Title: METFORMIN-P IOGLITAZONE FORMULATION WITH ANTIHYPERGLYCEMIC EFFECTS

Abstract: This invention relates to pharmaceutical products and manufacturing process which includes Metformin or pharmaceutical acceptable salts and especially hydrochloride salts with micronized Pioglitazone or its pharmaceutical acceptable salts and especially hydrochloride salts. The oral solid dosage form compound which is developed by this invention includes one or more filling, binder, disintegrant and/or lubricant with meformin and micronized pioglitazone, which is manufactured by wet granulation in same carrier for diabetes treatment and especially Type-2 diabetes treatment.
Published:
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DESCRIPTION

METFORMIN-PIOGLITAZONE FORMULATION WITH ANTIHYPERGLYCEMIC EFFECTS

FIELD OF THE INVENTION

The present invention relates to pharmaceutical products which include Metformin or its suitable pharmaceutically acceptable salts and especially hydrochloride salts and micronized Pioglitazone or its pharmaceutically acceptable salts especially hydrochloride salts and preparation processes of these pharmaceutical products.

BACKGROUND OF THE INVENTION

Type 2 diabetes, which is also extremely serious and progressive diseases, is appeared as health difficulties to either individual or society with complications such as nephropathy, neuropathy, retinopathy which are visibly in disease progression. According to estimate; diabetes prevalence quickly increases, amount of diabetes patients in worldwide will reach 300 million as per 2025 and Type 2 diabetes will likely constitute 90% of this amount (Hacettepe Medicine Journal 2004, 35:123-126).

This invention relates to preparing pharmaceutical dosage composition for oral administration, those compositions include two active ingredients and has antihyperglycemic effect. This formulation is used for treatment of dieabetes mellitus and especially Type-2 diabetes mellitus.

Antihyperglycemic agents which are Biguanid derivatives are commonly used on non insulin dependend diabetes mellitus (NIDDM-Type2). Fenformin, Buformin and Metformin are examples of this agent without limiting this invention.

Orally administered drugs which are used to decrease plasma glucose level such as metformin, which decreases hepatic glucose production and sulphonylureas which increases insulin release by stimulate pancreatic β-cells. Metformin decreases hepatic glucose production as well as it increases insulin sensitivity on tissue.

Metformin is an antihyperglycemic agent in the form of dimethylbiguanid and it belongs to biguanide class. This invention includes Metformin and pharmaceutically acceptable salts, solvates thereof.
Chemical formula of Metformin is "N^-dimemethylimidodicarbonimidic diamide, 1,1-dimetilbiguanide", molecular formula of Metformin is C₄H₁₁N₅ and its molecular weight is 129.16 g/mol. Metformin is a white crystalline powder. It is freely soluble in water (>300 mg/mL, 25°C) not soluble in acetone, ether and chloroform. The pH of a 1% aqueous solution of Metformin is 6.68. The pH of a 10% aqueous solution of Metformin is 7.30-7.45. Metformin's structural formula is shown below as Formula-I.

![Chemical structure of Metformin](image)

(Formula I)

Commerically available pharmaceutical dosage forms of Metformin are sustained release (SR) tablets, solutions, extended release (XR) tablets and osmotic extended release tablets. Trade names of these pharmaceuticals dosage forms are Glucophage® (Merck), Riomet® (Ranbaxy), Fortamet® (Andryx) and Glumetza® (Depomed).

The absolute bioavailability of a 500 mg Metformin tablet given under fasting conditions is approximately 50%-60%. Studies using single oral doses of Metformin tablets of 500 mg to 1500 mg and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of Metformin, as shown by approximately a 40% lower mean peak plasma concentration, a 25% lower AUC in plasma concentration versus time curve and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of Metformin with food, compared to the same tablet strength administered fasting.

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, intestinal absorption of glucose and improves insulin sensitivity.

Metformin and many salts of Metformin including hydrochloride salt are explained first on US Patent Publication Number 3174901 as antihyperglycemic agents

Usage of Hydrocolloids for their retarding effect in Metformin formulations are explained on European Patent Number 955976 and 781129 and international patent application number WO 96/08243 and WO 96/08224.

Formulation which prepared with direct compression method include matrix system which has extended effect is defined on US Patent Number 6524618.


Using active substances which belong to Thiazolidinedione class for the treatment of Type 2 diabetes is well known. Pioglitazone, Troglitazone and Rosiglitazone are examples of Thiazolidinedione class without limiting the present invention. Metformin was used as most effective antidiabetic agent till Troglitazone, which is first drug of Tiazolidindione class, was released to market in 1997. Troglitazone, which was marketed between March 1997-March 2000, and was withdrawn from market due to serious hepatic toxicity which may have caused death.

Thiazolidinediones are synthetic molecules and they are mostly connected to "nuclear peroxisome proliferator-activated receptor-gamma (PPAR-γ)" and show their effects by activated gene transcription which affected adipogenesis, adiposit differentiation, glucose and lipid metabolism.

Pioglitazone inhibits hepatic gluconeogenesis and improves peripheral glucose re-uptake. Thus removes insulin resistance by improving the hepatic and peripheral insulin sensitivity. Pioglitazone is indicated with diet and exercise as monotherapy for providing glycemic controls in the treatment of Type-2 diabetes also Pioglitazone is used in combination with second antidiabetic agent such as Sulphonylureas or Metformin, Repaglinide, Insulin due to providing more effective glycemic controls under non adequate glycemic control conditions.

Pioglitazone is an odorless white crystalline powder that has a chemical name "(±)-5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-)thiazolidinedione" and a molecular formula of $C_{19}H_{20}N_2O_3S$, having molecular weight of 356.45 g/mol. It is soluble in N,N-dimethylformamide, slightly soluble in ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water and insoluble in ether. Structural formula of Pioglitazone is shown below as Formula-II.
Pioglitazone and thereof salts were firstly explained as antidiabetic and hyperlipidemic agent on European Patent Number 0193256. Also Pioglitazone can be combined with lactose, maize starch, calcium carboxymethylcellulose and magnesium stearate for tablet formulations. Tablets can be prepared by wet granulation method according to above mentioned patent.

Commercially available pharmaceutical dosage form of Pioglitazone is tablet. Pioglitazone has trade names such as Actos® (Lilly, Takeda), Glifix®(Bilim), Piogtan®(Ecz.Zentiva) and Dropia®(Sanovel).

Pioglitazone is shown approximately 30-50% total peak plasma concentration and 20-25% total AUC.

Saccharide, polyanionic polymer, Na-glutamate, Na-5’-inosinate, Na-5’-guanilate, Na-aspartate e.g. and carboxymethylcellulose used in Pioglitazone formulations were explained on European Patent Number 1329217 and International Patent Application Number WO 02/30400.

Solid pharmaceutical formulation disintegrating quickly comprising hydroxypropylcellulose which has 5-7% hydroxypropyl group (low substitute) and sucrose was explained on WO 00/06126 and European Patent Number EP 1561458.

Coatings which may be used on formulations were defined on WO 00/44554, WO 2004/067001 and European Patent Number EP 1588708.

USA Patent Application Publication Number US 2006/0089387 includes basically Pioglitazone used with stabilizer (e.g. maleic, citric, ascorbic, malic, fumaric, tartaric).

International Patent Application number WO 2005/023228 has mentioned about Pioglitazone formulation which includes Meglumin.

Thiazolidinedions has been in the market nowadays and they have been most effective agents for breaking insulin resistance. Taking into consideration of good effects of these agents on lipid profile, arterial tension, inflammation in addition to good effects on glycemic control, they are used as combination therapy (especially with Metformin) or
monotherapy on diabetic patient population. They seem to be reliable agents when used with precautions for their side effects and patient compliance like other drugs. Pioglitazone are proven to be successful when used in combination therapy (Clin. Ther. 2000,22:1395-409). When Pioglitazone is used with Sulphonylureas, it seems gain weight according to dose as side effect. On the other hand; when it is used with Metformin, this side effect is not observed.

Metformin and Pioglitazone combination and usage of this combination for the treatment of diabetes was identified on European Patent Number EP 0861666 and USA Patent Number US 6166043 and US 5965584. Besides, any excipients which may be used in the combination formulation were defined. Lactose, sucrose, starch, mannitol can be used as excipients; calcium carbonate, calcium carboxymethyl cellulose can be used as disintegrant; α-starch, gum arabic, carboxymethyl cellulose, polyvinylpyrrolidone, hydroxypropylcellulose can be used as binder; talc, magnesium stearate, polyethylene glycol 6000 can be used as lubricant, ethyl cellulose, hydroxypropylmethyl cellulose, polyoxyethyleneglycol, celluloseacetatephthalate, hydroxypropylmethylcellulose phthalate and Eudragit® can be used as coating agent.

Solid pharmaceutical formulation which include first layer containing Pioglitazone and Metformin, second layer containing microcrystalline cellulose having a mean particle size of 5-25 µm between 30-100 µm and polyvinylpyrrolidone K-90 is explained on EP 1738754 and WO 2005/099760.

Pioglitazone and Metformin formulation that each antidiabetic agent dispersed own different carrier explained on WO 01/35941 and EP 1231918.


Multilayer tablet which included Pioglitazone-Metformin combination is explained on application number WO 03/105809.

**The Aim of Invention**

The present invention is the development of Metformin-Pioglitazone formulation which it has antihyperglycemic effect;

- Type 2 diabetes treatment included 90% of diabetic patients on nowadays,
- Quick dissolution of Pioglitazone Molecule without effected by changed pH of media in Metformin - Pioglitazone formulations,

- Quick dissolution of Pioglitazone Molecule provided by used micronize Pioglitazone,

- High therapeutic characteristics with improved bioavailability provided by quick dissolution of Pioglitazone molecule,

- Compared to granulation with two different carrier, simplifying the manufacturing process and decreasing economical costs due to manufacturing type which is done with common granule is intended.

Description of the Figures:

Figures are given below to explain well of the invention of Metformin - Pioglitazone formulation which has antihyperglycemics effect.

Figure 1- The graphic for Pioglitazon experiments with micronize and non micronize Pioglitazon

Figure 2- The graphic for Metformin experiments with micronize and non micronize Pioglitazon

| Table - 1 Dissolution rate of Pioglitazone experiments with micronize and non micronize Pioglitazone (as %) |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Time(min.) | Dissolution rate (%) | 0 Min. | 5 Min. | 10 Min. | 15 Min. | 20 Min. | 30 Min. | 45 Min. | 60 Min. |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| PIOGLITAZON-ACTOPLUS MET-A12591                               | 0.0                                                           | 9.5                                                           | 37.5                                                           | 63.5                                                           | 82.2                                                           | 93.5                                                           | 97.1                                                           | 98.5                                                           |
| PIOGLITAZONE-Bilik-0710/D33B                                  | 0.0                                                           | 18.5                                                           | 47.4                                                           | 63.3                                                           | 73.9                                                           | 81.7                                                           | 86.6                                                           | 90.3                                                           |
| PIOGLITAZON-Bilik-0801/D55                                    | 0.0                                                           | 16.4                                                           | 37.1                                                           | 59.5                                                           | 75.7                                                           | 89.2                                                           | 93.3                                                           | 94.3                                                           |
Table - 2 Dissolution rate of Metformin experiments with micronize and non micronize Pioglitazone (as %)

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>0 Min.</th>
<th>5 Min.</th>
<th>10 Min.</th>
<th>15 Min.</th>
<th>20 Min.</th>
<th>30 Min.</th>
<th>45 Min.</th>
<th>60 Min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>METFORMIN HCI-ACTOPLUS MET-A12591</td>
<td>0.0</td>
<td>16.7</td>
<td>47.1</td>
<td>73.8</td>
<td>91.8</td>
<td>97.8</td>
<td>98.2</td>
<td>98.1</td>
</tr>
<tr>
<td>METFORMIN HCI-Bilim-0710/D338</td>
<td>0.0</td>
<td>34.7</td>
<td>75.4</td>
<td>88.3</td>
<td>92.1</td>
<td>92.6</td>
<td>92.7</td>
<td>92.8</td>
</tr>
<tr>
<td>METFORMIN HCI-Bilim-0801/D55</td>
<td>0.0</td>
<td>26.3</td>
<td>48.2</td>
<td>70.4</td>
<td>85.9</td>
<td>95.1</td>
<td>96.1</td>
<td>96.2</td>
</tr>
</tbody>
</table>

5 Detailed Description of The Invention

This invention relates to pharmaceutical products which includes Metformin or its acceptable pharmaceutical salts and Pioglitazone or its acceptable pharmaceutical salts and their manufacturing process. The subject of the invention includes micronize active substances, which belongs to thiazolidindione class, and especially micronize Pioglitazone and its pharmaceutical acceptable salts (hereafter it will mention as Pioglitazone), solvates (hereafter it will mention as Pioglitazone).

Pioglitzone is included in Class-II (low soluble, high permeable) group according to Biopharmaceutical Classification System. Therefore absorption of drug in interbody is depended on the solubility of drug.

Particle size of Pioglitazone effects the solubility characteristics of pharmaceutical compound on formulation that included Pioglitazone. Due to decrease of particle size of Pioglitazone, contact surface with liquid increases. Therefore increases solubility of pharmaceutical compund. But the decrease of particle size does not increase maximum Pioglitazone amount that can be soluble in solvent. It only increases rate of solubility.

There are some difficulties on oral antidiabetic drug formulations which includes two different active matters in Biguanide and thiazolidindione class (especially Metformin - Pioglitazone).

The most important difficulty that is encountered is that the solubility of Pioglitazone depends on pH. Because, when the Metformin-Pioglitazone tablets are solubilized in dissolution media, pH is increased due to the greater amount of Metformin, which effects the solubility of Pioglitazone negatively.

It is surprisingly provided in this invention that quick dissolution of Pioglitazone molecules are not effected by the pH of the medium. Therefore Pioglitazone which has a low
particle size (micronize) is used in formulation. Micronize which is mentioned in invention is $d_{90} < 90 \, \mu m$, especially $d_{90} < 50 \, \mu m$, preferably $d_{90} < 10 \, \mu m$.

Quick dissolution of Pioglitazone molecule which has a low particle size is contributed to show high in-vitro solubility. Hence high therapeutic characteristics are provided by the increase of bioavailability.

Experiments which are made with micronize and non micronize Pioglitazone are shown in Figure-1. $f_2$ similarity factor is used to compare the solubility of Pioglitazone. Experiment in which non micronize Pioglitazone (0710D33B) is used is resulted as $f_2=52.2$. Experiment in which micronize Pioglitazone (0801D55) is used is resulted as $f_2=65.78$.

Consequently it is shown that the increased solubility of product is reasoned by using micronize Pioglitazone. Results of Metformin on same experiment are shown in Figure-2 and $f_2$ of Metformin is resulted as 42.24 on compound in which non micronize Pioglitazone is used (0710D33B) and $f_2$ of Metformin is resulted as 65.83 on compound in which micronize Pioglitazone is used (0810D55). Therefore it shows that meaningful increase bioavailability of compound is provided using micronize Pioglitazone.

One of the matter that must be carefully considered is that the compressibility difficulties of tablet formulations of Metformin-Pioglitazone containing formulations, reasoned by the low compressibility characteristics of active substance, Metformin.

For this reason flowability and compressibility characteristics of powder should be improved by granulation. Water, ethyl alcohol can be used alone as pharmaceutical acceptable solvents as well as they can be used with different proportions in mixture of this solvents.

Manufacturing method made by common granule, which is mentioned in invention, provides both low costs economically and simplifies the procedure, when compared with the granulation procedure which is done with two different carriers, which is mentioned in EP 1231 918 Bl. Dissolution difficulties of Pioglitazon in such a manufacture method are overcome by decrease of particule size.

Active substance which is selected from $\text{on}$ biguanide class mentioned in invention is preferably Metformin and the amount of Metformin is 500-2250 mg, preferably 500-850 mg. Composition may contain 50-95% by weight, preferably 70-80% by weight of Metformin.

Active substance which is selected from thiazolidindione class mentioned $\text{on}$ in invention is preferably Pioglitazone and amount of Pioglitazone is must be 15-45 mg.
preferably 15 mg. Composition may contain 1-5% by weight, preferably 1-3% by weight of Pioglitazone.

The proportions of two active substances in metformin-pioglitazone formulation which has antihyperglycemic effect is 1:100 between 100:1.

Binder which used on formulation is selected from a group which includes polyvinylpyrrolidone, lactose, starches, modified starches, sugars, acaica gum, tragantnhe gum, guar gum, pectine, beeswax binders, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, copolividone, gelatine and sodium alginate. The usage ratio on formula is must be 1-10%.

Disintegrant which used on formulation is selected from a group which includes crospovidone, croscarmellose sodium, polyvinylpyrrolidone, sodium starch glycolate, corn starch, microcrystalline cellulose, hydroxypropylmethyl cellulose and hydroxypropyl cellulose. The usage ratio on formula must be 1-10%.

Lubricant which used on formulation is selected from a group which includes magnesium stearate, stearic acid, palmitic acid, calcium stearate, talk, camauba beeswax, hydrogenated vegetable oil, mineral oil, polyethylene glycols and sodium stearyl fumarate. The usage ratio on formula must be 1-5%.

The following pharmaceutical compounds are illustrative of the present invention is not limited to these examples.

**Example 1**

| Metformin HCl | 850 |
| Pioglitazone HCl | 16,54 |
| Lactose | 94,5 |
| Croscarmellose sodium | 50,66 |
| Povidone | 55,0 |
| Magnesium stearate | 3,30 |

Metformin, micronize Pioglitazone, a part of croscarmellose sodium and Povidone are mixed to give homogeneous mixture. This mixture is granulated with water. Remaining croscarmellose sodium and lactose are added to dry granules and mixed. Magnesium
stearate is added to dry powder compound and mixed. The total composition is compressed into tablets.

**Example 2**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin HCl</td>
<td>850</td>
</tr>
<tr>
<td>Pioglitazone HCl</td>
<td>16,54</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>94,5</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>50,66</td>
</tr>
<tr>
<td>Povidone</td>
<td>55,0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3,30</td>
</tr>
</tbody>
</table>

Metformin, micronize Pioglitazone, a part of croscarmellose sodium and povidone are mixed to give homogeneous mixture. This mixture is granulated with water. Remaining croscarmellose sodium and microcrystalline cellulose are added to dry granules and mixed. Magnesium stearate is added to dry powder compound and mixed. The total composition is compressed into tablets.
CLAIMS

1- An oral solid pharmaceutical dosage form; comprising,
   • 50-95%, preferably 70-90%, especially 70-80% by weight of an active substance selected from biguanide class;
   • 1-10%, preferably 1-5%, especially 1.5-3% by weight of second active substances selected from thiazolidinedione class, and
   • the particle size of the active substance selected from thiazolidinedione group is $d_{90} < 50\mu$m and micronized.

2- An oral solid dosage form; comprising,
   • 50-95%, preferably 70-90%, especially 70-80% by weight of 1,1-dimethylbiguanide hydrochloride from biguanide class,
   • 1-10%, preferably 1-5%, especially 1.5-3% by weight of $\left[(\pm)-5-[4-[2-(5\text{-ethyl-2-pyridinyl})\text{ethoxy}][\text{phenyl}][\text{methyl}]-2,4-\right]$ thiazolidinedione monohydrochloride from thiazolidinedione class, and
   • the particle size of the active substance selected from thiazolidinedione group is $d_{90} < 50\mu$m and micronized.

3- The pharmaceutical compound according to claim 1 and 2; wherein active substance which is selected from from biguanide class is metformin.

4- The pharmaceutical compound according to claim 1 and 2; wherein active substance selected from from thiazolidinedione class is micronized pioglitazone.

5- The pharmaceutical compound according to claim 1 and 4; wherein ratio of the two active substances in the pharmaceutical compound is in between 1:100 and 100:1.

6- The pharmaceutical compound according to claim 1-5; comprising one or more filler, binder, disintegrant and/or lubricant.

7- The pharmaceutical compound according to claim 1-6; particle size of active substances which from thiazolidinedione class is especially $d_{90} < 20\mu$m.

8- The pharmaceutical compound according to claim 1-6; wherein particle size of active substance which belong thiazolidinedione class is preferably $d_{90} < 10\mu$m.
9. The oral solid dosage form; wherein active substances which is selected from biguanide class and active substances which is selected from thiazolidinedione class are into common carrier.

10. The oral solid dosage form; wherein the pharmaceutical compound is prepared by the method of wet granulation with active substances selected from biguanide class and micronized active substances selected from thiazolidinedione class in common carrier.

11. The pharmaceutical compound according to claim 1-10, for the treatment of diabetes and especially Type-2 diabetes.
Figure - 1