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(54) Title: A PROCESS FOR PREPARING SOLID DOSAGE FORMS FOR EXTENDED-RELEASE OF BIGUANIDE AND SULFONYLUREA

(57) Abstract: The present invention relates to a solid dosage form for the combination of biguanide and sulfonylurea wherein the dosage form provides extended-release of biguanide as well as of sulfonylurea. Particularly the invention relates to a layered tablet for the combination of highly water-soluble, high dose metformin and water-insoluble, low-dose glipizide wherein the tablet provides extended-release of both metformin and glipizide.



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## **A PROCESS FOR PREPARING SOLID DOSAGE FORMS FOR EXTENDED- RELEASE OF BIGUANIDE AND SULFONYLUREA**

### Field of the Invention

The present invention relates to solid extended-release dosage forms comprising  
5 biguanide and sulfonylurea. In particular, the invention relates to layered extended-release  
tablets combining highly water-soluble, high dose metformin and water-insoluble, low-dose  
glipizide.

### Background of the Invention

People suffering from Type 2 diabetes may eventually require more than one category  
10 of antidiabetic medication. Studies show that when needed, combining 2 or more antidiabetic  
drugs with different mechanisms of action can be very effective due to complementary and  
additive effects of such combinations. For example, 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. Such combination therapies can facilitate effective  
15 metabolic control in Non Insulin Dependent Diabetes Mellitus (NIDDM) patients where  
monotherapy using only sulfonylurea or only biguanide becomes ineffective over the course  
of treatment. Other advantages of fixed dose combinations include, for example, providing  
simple regimen due to lesser dosage, resulting in improved patient compliance and  
convenience; and reducing overall cost of therapy by combining two or more drugs in one  
20 dosage form when compared to individual administration of dosage forms.

Pharmaceutical compositions having combinations of biguanides and sulfonylureas  
providing for controlled or immediate release of both the drugs have been disclosed. 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 more effective in  
25 lowering blood sugar levels than either glipizide or metformin when used alone in patients  
with type 2 diabetes. Thus, the concomitant use of metformin and a sulfonylurea, including  
glipizide, is known. Both metformin hydrochloride and glipizide are commercially available  
individually 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 costlier to prepare. These also exhibit another disadvantage of an initial lag in the release of glipizide. Similarly, extended-release metformin formulations are currently marketed as biphasic dosage forms (Glucophage XR<sup>TM</sup>). However, no such formulation is available that  
5 contains extended-release metformin in combination with an extended-release glipizide in one single dosage form so as to achieve a once-daily administration for both the drugs.

Formulating a metformin/glipizide extended-release combination in a single dosage form poses many challenges. First, the dosage amounts for each active ingredient are very different. Metformin is commercially available as a tablet in the dose range of 500-1000 mg.  
10 Glipizide is available as 2.5, 5.0 and 10 mg tablets. Moreover, glipizide is used in a micronized form due to its poor solubility, whereas metformin is freely soluble. Given the differences in the dosage amounts of the two active ingredients and the differences in their particle sizes, content uniformity of glipizide poses significant problems. Further, the different solubilities of glipizide and metformin make selecting suitable rate-controlling  
15 polymers difficult.

Owing to the difference between the properties of the two active ingredients, large amounts of polymers and other pharmaceutically acceptable excipients are required to obtain the desired release. This results in an increase in the size of the dosage form, which is uncomfortable for the patients to swallow. WO 2005/107717 discloses various ways of  
20 combining a biguanide and a sulfonylurea, *i.e.*, monolithic matrix dosage forms, bi- or multi-layered tablets, multi-particulates, etc.

In view of the above, there remains a need for extended-release formulations containing biguanides and sulfonylurea.

#### Summary of the Invention

25 Provided herein are layered tablets comprising a layer containing a first portion of biguanide and a second layer containing sulfonylurea and a second portion of biguanide. The layered tablets provide rapid onset of action for biguanide as the presence of biguanide in both the layers results in simultaneous release of the highly water-soluble drug from the two layers.

Layered tablets described herein can completely and rapidly release sulfonylurea. Preferred biguanides include metformin and preferred sulfonylurea sulfonylureas include glipizide. Glipizide is highly hydrophobic in nature, facilitating delayed release from a polymeric matrix. When metformin is also present, glipizide is rapidly and completely released due to the highly hydrophilic nature of glipizide. Further, the total amount of polymer(s) required to achieve the desired drug release rate is reduced because high dosage amounts of metformin is present in both the layers. As a result, tablet sizes can be decreased. Another advantage of these bilayered tablets is the reduction in layer separation problem commonly observed with bilayered tablets, particularly when similar types of polymers are incorporated in both the layers, which increases adhesion between these layers.

Thus provided herein are extended-release layered tablets comprising:  
a first layer comprising one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients, and  
a second layer comprising one or more sulfonylureas, one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients.

Such extended-release layered tablets can include one or more of the following embodiments. For example, the one or more biguanides can be metformin and the one or more sulfonylureas can be glipizide, glimeperide or a mixture thereof. Metformin can be present from about 20 % to about 80% by weight of the extended-release layered tablet.

Glipizide can be present in about 0.05 % to about 10% by weight of the extended-release layered tablet. Glimepiride can be present in about 0.05 % to about 10% by weight of the extended-release layered tablet.

The one or more rate-controlling polymers can be hydrophilic polymers, hydrophobic polymers or a combination thereof. The hydrophilic polymers can be selected from cellulose derivatives; polyvinylpyrrolidone, vinyl acetate/vinyl pyrrolidone copolymer, microcrystalline cellulose, polysaccharides, polyalkylene glycols, starch or derivatives thereof, or mixtures thereof. The cellulose derivatives can be selected from hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxy ethylcellulose, hydroxymethylcellulose,

carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose or mixtures thereof. The hydrophobic polymers can be selected from ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, poly(alkyl)methacrylate, copolymers of acrylic or methacrylic acid esters, waxes, shellac, hydrogenated vegetable oils or mixtures thereof. The one or more rate-controlling polymers can be present in about 5 % to about 60 % w/w of the extended-release layered tablet.

The first and second layers are prepared by dry granulation, wet granulation, direct compression or a combination thereof. The one or more pharmaceutically acceptable excipients are selected from diluents, binders, lubricants, glidants, colorants, flavoring agents or mixtures thereof. The second layer further comprises one or more alkalizing agents.

The extended-release layered tablets can further comprise one or more outer protective coating layers, one or more separating layers between the first layer and the second layer, or a combinations thereof. The extended-release layered tablets can provides an in-vitro release of glipizide of from about 8 % to about 15 % by weight after one hour, from about 15 % to about 30 % by weight after 2 hours and from about 20 % to about 50 % by weight after 4 hours, when measured by the USP Paddle Method at 50 rpm in 900 mL of simulated intestinal fluid at 37 °C.

Also provided are processes for preparing layered tablets comprising the steps of:

- a. preparing a first mixture comprising one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients,
- b. preparing a second mixture comprising one or more sulfonylureas, one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients, and
- c. forming a first layer and a second layer and combining the layers in a single tablet to form a layered tablet.

Also provided are methods for treating non-insulin dependent diabetes mellitus, comprising administering to a patient in need thereof an extended-release layered tablet comprising:

a first layer comprising one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients, and

a second layer comprising one or more sulfonylureas, one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients.

#### Detailed Description

Provided herein are layered tablets comprising:

- a layer comprising one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients; and
- a second layer comprising one or more sulfonylureas, one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients.

Such tablets provide extended-release of biguanide and sulfonylurea.

Another aspect provides layered tablets comprising:

- a layer comprising metformin, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients, and

a second layer comprising glipizide, metformin, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients.

Such tablets provide extended-release of metformin and glipizide.

Another aspect provides layered tablets comprising:

a layer comprising metformin, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients, and

a second layer comprising glimepiride, metformin, one or more rate-controlling polymers and

5 one or more pharmaceutically acceptable excipients.

Such tablets provide extended-release of metformin and glimepiride.

In one embodiment, the rate-controlling polymers used in each layer are similar, particularly in chemical structure, chemical properties and/or physical properties. Using similar rate-controlling polymers improves adhesion between the two layers and reduces the possibility of separation of layers, for example, on storage, as well as after coming in contact with gastric fluids.

Another aspect provides layered tablets comprising sulfonylurea and high dosage amounts of one or more biguanides and such tablets are of size sufficient for convenient oral administration.

15 Another aspect provides layered tablets comprising metformin and glipizide, which exhibit an in-vitro release of glipizide of from about 8 % to about 15 % by weight after one hour, from about 15 % to about 30 % by weight after 2 hours and from about 20 % to about 50 % by weight after 4 hours, when measured by the USP Paddle Method at 50 rpm in 900 mL of simulated intestinal fluid at 37 °C.

20 Another aspect provides processes for preparing a layered tablet comprising the steps of:

- a. preparing a first mixture comprising one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients,
- b. preparing a second mixture comprising one or more sulfonylureas, one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients, and
- 25 c. forming a first layer and a second layer and combining the layers in a single tablet to form a layered tablet.

In one embodiment, the first layer can be formed by compressing the first mixture and the second layer can be formed by compressing the second mixture. In another embodiment, the first mixture can be granulated to form granules prior to compression to form the first layer. In yet another embodiment, the second mixture can be granulated to form granules

5 comprising one or more sulfonylureas, one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients. When granules are used, they may be formed by wet granulation or dry granulation.

Another aspect provides methods for treating non-insulin dependent diabetes mellitus comprising administering to a patient in need thereof a layered extended-release tablet  
10 comprising:

a first layer comprising one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients, and  
a second layer comprising one or more sulfonylureas, one or more biguanides, one or more rate-controlling polymers and one or more pharmaceutically acceptable  
15 excipients.

Such extended-release tablets provide extended-release of biguanide and sulfonylurea.

Layered tablets described herein may further include one or more of glitazones, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene synthesis inhibitors, angiotensin-converting enzyme inhibitors or mixtures thereof.

20 In addition to the layers comprising one or more drugs, layered tablets described herein may also comprise one or more additional non-drug containing layers, for example, separating layers or coating layers.

Other features, advantages and embodiments of the invention will become apparent to those of ordinary skill in the art by the following description.

25 No combination of simultaneous controlled delivery of a biguanide along with a sulfonylurea in one single dosage form for ready administration exists. Such combination single dosage form can provide a synergistic effect in treating NIDDM. Thus, dosage forms that can provide therapeutic levels of sulfonylurea and biguanide in the same unit-dose

composition over a period of about 12-24 hours would be extremely advantageous in clinical practice for glycemic control in the treatment of NIDDM. Such dosage forms can be administered once-a-day and provide both increased convenience and improved patient compliance resulting from avoidance of missed doses through patient noncompliance, as well as reduced dosing frequency. There can also be a significant reduction in the doses of the drug substances used in combination because of the synergistic action and thus a possible reduction in toxicity.

Biguanides as used herein includes metformin, phenformin and buformin, as well as their salts, solvates, hydrates and polymorphs thereof. A particularly preferred biguanide is metformin.

Metformin as used herein includes the base *per se* or a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt may be a hydrochloride, fumarate, hydrobromide, succinate or embonate salt. Daily effective doses of biguanides, for example, metformin, may range from about 500 mg to 2550 mg, and in particular, the dose is a single dose of about 250 mg to 1000 mg.

Biguanides can be present in amounts from about 20 % to about 80 % by weight of the tablet, from about 25 % to about 75 % by weight of the tablet, and even from about 27.5 % to about 55 % by weight of the tablet.

Sulfonylurea as used herein is intended to include, but not limited to, glipizide, glimepiride, glibornuride, glyburide, glisoxepide, gliclazide, acetohexamide, chlorpropamide, tolazamide, tolbutamide, and the like, as well as other medicinally active and pharmaceutically acceptable forms from the sulfonylurea class of compounds, including their salts, solvates, hydrates, polymorphs, complexes or such other products. A particularly preferred sulfonylurea is glipizide.

The daily effective dose of sulfonylureas, for example, glipizide, may range from about 2.5 mg to 20 mg, and in particular, the dose is a single dose of about 2.5 mg to 10 mg,.

Sulfonylureas, for example glipizide, can be present in an amount from about 0.05 % to about 10 % by weight of the tablet and even from about 0.1 % to about 5 % by weight of the tablet.

Rate-controlling polymers may be hydrophilic, hydrophobic or a combination thereof.

5 Rate-controlling polymers can comprise from about 5 % to 60 % w/w of the tablet.

Suitable hydrophilic polymers include one or more of cellulose derivatives (for example, hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose or mixtures thereof); polyvinyl pyrrolidone; vinyl acetate/vinyl  
10 pyrrolidone copolymer; microcrystalline cellulose; polysaccharides; polyalkylene glycols; starch and derivatives thereof; or mixtures 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,  
15 hydrogenated vegetable oils or mixtures thereof.

Tablet layers may be prepared by any pharmaceutically acceptable technique that achieves uniform blending, *e.g.* dry granulation, wet granulation or direct compression.

Tablet layers may contain other pharmaceutically acceptable excipients, which act in one or more capacities as diluents, binders, lubricants, glidants, colorants or flavoring agents.

20 Suitable diluents include, for example, pharmaceutically acceptable inert fillers, for example, microcrystalline cellulose, lactose, dibasic calcium phosphate, mannitol, starch, sorbitol, sucrose, dextrose, maltodextrin or mixtures thereof.

Suitable binders include, for example, polyvinyl pyrrolidone, vinyl acetate/vinyl pyrrolidone copolymer, microcrystalline cellulose, lactose, starches, gums, waxes, gelatin,  
25 polymers or mixtures thereof.

Suitable lubricants include, for example, colloidal silicon dioxide, talc, stearic acid, magnesium stearate, magnesium silicate, sodium benzoate, polyethylene glycol, sodium lauryl sulphate, fumaric acid, zinc stearate, paraffin, glyceryl behenate or mixtures thereof.

5      Suitable glidants include, for example, talc, colloidal silicon dioxide or mixtures thereof.

One or more alkalizing agents may be included in the layer comprising glipizide to facilitate optimal dissolution and release of active agents from the layer. Such alkalizing agents also ensure substantially complete bioavailability of glipizide. Suitable alkalizing excipients include sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium  
10      hydroxide, magnesium oxide, ammonia, tertiary sodium phosphate, basic amino acids (for example, diethanolamine, ethylenediamine, N-methylglucamine, 6 N-methyl-glucamine or L-lysine and/or mixtures thereof), or mixtures thereof. Alkalizing agents may be added to the layer comprising glipizide extragranularly.

Each layer comprising sulfonylurea and/or biguanide may be formed by compressing  
15      mixtures thereof separately and the layers combined and compressed together to form a layered tablet employing conventional layered tableting techniques and equipment.

Alternatively, each layer may be compressed in such a manner that one layer envelopes the second layer on all the sides except the top surface to produce inlay tablets. For example, the first layer can be compressed first and then the enveloping layer can be  
20      compressed around it, leaving only the top surface of the first layer exposed.

Other conventional ingredients, which may optionally be present in any layer, include preservatives, stabilizers, colorants, anti-adherents, antioxidants or mixtures thereof.

Layered tablets may also include one or more outer protective coating layer or one or more separating layer between the two drug layers. Protective coating layers or separating  
25      layers may include one or more film-formers or binders, for example, hydrophilic polymers (*e.g.*, hydroxypropyl methyl cellulose) hydrophobic polymers (*e.g.*, ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, acrylic copolymers, glyceryl esters of wood resins or mixtures thereof), enteric polymers (*e.g.*, polyacrylate material, cellulose

acetate phthalate, cellulose phthalate hydroxy propyl methyl ether, polyvinyl acetate phthalate, hydroxy propyl methyl cellulose acetate succinate, cellulose acetate trimellitate, shellac or mixtures thereof), or mixtures thereof. In addition to the hydrophobic polymers, hydrophilic polymers and/or enteric polymers, the protective coating layers can also include  
5 other pharmaceutically acceptable excipients, such as plasticizers, lubricants, colors or mixtures thereof. Suitable plasticizers include, for example, polyethylene glycol, triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, castor oil or mixtures thereof.

Film formers can be applied from a solvent system containing one or more solvents  
10 including, for example, water, one or more alcohols (*e.g.*, methyl alcohol, ethyl alcohol, isopropyl alcohol or mixtures thereof), ketones (*e.g.*, acetone, ethylmethyl ketone or mixtures thereof), chlorinated hydrocarbons (*e.g.*, methylene chloride, dichloroethane, 1,1,1-trichloroethane or mixtures thereof), or mixtures thereof.

While the present invention has been described in terms of its specific embodiments,  
15 certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples**EXAMPLE 1****Layered tablet****Metformin Hydrochloride 500 mg + Glipizide 5 mg**

|                        | INGREDIENTS                   | Percent w/w<br>of the tablet |
|------------------------|-------------------------------|------------------------------|
| <b><u>Layer I</u></b>  | Metformin hydrochloride       | 40.94                        |
|                        | Hydroxypropyl methylcellulose | 28.66                        |
|                        | Polyvinylpyrrolidone          | 1.64                         |
|                        | Magnesium stearate            | 0.41                         |
|                        | Talc                          | 0.41                         |
|                        | Purified Water                | 2.15                         |
| <b><u>Layer II</u></b> | Metformin hydrochloride       | 13.65                        |
|                        | Glipizide                     | 0.55                         |
|                        | Hydroxypropyl methylcellulose | 9.55                         |
|                        | Colorant                      | 0.05                         |
|                        | Polyvinylpyrrolidone          | 0.55                         |
|                        | Magnesium oxide               | 0.44                         |
|                        | Magnesium Stearate            | 0.14                         |
|                        | Talc                          | 0.14                         |
|                        | Purified Water                | 0.72                         |

5

## Procedure:

**Layer I**

1. Metformin hydrochloride was blended with hydroxypropyl methylcellulose, and granulated with an aqueous solution of polyvinyl pyrrolidone.
- 10 2. The resulting wet mass was dried and milled to size – British Standard Sieve (BSS) mesh size 18.
3. The milled granules were lubricated with magnesium stearate and talc.

Layer II

4. Metformin hydrochloride, glipizide and colorant were blended with hydroxypropyl methylcellulose, colorant, and granulated with an aqueous solution of polyvinyl pyrrolidone.
5. The resulting wet mass was dried and milled to size – BSS mesh size 18.
6. Sized granules were blended with magnesium oxide, talc and magnesium stearate.

The two layers were compressed over each other to form a layered tablet.

**EXAMPLE 2**Layered tablet10 Metformin Hydrochloride 500 mg + Glipizide 2.5 mg

|                 | INGREDIENTS                   | Percent w/w of the tablet |
|-----------------|-------------------------------|---------------------------|
| <u>Layer I</u>  | Metformin hydrochloride       | 41.06                     |
|                 | Hydroxypropyl methylcellulose | 28.74                     |
|                 | Polyvinylpyrrolidone          | 1.64                      |
|                 | Magnesium stearate            | 0.41                      |
|                 | Talc                          | 0.41                      |
|                 | Purified Water                | 2.17                      |
| <u>Layer II</u> | Metformin hydrochloride       | 13.68                     |
|                 | Glipizide                     | 0.27                      |
|                 | Hydroxypropyl methylcellulose | 9.58                      |
|                 | Colorant                      | 0.05                      |
|                 | Polyvinylpyrrolidone          | 0.55                      |
|                 | Magnesium oxide               | 0.44                      |
|                 | Magnesium Stearate            | 0.14                      |
|                 | Talc                          | 0.14                      |
|                 | Purified Water                | 0.72                      |

Procedure:

Layer I

7. Metformin hydrochloride was blended with hydroxypropyl methylcellulose, and granulated with an aqueous solution of polyvinyl pyrrolidone.
- 5 8. The resulting wet mass was dried and milled to size – BSS mesh size 18.
9. The milled granules were lubricated with magnesium stearate and talc.

Layer II

10. Metformin hydrochloride, glipizide and colorant were blended with hydroxypropyl methylcellulose and granulated with an aqueous solution of polyvinyl pyrrolidone.
  - 10 11. The resulting wet mass was dried and milled to size – BSS mesh size 18.
  12. Sized granules were blended with magnesium oxide, talc and magnesium stearate.
- The two layers were compressed over each other to form a layered tablet.

**EXAMPLE 3****Layered tablet****Metformin Hydrochloride 250 mg + Glipizide 2.5 mg**

|                        | <b>INGREDIENTS</b>            | <b>Percent w/w<br/>of the tablet</b> |
|------------------------|-------------------------------|--------------------------------------|
| <b><u>Layer I</u></b>  | Metformin hydrochloride       | 20.53                                |
|                        | Lactose                       | 20.53                                |
|                        | Hydroxypropyl methylcellulose | 28.76                                |
|                        | Polyvinylpyrrolidone          | 1.64                                 |
|                        | Magnesium stearate            | 0.41                                 |
|                        | Talc                          | 0.41                                 |
|                        | Purified Water                | 2.17                                 |
| <b><u>Layer II</u></b> | Metformin hydrochloride       | 6.84                                 |
|                        | Glipizide                     | 0.27                                 |
|                        | Lactose                       | 6.84                                 |
|                        | Hydroxypropyl methylcellulose | 9.58                                 |
|                        | Colorant                      | 0.03                                 |
|                        | Polyvinylpyrrolidone          | 0.55                                 |
|                        | Magnesium oxide               | 0.44                                 |
|                        | Magnesium Stearate            | 0.14                                 |
|                        | Talc                          | 0.14                                 |
|                        | Purified Water                | 0.72                                 |

Procedure:

Layer I

13. Metformin hydrochloride was blended with hydroxypropyl methylcellulose and granulated with an aqueous solution of polyvinyl pyrrolidone.
- 5 14. The resulting wet mass was dried and milled to size – BSS mesh size 18.
15. The milled granules were lubricated with magnesium stearate and talc.

Layer II

16. Metformin hydrochloride, glipizide and colorant were blended with hydroxypropyl methylcellulose and granulated with an aqueous solution of polyvinyl pyrrolidone.
- 10 17. The resulting wet mass was dried and milled to size – BSS mesh size 18.
18. Sized granules were blended with lactose, magnesium oxide, talc and magnesium stearate.

The two layers were compressed over each other to form a layered tablet.

- Tables 1 and 2 provide the in-vitro release profiles of metformin and glipizide, respectively, from layered tablets prepared by the composition and process of Examples 1-3 in simulated
- 15 intestinal fluid (phosphate buffer pH 6.8), 900 mL, USP Apparatus 2 at 50 rpm.

**Table 1: Release profile of metformin from layered tablets prepared as per Examples 1-3 in simulated intestinal fluid (Phosphate buffer pH 6.8), 900 mL, USP 2 at 50 rpm.**

| Time (hrs) | Percent release of metformin (%) |           |           |
|------------|----------------------------------|-----------|-----------|
|            | Example 1                        | Example 2 | Example 3 |
| 1.0        | 30                               | 30        | 33        |
| 2.0        | 46                               | 46        | 49        |
| 4.0        | 67                               | 66        | 69        |
| 8.0        | 88                               | 85        | 91        |
| 12.0       | 100                              | 92        | 100       |

5 **Table 2: Release profile of glipizide from layered tablets prepared as per Examples 1-3 in simulated intestinal fluid (Phosphate buffer pH 6.8), 900 mL, USP 2 at 50 rpm.**

| Time (hrs) | Percent release of glipizide (%) |           |           |
|------------|----------------------------------|-----------|-----------|
|            | Example 1                        | Example 2 | Example 3 |
| 1.0        | 10                               | 14        | 12        |
| 2.0        | 18                               | 24        | 21        |
| 4.0        | 32                               | 39        | 35        |
| 8.0        | 52                               | 61        | 56        |
| 12.0       | 70                               | 73        | 70        |
| 16.0       | 82                               | 84        | 80        |
| 20.0       | 90                               | 91        | 87        |
| 24.0       | 97                               | 93        | 88        |

**Pharmacokinetic studies under fed conditions:**

A single fixed dose combination of Metformin ER 500 mg and Glipizide ER 5 mg tablet of Example 1 was compared with twice a day administration of single fixed dose combination of Metformin hydrochloride 250 mg and Glipizide 2.5 mg tablets (Metaglip™ tablets; Bristol Myers Squibb) under fed conditions.

Values for pharmacokinetic parameters, including observed  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$ , were calculated using standard non-compartmental methods. The results as indicated by ratio of test to reference, are shown in Tables 3 and 4.

Reference R: Metaglip™ (Metformin hydrochloride 250 mg and Glipizide 2.5 mg) tablets,  
Mfd. By Bristol Myers Squibb

Test T: Metformin ER + Glipizide ER layered tablets (Example 1)

**Table 3: Summary of pharmacokinetic parameters for metformin**

| Product /Statistics | <b><u>Parameters</u></b> |                             |                                  |
|---------------------|--------------------------|-----------------------------|----------------------------------|
|                     | $C_{max}$<br>(ng/mL)     | $AUC_{(0-t)}$<br>(ng·hr/mL) | $AUC_{(0-\infty)}$<br>(ng·hr/mL) |
| Ratio % (T/R)       | 126.54                   | 86.76                       | 86.31                            |
| Lower limit         | 115.61                   | 79.76                       | 79.44                            |
| Upper limit         | 138.51                   | 94.36                       | 93.77                            |

**Table 4: Summary of pharmacokinetic parameters for glipizide**

| Product /Statistics | <b><u>Parameters</u></b> |                             |                                  |
|---------------------|--------------------------|-----------------------------|----------------------------------|
|                     | $C_{max}$<br>(ng/mL)     | $AUC_{(0-t)}$<br>(ng·hr/mL) | $AUC_{(0-\infty)}$<br>(ng·hr/mL) |
| Ratio % (T/R)       | 103.52                   | 98.95                       | 99.67                            |
| Lower limit         | 92.19                    | 91.73                       | 92.21                            |
| Upper limit         | 116.24                   | 106.75                      | 107.73                           |

**EXAMPLE 4****Layered tablet****Metformin Hydrochloride 500 mg + Glimepiride 3.0 mg**

|                        | INGREDIENTS                   | Percent w/w<br>of the tablet |
|------------------------|-------------------------------|------------------------------|
| <b><u>Layer I</u></b>  | Metformin hydrochloride       | 41.78                        |
|                        | Hydroxypropyl methylcellulose | 29.25                        |
|                        | Polyvinylpyrrolidone          | 1.67                         |
|                        | Magnesium stearate            | 0.42                         |
|                        | Talc                          | 0.42                         |
|                        | Purified Water                | 2.23                         |
| <b><u>Layer II</u></b> | Metformin hydrochloride       | 0.28                         |
|                        | Glimepiride                   | 4.64                         |
|                        | Hydroxypropyl methylcellulose | 8.36                         |
|                        | Lactose                       | 4.64                         |
|                        | Microcrystalline cellulose    | 4.81                         |
|                        | Colorant                      | 0.02                         |
|                        | Polyvinylpyrrolidone          | 0.93                         |
|                        | Magnesium oxide               | 0.37                         |
|                        | Magnesium Stearate            | 0.09                         |
|                        | Talc                          | 0.09                         |
|                        | Purified Water                | qs                           |

5 Procedure:

**Layer I**

- i. Metformin hydrochloride was blended with hydroxypropyl methylcellulose and granulated with an aqueous solution of polyvinyl pyrrolidone.
- ii. The wet mass was dried and milled to size – BSS mesh size 18.
- 10 iii. The milled granules were lubricated with magnesium stearate and talc.

Layer II

1. Metformin hydrochloride, glimepiride and colorant were blended with hydroxypropyl methylcellulose, lactose, microcrystalline cellulose and granulated with an aqueous solution of polyvinyl pyrrolidone.
- 5      2. The wet mass was dried and milled to size – BSS mesh size 18.
3. Sized granules were blended with lactose, magnesium oxide, talc and magnesium stearate.

The two layers were compressed over each other to form a layered tablet.

- While several particular forms of the invention have been illustrated and described, it
- 10      will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention.

We Claim:

- 1 1. An extended-release layered tablet comprising:  
2 a first layer comprising one or more biguanides, one or more rate-controlling polymers and  
3 one or more pharmaceutically acceptable excipients, and  
4 a second layer comprising one or more sulfonylureas, one or more biguanides, one or more  
5 rate-controlling polymers and one or more pharmaceutically acceptable excipients.
- 1 2. The extended-release layered tablet of claim 1, wherein the one or more biguanides is  
2 metformin and one or more sulfonylureas is glipizide, glimeperide or a mixture thereof.
- 1 3. The extended-release layered tablet of claim 2, wherein metformin is present in about  
2 20 % to about 80% by weight of the extended-release layered tablet.
- 1 4. The extended-release layered tablet of claim 2, wherein glipizide is present in about  
2 0.05 % to about 10% by weight of the extended-release layered tablet.
- 1 5. The extended-release layered tablet of claim 2, wherein glimepiride is present in about  
2 0.05 % to about 10% by weight of the extended-release layered tablet.
- 1 6. The extended-release layered tablet of claim 1, wherein the one or more rate-  
2 controlling polymers are hydrophilic polymers, hydrophobic polymers or a combination  
3 thereof.
- 1 7. The extended-release layered tablet of claim 6, wherein the hydrophilic polymers are  
2 selected from cellulose derivatives; polyvinylpyrrolidone, vinyl acetate/vinyl pyrrolidone  
3 copolymer, microcrystalline cellulose, polysaccharides, polyalkylene glycols, starch or  
4 derivatives thereof, or mixtures thereof.
- 1 8. The extended-release layered tablet of claim 7, wherein the cellulose derivatives are  
2 selected from hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxy  
3 ethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium  
4 carboxymethylcellulose or mixtures thereof.

1 9. The extended-release layered tablet of claim 6, wherein the hydrophobic polymers are  
2 selected from ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl  
3 methylcellulose phthalate, poly(alkyl)methacrylate, copolymers of acrylic or methacrylic acid  
4 esters, waxes, shellac, hydrogenated vegetable oils or mixtures thereof.

1 10. The extended-release layered tablet of claim 1, wherein the one or more rate-  
2 controlling polymers are present in about 5 % to about 60 % w/w of the extended-release  
3 layered tablet.

1 11. The extended-release layered tablet of claim 1, wherein the first and second layers are  
2 prepared by dry granulation, wet granulation, direct compression or a combination thereof.

1 12. The extended-release layered tablet of claim 1, wherein the one or more  
2 pharmaceutically acceptable excipients are selected from diluents, binders, lubricants,  
3 glidants, colorants, flavoring agents or mixtures thereof.

1 13. The extended-release layered tablet of claim 2 wherein the second layer further  
2 comprises one or more alkalizing agents.

1 14. The extended-release layered tablet of claim 1 further comprising one or more outer  
2 protective coating layers, one or more separating layers between the first layer and the second  
3 layer, or a combinations thereof.

1 15. The extended-release layered tablet of claim 2, wherein the tablet provides an in-vitro  
2 release of glipizide of from about 8 % to about 15 % by weight after one hour, from about 15  
3 % to about 30 % by weight after 2 hours and from about 20 % to about 50 % by weight after 4  
4 hours, when measured by the USP Paddle Method at 50 rpm in 900 mL of simulated intestinal  
5 fluid at 37 °C.

1 16. A process for preparing a layered tablet comprising the steps of:  
2 a. preparing a first mixture comprising one or more biguanides, one or more rate-  
3 controlling polymers and one or more pharmaceutically acceptable excipients,  
4 b. preparing a second mixture comprising one or more sulfonylureas, one or more  
5 biguanides, one or more rate-controlling polymers and one or more  
6 pharmaceutically acceptable excipients, and

7           c.       forming a first layer and a second layer and combining the layers in a single  
8                    tablet to form a layered tablet.

1    17.    A method for treating non-insulin dependent diabetes mellitus, comprising  
2    administering to a patient in need thereof an extended-release layered tablet comprising:  
3    a first layer comprising one or more biguanides, one or more rate-controlling polymers and  
4    one or more pharmaceutically acceptable excipients, and  
5    a second layer comprising one or more sulfonylureas, one or more biguanides, one or more  
6    rate-controlling polymers and one or more pharmaceutically acceptable excipients.