylpyrrolidone in purified water.

10

2. The wet mass of step 1 was dried and milled to obtain the desired particle size.
3. The milled granulation was blended with the remaining part of microcrystalline cellulose, hydroxypropyl methylcellulose, talc and magnesium stearate.

#### Metformin layer

- 5 1. Metformin hydrochloride was blended with hydroxypropyl methylcellulose and granulated with an aqueous solution of polyvinylpyrrolidone.
2. The wet mass was dried and milled to obtain the desired size.
3. The milled granules were lubricated with magnesium stearate and talc.

The two layers, metformin layer and glipizide layer, were compressed over each other to form a bilayered tablet.

Tables 5 provides the in-vitro release profile of glipizide from the bilayered tablets prepared by the composition and process of Example 3 in phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.

**Table 5: Release profile of glipizide from bilayered tablets prepared as per Example 3 in Phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.**

| Time (hrs) | Percent release of glipizide from tablets of Example 3 (%) |
|------------|------------------------------------------------------------|
| 1.0        | 16                                                         |
| 2.0        | 28                                                         |
| 4.0        | 44                                                         |
| 6.0        | 55                                                         |
| 8.0        | 64                                                         |
| 12.0       | 76                                                         |
| 16.0       | 83                                                         |

**EXAMPLE 4****Bilayered tablet**

|                               | <b>INGREDIENTS</b>              | <b>Percent w/w of the tablet</b> |
|-------------------------------|---------------------------------|----------------------------------|
| <b><u>Glipizide layer</u></b> | Glipizide                       | 0.46                             |
|                               | Polyethylene glycol             | 2.31                             |
|                               | Hydroxy propyl methyl cellulose | 7.41                             |
|                               | Microcrystalline Cellulose      | 5.09                             |
|                               | Lactose                         | 2.82                             |
|                               | Magnesium oxide                 | 0.23                             |
|                               | Talc                            | 0.09                             |
|                               | Magnesium Stearate              | 0.09                             |
| <b><u>Metformin layer</u></b> | Metformin hydrochloride         | 46.29                            |
|                               | Hydroxypropyl methylcellulose   | 32.41                            |
|                               | Polyvinyl pyrrolidone           | 1.85                             |
|                               | Magnesium stearate              | 0.46                             |
|                               | Talc                            | 0.46                             |
|                               | Purified Water                  | qs                               |

Procedure:

5 **Glipizide layer**

1. Polyethylene glycol was melted and glipizide and magnesium oxide were dispersed into the melt.
2. The melt was stirred and cooled to obtain the dispersion.
3. The dispersion was milled and sized.
- 10 4. The dispersion of step 3 was blended with hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, talc and magnesium stearate.

**Metformin layer**

1. Metformin hydrochloride was blended with hydroxypropyl methylcellulose and granulated with an aqueous solution of polyvinylpyrrolidone.
- 15 2. The wet mass was dried, sized and lubricated.

The two layers, metformin layer and glipizide layer were compressed over each other to form a bilayered tablet.

Tables 7 and 8 provide the in-vitro release profiles of metformin and glipizide, respectively, from bilayered tablets prepared by the composition and process of Example 4  
5 in phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.

**Table 7: Release profile of metformin from bilayered tablets prepared as per Example 4 in Phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.**

| <b>Time (hrs)</b> | <b>Percent release of metformin from tablets of Example 4 (%)</b> |
|-------------------|-------------------------------------------------------------------|
| 1.0               | 23                                                                |
| 2.0               | 36                                                                |
| 4.0               | 57                                                                |
| 6.0               | 73                                                                |
| 8.0               | 85                                                                |
| 12.0              | 97                                                                |

10 **Table 8: Release profile of glipizide from bilayered tablets prepared as per Example 4 in Phosphate buffer pH 6.8 (900ml), USP 2 at 50 rpm.**

| <b>Time (hrs)</b> | <b>Percent release of glipizide from tablets of Example 4 (%)</b> |
|-------------------|-------------------------------------------------------------------|
| 1.0               | 15                                                                |
| 2.0               | 30                                                                |
| 4.0               | 48                                                                |
| 6.0               | 61                                                                |
| 8.0               | 71                                                                |
| 12.0              | 87                                                                |
| 16.0              | 95                                                                |

**EXAMPLE 5****Bilayered tablet**

|                               | <b>INGREDIENTS</b>                        | <b>Percent w/w of the tablet</b> |
|-------------------------------|-------------------------------------------|----------------------------------|
| <b><u>Glipizide layer</u></b> | Glipizide                                 | 0.46                             |
|                               | Polyethylene glycol                       | 2.27                             |
|                               | Hydroxy propyl methyl cellulose K4M CR    | 0.91                             |
|                               | Hydroxy propyl methyl cellulose K100 LVCR | 6.36                             |
|                               | Carbopol                                  | 0.02                             |
|                               | Microcrystalline Cellulose                | 4.55                             |
|                               | Lactose                                   | 5.15                             |
|                               | Colloidal silicon dioxide                 | 0.09                             |
|                               | Talc                                      | 0.09                             |
|                               | Magnesium Stearate                        | 0.09                             |
|                               | Purified water                            | q.s                              |
|                               | Isopropyl alcohol                         | q.s                              |
| <b><u>Metformin layer</u></b> | Metformin hydrochloride                   | 45.45                            |
|                               | Hydroxypropyl methylcellulose             | 31.82                            |
|                               | Polyvinyl pyrrolidone                     | 1.83                             |
|                               | Magnesium stearate                        | 0.46                             |
|                               | Talc                                      | 0.46                             |

Procedure: Similar to Example 1.

5

Tables 9 and 10 provide the in-vitro release profiles of metformin and glipizide, respectively, from bilayered tablets prepared by the composition and process of Example 5 in phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.

**Table 9: Release profile of metformin from bilayered tablets prepared as per Example 5 in Phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.**

| <b>Time (hrs)</b> | <b>Percent release of metformin from tablets of Example 5 (%)</b> |
|-------------------|-------------------------------------------------------------------|
| 1.0               | 27                                                                |
| 2.0               | 39                                                                |
| 4.0               | 60                                                                |
| 6.0               | 75                                                                |
| 8.0               | 87                                                                |
| 10.0              | 99                                                                |
| 12.0              | 103                                                               |

**Table 10: Release profile of glipizide from bilayered tablets prepared as per Example 5 in Phosphate buffer pH 6.8 (900 ml), USP 2 at 50 rpm.**

| <b>Time (hrs)</b> | <b>Percent release of glipizide from tablets of Example 5 (%)</b> |
|-------------------|-------------------------------------------------------------------|
| 1.0               | 6                                                                 |
| 2.0               | 12                                                                |
| 4.0               | 23                                                                |
| 8.0               | 49                                                                |
| 12.0              | 72                                                                |
| 16.0              | 87                                                                |
| 20.0              | 96                                                                |
| 24.0              | 102                                                               |

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

We Claim:

- 1 1. A solid dosage form comprising a biguanide and a sulfonylurea, wherein the dosage  
2 form provides extended release of the biguanide and the sulfonylurea.
- 1 2. The dosage form according to claim 1, wherein the biguanide comprises metformin,  
2 phenformin or buformin.
- 1 3. The dosage form according to claim 1, wherein the biguanide comprises about 25%  
2 to about 80% by weight of the dosage form.
- 1 4. The dosage form according to claim 1, wherein the sulfonylurea comprises glipizide,  
2 glimepiride, glibornuride, glyburide, glisoxepide, gliclazide, acetohexamide,  
3 chlorpropamide, tolazamide or tolbutamide.
- 1 5. The dosage form according to claim 1, wherein the sulfonylurea comprises about  
2 0.05% to about 10% by weight of the dosage form.
- 1 6. The dosage form according to claim 4, wherein the particle size of the sulfonylurea  
2 is equal to or less than about 10 microns.
- 1 7. The dosage form according to claim 1, wherein the biguanide is incorporated into a  
2 solid matrix.
- 1 8. The dosage form according to claim 1, wherein the sulfonylurea is dispersed in one  
2 or more inert carriers to make a dispersion.
- 1 9. The dosage form according to claim 8, wherein the inert carriers comprise one or  
2 more of polyvinylpyrrolidone, polyethylene glycol, urea, citric acid, vinyl acetate  
3 copolymer, methacrylic and acrylic polymers, succinic acid, sugars and mixtures thereof.
- 1 10. The dosage form according to claim 8, wherein the dispersion comprises the  
2 sulfonylurea and the one or more inert carriers in a ratio ranging from about 1:1 to about  
3 1:20.
- 1 11. The dosage form according to claim 8, wherein the dispersion further comprises one  
2 or more of tableting aids, alkalizing agents, surfactants, water-soluble polymers, pH  
3 modifiers, fillers, binders, colorants, disintegrants, lubricants and flavorants.
- 1 12. The dosage form according to claim 8, wherein the dispersion is incorporated into a  
2 solid matrix.

1 13. The dosage form according to claims 7, wherein the solid matrix comprises one or  
2 more rate controlling polymers and one or more pharmaceutically acceptable excipients.

1 14. The dosage form according to claim 13, wherein the rate controlling polymers  
2 comprise one or more of hydrophilic polymers, hydrophobic polymers and combinations  
3 thereof.

1 15. The dosage form according to claim 14, wherein the pharmaceutically acceptable  
2 excipients comprise one or more of diluents, binders, lubricants, glidants, colorants and  
3 flavoring agents.

1 16. The dosage form according to claim 7, wherein the solid matrix further comprises  
2 one or more alkalizing agents.

1 17. The dosage form according to claim 16, wherein the alkalizing agent comprises one  
2 or more of sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium  
3 hydroxide, magnesium oxide, ammonia, tertiary sodium phosphate, diethanolamine,  
4 ethylenediamine, N-methylglucamine, 6 N-methyl-glucamine, L-lysine and mixtures  
5 thereof.

1 18. The dosage form according to claim 1, wherein the dosage form is a single matrix,  
2 bilayered or multilayered tablet.

1 19. A bilayered tablet comprising:

2 a. a first layer comprising metformin and one or more rate controlling polymers;  
3 and

4 b. a second layer comprising glipizide, one or more rate controlling polymers and  
5 optionally one or more alkalizing agents,

6 wherein the glipizide is dispersed in one or more inert carriers.

1 20. The bilayered tablets according to claim 19, further comprising a separating layer in  
2 between the first and the second layers.

1 21. A process for preparing a bilayered tablet of metformin and glipizide, the process  
2 comprising:

3 a. dispersing metformin in a solid matrix to form a first blend;

- 4           b. dispersing glipizide in a solid matrix to form a second blend; and
- 5           c. compressing the first and second blends to form bilayered tablet.
- 1   22. The process according to claim 21, wherein the first and the second blend comprise
- 2   granules.
- 1   23. The process according to claim 21, wherein the glipizide matrix blend further
- 2   comprises one or more alkalizing agents.
- 1   24. The process according to claim 21, wherein the glipizide is dispersed in one or more
- 2   inert carriers prior to dispersing in a solid matrix.
- 1   25. A method for the treatment of non-insulin dependent diabetes mellitus in a patient in
- 2   need thereof, the method comprising administering a solid dosage form comprising a
- 3   biguanide and a sulfonylurea, wherein the dosage form provides extended release of the
- 4   biguanide and the sulfonylurea.
- 1   26. The method according to claim 25, wherein the solid dosage form further comprising
- 2   one or more of glitazones, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates,
- 3   statins, squalene synthesis inhibitors and angiotensin-converting enzyme inhibitors.