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(54) Title: A STABLE, ORAL SOLID DOSAGE FORM

(57) Abstract: A stable, oral, solid dosage form comprising uncoated rosiglitazone acid addition salt, uncoated biguanide (s), citric acid and other pharmaceutically acceptable excipients.

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A STABLE, ORAL SOLID DOSAGE FORM

The present invention relates to a stable, oral, solid dosage form comprising rosiglitazone acid addition salt and biguanide (s).

BACKGROUND OF THE INVENTION

The literature reveals prior arts related to the formulations comprising a combination of rosiglitazone acid addition salt and metformin or its pharmaceutically acceptable salt. An important consideration in the preparation of formulations containing combination of active agents is the stability of the active agents with each other as well with the pharmaceutically acceptable excipients that are used in formulations.

United States Patent 5,741,803 (hereinafter referred to as '803) disclosed acid addition salt of rosiglitazone base to be particularly stable. Useful acids included mineral acids such as hydrochloride and mineral acids and organic acids such as tartaric acid and maleic acid. United States patent application number US2006/0089387 further disclosed that a stable composition can be prepared from rosiglitazone base without the need to particularly convert it into an acid addition salt simply by incorporating into the mixture of rosiglitazone and pharmaceutical excipients, a suitable quantity of the acid. However, when preparing a composition of rosiglitazone acid addition salt and a biguanide, the problem of instability arises in spite of use of acid addition salt rosiglitazone as is discussed below.

Metformin hydrochloride, the commonly administered salt, is known to have poor compressibility. This lack of compressibility combined with the large unit dosage requirements, results in significant formulation problems, especially in compressed dosage forms. United States Patent Number 5,955,106 (herein after referred to as '106 patent) enumerates several formulation problems associated with metformin such as for example, capping. The '106 patent provides solution to these problems by using a hydrocolloid-forming agent as a retardant and maintaining a residual moisture content of the composition of 0.45 to 3 % by weight. The '106 patent further states that it was surprisingly found that the use of hydrocolloid-forming retarding agent enabled for the first time the known poor compressibility of metformin to be brought under control in a technically satisfactory manner. The '106 patent therefore teaches use of a hydrocolloid forming agents such as polyvinyl pyrrolidone, hydroxypropyl methyl cellulose in the formulations of metformin to avoid the compressibility problems.

Another prior art namely, WO2001035941 (hereafter referred to as PCT publication '941) says that although polyvinyl pyrrolidone is particularly effective as a binder with metformin hydrochloride providing excellent flow and compressibility properties, it is indicated that its use in the formulation destabilizes rosiglitazone maleate. The PCT publication '941 solves this problem by separating the two drugs in separate carrier. The '941 publication therefore teaches that the two drugs are located in discrete zones with respect to each other, wherein

each zone comprises the active agent. The two drugs along with its carrier are in different phases and the two phases do not come in physical contact with each other.

PCT publication WO200135940 (hereafter referred to as patent publication '940) discloses a pharmaceutical composition wherein rosiglitazone maleate composition is deposited on the surface of a core containing metformin hydrochloride. The '940 publication states that the instability of rosiglitazone maleate is prevented by avoiding the mutual interaction between the two drugs by physically separating them, for example, by coating the thiazolidinedione on the surface of metformin or making multilayer compositions.

PCT publication WO2005065663 (hereafter referred to as patent publication '663) discloses fast dissolving dosage form comprising microparticles of rosiglitazone and/or metformin together with a protective material substantially shielding rosiglitazone and/ or metformin from coming in contact with the environment outside of the microparticle. It discloses use of an effervescent couple for example, acids such as citric acid, tartaric acid, malic acid and an alkali metal carbonate. The '663 patent publication teaches to provide a taste masking coating on the rosiglitazone maleate and/or metformin and further mixing these coated particles with effervescent couple to make the chewable tablets.

Thus, it may be concluded that the prior arts suggest that certain excipients which are compatible with metformin or its pharmaceutically acceptable salt may not be compatible with rosiglitazone acid addition salt. Therefore making a dosage form using excipients that are suitable for both active ingredients, i.e, rosiglitazone acid addition salt and metformin or its pharmaceutically acceptable salt is a task to formulators. Moreover, high dose of metformin salts for example, hydrochloride salt and its poor compressibility adds to the problem in terms of achieving optimum physical characteristics when the dosage form is a compressed dosage form, such as tablets. Therefore, there lies a need to provide a balance between achieving the optimum physical characteristics while maintaining a desirable chemical stability, for the dosage form of rosiglitazone acid addition salt and metformin or its pharmaceutically acceptable salts.

We have surprisingly found that the addition of citric acid to the uncoated rosiglitazone acid addition salt and uncoated biguanide solves the stability problems associated with rosiglitazone acid addition salt while providing a formulator the flexibility to choose the excipients that are recommended for the metformin which are otherwise not compatible with rosiglitazone acid addition salt. Further, even more surprisingly, it was found that citric acid provides the required solution to the problem which was otherwise not solved by the addition of another acid, namely maleic acid.

OBJECTS OF THE INVENTION

It is the object of the present invention to provide a dosage form of rosiglitazone acid addition salt and metformin or its pharmaceutically acceptable salt in a single dosage form.

It is also the object of the present invention to provide an easy method to prevent destabilization of rosiglitazone acid addition salt when formulated with metformin or its pharmaceutically acceptable salt, in a single dosage form.

It is another object of the present invention to find means which allow the use of the excipients that are incompatible with rosiglitazone acid addition salt but are essential for metformin or its pharmaceutically acceptable salt portion.

It is also the object of the present invention to provide a dosage form to get satisfactory physical parameters such as hardness, capping etc. of the solid dosage form.

SUMMARY OF THE INVENTION

The present invention provides a stable, oral, solid dosage form comprising uncoated rosiglitazone acid addition salt, uncoated biguanide (s), citric acid and other pharmaceutically acceptable excipients.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a stable, oral, solid dosage form comprising uncoated rosiglitazone acid addition salt, uncoated biguanide (s), citric acid and other pharmaceutically acceptable excipients.

The term 'stable' as used herein means that when the solid dosage form is stored at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months, the total impurities are less than 1 % of the labeled amount of rosiglitazone acid addition salt.

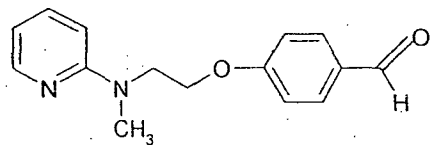
The term 'uncoated' as used herein means that the rosiglitazone acid addition salt and the biguanide are not coated with any protective coating substantially encompassing the particles and is not isolated from coming in contact with the other pharmaceutically acceptable excipients.

The acid addition salts of rosiglitazone used in the solid dosage form of the present invention, includes, but are not limited to, salts with the mineral acids such as hydrobromic acid, hydrochloric acid, sulfuric acids, or salts with organic acids such as methanesulphonic, tartaric and maleic acid and the like. In preferred embodiment of the present invention, rosiglitazone maleate is used.

The oral solid dosage form of the present invention comprises biguanide (s). Biguanide used in the oral, solid dosage form of the present invention include, but are not limited to, metformin, phenformin, buformin, their pharmaceutically acceptable salts, hydrates, solvates and the like. Preferably a hydrochloride salt of metformin is used. The amount of metformin hydrochloride used in the oral solid, dosage form of the present invention, may

range from about 100 mg to about 2000 mg, preferably from about 200 mg to about 1500 mg by weight of the solid dosage form.

In one embodiment of the present invention, maleate salt of rosiglitazone is used. Impurities arising from the degradation of the rosiglitazone maleate were identified by their chemical structures. Amongst them, Structure I was identified as 5-[4-{2-(N-methyl, N-(2-pyridyl))amino}ethoxy benzaldehyde and was termed as impurity B. This impurity B was monitored as the known impurity along with the other unknown impurities.



I (Impurity B)

5-[4-{2-(N-methyl, N-(2-pyridyl))amino}ethoxy benzaldehyde

The content of the impurity B was determined by first separating it by known separation. In one embodiment of the present invention, gradient High performance liquid chromatography (HPLC) method is used; however it is possible to use any other suitable technique. In the gradient HPLC method, C_{18} column (250 x 4.6 mm, 5 µ, Waters Symmetry) is used as a stationary phase and a mixture of acetonitrile, triethylamine and orthophosphoric acid in varying proportions, is used as the mobile phase.

According to the present invention, the solid dosage form of the present invention is stable that is when stored under accelerated stability conditions such as, for example, at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months, the total impurities i.e total of known and unknown impurities were less than 1 % of the labeled amount of rosiglitazone acid addition salt, preferably the impurities were less than 0.50 % of the labeled amount of rosiglitazone acid addition salt.

According to one embodiment of the present invention, the rosiglitazone maleate is present in the amount ranging from about 0.1 % to about 10 %, preferably about 0.2 % to about 5 % and most preferably about 0.5 % by total weight of the unit dosage form.

According to one embodiment of the present invention, the citric acid is present in the amount ranging from about 0.5 % to about 15 %, preferably about 1 % to about 5 % and most preferably about 2.5 % by total weight of the unit dosage form.

The oral, solid dosage form of the present invention may be in the form of powder mixture, granules, pills, powder or granules filled into capsules, sachets, slugs and tablets. In one embodiment of the present invention, the oral solid dosage form is swallowable tablet. Accordingly, the solid dosage form of the present invention comprises conventional excipients such as diluents, fillers, binding agent, disintegrants, and lubricants/glidants.

Examples of fillers that may be used in the pharmaceutically acceptable carrier medium include, but are not limited to, starch and its derivatives like corn starch, pregelatinized starch and the like, mannitol, sorbitol, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, lactose, dextrose, dextrin, sugar compressible and the like and mixture thereof. The amount of fillers used in the solid oral dosage form of the present invention may range from about 0.1 % to about 50 %, preferably from about 2 % to about 25 %, most preferably from about 3 % to about 15 % by weight of the solid dosage form.

Examples of the binders that may be used in the pharmaceutically acceptable carrier medium include, but are not limited to, low viscosity cellulose derivatives like methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, gelatin, tragacanth, sodium alginate and the like and mixture thereof. Preferably low viscosity cellulose derivatives are used, for example, hydroxypropyl methyl cellulose 5 cps grade is used. The amount of binders used in the solid dosage form of the present invention may range form about 0.5 % to about 5 %, preferably from about 1 % to about 3 % by weight of the solid dosage form.

Examples of the disintegrants that may be used in the pharmaceutically acceptable carrier medium include, but are not limited to polyvinyl pyrrolidone, sodium starch glycolate, pregelatinised starch, hydroxypropyl cellulose, croscarmellose and the like, and mixtures thereof. The amount of the disintegrants that are used in the solid dosage form of the present invention may range from about 2 % to about 15 %, preferably from about 4 % to about 10 % by weight of solid dosage form.

Examples of lubricants/ glidants that may be used that may be used in the pharmaceutically acceptable carrier medium include, but are not limited to, colloidal silicon dioxide, magnesium stearate, calcium stearate, sodium stearyl fumarate, stearic acid, zinc stearate, talc and the like and mixture thereof.

According to one embodiment of the present invention, the uncoated rosiglitazone acid addition salt and citric acid may be made into a homogenous admixture. For example, rosiglitazone acid addition salt may be mixed with a solution of citric acid dissolved in pharmaceutically acceptable solvents. Pharmaceutically acceptable solvents used to dissolve citric acid may include, but are not limited to, water, ethanol, isopropyl alcohol, acetone and the like and mixture thereof. In one embodiment of the present invention, rosiglitazone maleate is suspended in the aqueous solution of citric acid and the water is evaporated till the solvent is completely removed. In one preferred embodiment of the present invention, rosiglitazone acid addition salts along with other pharmaceutically acceptable excipients are granulated with a solution of citric acid. Alternatively it is possible to

dry mix the two to get a homogeneous admixture and then the admixture is granulated with suitable granulating solution. In one preferred embodiment, the uncoated rosiglitazone maleate and citric acid are in homogeneous admixture with other pharmaceutically acceptable excipients. Metformin is prepared in the form of granules. The dry powder blend of rosiglitazone maleate and citric acid are added to the metformin granules and the mixture of the powder blend and granules is converted into a solid dosage form. Particularly, in more preferred embodiment, the granules of metformin and blend of rosiglitazone acid addition salt and citric acid are mixed, lubricated and compressed into tablets. In another embodiment, the blend is filled into hard gelatin capsules.

In yet another embodiment, all the ingredients namely, uncoated rosiglitazone acid addition salt, citric acid, uncoated metformin hydrochloride are in a homogeneous admixture for example, are dry blended with the other pharmaceutically acceptable excipients. The blend is either filled into hard gelatin capsules or converted into granules and the granules are filled into capsules or the granules are compressed into tablets. In one preferred embodiment, the granules comprising rosiglitazone acid addition salt, citric acid and metformin hydrochloride are lubricated with conventional lubricants and compressed into tablets.

In the comparative examples, the oral solid dosage form was prepared in the absence of citric acid. Polyvinyl pyrrolidone is used as either dry binder or wet binder. The comparative example 1 and 2 differed in the addition of rosiglitazone maleate i.e. in comparative example 1 rosiglitazone maleate was added extragranularly to the metformin hydrochloride granule and in comparative example 2 rosiglitazone maleate was added intragranularly along with metformin hydrochloride.

The tablets of comparative example 1 when stored under accelerated stability conditions for example, at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months, the total impurities were beyond acceptable limits, for example, 3.83 % by weight of the labeled amount rosiglitazone maleate (stability data given in table no 8). The tablets of comparative example 2 when stored under accelerated stability condition of temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months, the total impurities were 1.9 % by weight of the labeled amount rosiglitazone maleate (stability data is provided in Table no 8).

The tablets prepared according to comparative example 4 were prepared by using hydroxypropyl methyl cellulose as the binder in the granulating fluid. Polyvinyl pyrrolidone was added as a dry binder. The tablets of so prepared when stored under accelerated stability condition for example, at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of one month, the total impurities were 0.82 % by weight of the labeled amount of rosiglitazone maleate (Table no. 8).

It was surprisingly found that citric acid was capable of stabilizing the dosage form as evidenced by the example I and example II. The tablets according to comparative example 3 which used maleic acid along with a mixture

of metformin hydrochloride, rosiglitazone maleate, polyvinyl pyrrolidone and hydroxypropyl methylcellulose when stored at a temperature of 40^0 C ± 2 ^{0}C and 75 % ± 5 % relative humidity for one month, showed very high total impurities i.e 1.38 % by weight of rosiglitazone maleate.

In one embodiment, the solid dosage form of the present invention may be in the form of powder or granules filled into capsules. When the dosage form of the present invention is in the form of powder filled into capsules, the citric acid, uncoated rosiglitazone maleate and other pharmaceutically acceptable excipients are dry blended in a suitable mixer to get a homogeneous admixture. To this homogeneous admixture, metformin hydrochloride is added. Other suitable excipients are added and the powder mixture is filled into capsules. Alternatively, the powder mixture is granulated with suitable binders such as hydroxypropyl methyl cellulose, polyvinyl pyrrolidone and then the dried granules are filled into capsules. In one preferred embodiment, the oral solid dosage form of the present invention is in the form of granules compressed into tablets. Accordingly, the tablets are prepared by conventional methods such as dry granulation, wet granulation, compaction or slugging. In this embodiment, metformin is either granulated with a solution of polyvinyl pyrrolidone or a dry powder of polyvinyl pyrrolidone is added and the blend is granulated with a suitable solvent. The granules are dried and a mixture of rosiglitazone acid addition salt and citric acid along with other suitable excipients, for example, microcrystalline cellulose, sodium starch glycolate, colloidal silicone dioxide, magnesium stearate are added and the granules are compressed into tablets. Optionally the tablet may be coated with suitable coating composition known in the art. Alternatively, the mixture of rosiglitazone maleate, metformin hydrochloride and polyvinyl pyrrolidone are granulated with granulating fluid having citric acid dissolved therein. The granules are dried and other suitable excipients, for example, microcrystalline cellulose, sodium starch glycolate, colloidal silicone dioxide, magnesium stearate are added and the granules are compressed into tablets. Optionally the tablet may be coated with suitable coating composition known in the art.

The examples that follow are provided as illustrations only and do not limit the scope of the present invention.

EXAMPLE I

The solid dosage form was prepared using the ingredients as tabulated in table 1.

Table 1

Ingredients	mg per tablet	% by weight of the coated tablet
metformin hydrochloride	1000	79.58
microcrystalline cellulose	76.8	6.11
colloidal silicon dioxide	12.35	0.98
sodium starch glycolate	55.5	4.42
polyvinyl pyrrolidone	36.3	2.88
hydroxypropyl methyl cellulose	18.15	1.44
rosiglitazone maleate	2.65	0.21
citric acid	12.2	0.971
magnesium stearate	6.05	0.48
Opadry II coating	36.6	2.91

Specified amount of metformin hydrochloride was milled through 0.5 mm screen. Colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate and polyvinyl pyrrolidone were sifted through ASTM 60 mesh. Milled metformin hydrochloride was mixed with part of colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate and polyvinyl pyrrolidone. The blend was granulated with solution of hydroxypropyl methyl cellulose in purified water. The wet mass was dried and sized through about 1.0 mm screen. The dried granules were lubricated with a blend of specified amounts of rosiglitazone maleate, citric acid, magnesium stearate and remaining amount of microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide and. The lubricated granules were compressed into tablets. The compressed tablets were coated with Opadry II coating to a weight gain of about 3.0 %.

The compressed tablets prepared according to Example 1 were stored in High density polyethylene (HDPE) containers at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months. The tablets were analyzed for the content of rosiglitazone, known and unknown impurities. Results are represented in table no 3.

EXAMPLE II

The solid dosage form was prepared using the ingredients as tabulated in table 2.

Table 2

Ingredients	mg per tablet	% by weight of the coated tablet
metformin hydrochloride	1000	79.58
rosiglitazone maleate	2.65	0.21
colloidal silicon dioxide	12.35	0.983
microcrystalline cellulose	76.9	6.12
sodium starch glycolate	55.5	4.42
polyvinyl pyrrolidone	36.3	2.88
hydroxypropyl methylcellulose	18.15	1.44
citric acid	12.1	0.971
magnesium stearate	6.05	0.48
Opadry coating	36.6	2.91

Specified amount of metformin hydrochloride was milled through 0.5 mm screen. Rosiglitazone maleate, colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate and polyvinyl pyrrolidone were sifted through ASTM 60 mesh. Milled metformin hydrochloride was mixed with specified amount of rosiglitazone maleate, polyvinyl pyrrolidone and part of colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate. The blend was granulated with solution of citric acid and hydroxypropyl methyl cellulose dissolved in purified water. The wet mass was dried and sized through about 1.0 mm screen. The dried granules were lubricated with a magnesium stearate and remaining part of microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide. The lubricated granules were compressed into tablets. The compressed tablets were coated with Opadry II coating to a weight gain of about 3.0 %.

The compressed tablets prepared according to Example II were stored in HDPE containers at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months. The tablets were analyzed for the content of rosiglitazone, known and unknown impurities. Results are represented in table no 3.

Table 3

Storage condition and Duration	Example I		Example II	
	Initial	40^0 C 75 % RH 3 months	Initial	40^0 C 75 % RH 3 months
Assay	98.3	97	94.6	
Related substances (%w/w of Rosiglitazone)				
Impurity B	ND	ND	ND	ND
%unknown impurity	0.03	0.17	0.03	0.12
% total impurity	0.06	0.49	0.06	0.45

ND: not detectable; RH: Relative humidity

COMPARATIVE EXAMPLE I

The solid dosage form was prepared according to the formula given in table 4.

Table 4

Ingredients	mg per tablet	% by weight of the coated tablet
metformin hydrochloride	1000	80.23
microcrystalline cellulose	22.75	1.83
sodium starch glycolate	91.5	14.68
polyvinyl pyrrolidone K 30	70.0	5.62
rosiglitazone maleate	2.65	0.216
magnesium stearate	11	0.88
Opadry coating	36.3	2.91

Specified amount of metformin hydrochloride was milled through 0.5 mm screen. Microcrystalline cellulose, sodium starch glycolate and polyvinyl pyrrolidone were sifted through ASTM 60 mesh. Milled metformin hydrochloride was mixed with part of microcrystalline cellulose, sodium starch glycolate and polyvinyl pyrrolidone. The blend was granulated with solution of remaining part of polyvinyl pyrrolidone in purified water. The wet mass was dried and sized through about 1.0 mm screen. The dried granules were lubricated with a blend of specified amounts of rosiglitazone maleate, magnesium stearate and remaining portion of sodium starch glycolate, and colloidal silicon dioxide. The lubricated granules were compressed into tablets. The compressed tablets were coated with Opadry II coating to a weight gain of about 3.0 %.

The tablets according to the comparative example I were stored in HDPE containers at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months. The tablets were analyzed for the content of rosiglitazone, known and unknown impurities. Results are represented in table no 8.

COMPARATIVE EXAMPLE II

The solid dosage form was prepared according to the formula given in table 5

Table 5

Ingredients	mg per tablet	% by weight of the coated tablet
metformin hydrochloride	1000	80.24
rosiglitazone maleate	5.3	0.43
microcrystalline cellulose	39.6	3.18
sodium starch glycolate	72	5.77
polyvinyl pyrrolidone K 30	70.0	5.61
colloidal silicon dioxide	12	0.963
magnesium stearate	11	0.88
Opadry coating	36.3	2.91

Specified amount of metformin hydrochloride was milled through 0.5 mm screen. Rosiglitazone maleate, microcrystalline cellulose, sodium starch glycolate and polyvinyl pyrrolidone were sifted through ASTM 60 mesh. Milled metformin hydrochloride was mixed with specified amount of rosiglitazone maleate, microcrystalline cellulose and a part of sodium starch glycolate and polyvinyl pyrrolidone. The blend was granulated with solution of remaining portion of polyvinyl pyrrolidone in purified water. The wet mass was dried and sized through about 1.0 mm screen. The dried granules were lubricated with a blend of specified amounts of magnesium stearate and remaining portion of sodium starch glycolate and colloidal silicon dioxide. The lubricated granules were compressed into tablets. The compressed tablets were coated with Opadry II coating to a weight gain of about 3.0 %

The tablets according to the comparative example II were stored in HDPE containers at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months. The tablets were analyzed for the content of rosiglitazone, known and unknown impurities. Results are represented in table no 8.

COMPARATIVE EXAMPLE III

Solid dosage form was prepared according to the formula given in table 6

Table 6

Ingredients	mg per tablet	% by weight of the coated tablet
metformin hydrochloride	1000	79.58
rosiglitazone maleate	2.65	0.211
microcrystalline cellulose	76.9	6.12
sodium starch glycolate	55.5	4.42
polyvinyl pyrrolidone K 30	36.3	2.89
colloidal silicon dioxide	12.35	0.98
hydroxypropyl methyl cellulose	18.15	1.44
maleic acid	12.1	0.963
magnesium stearate	6.05	0.481
Opadry coating	36.6	2.91

Specified amount of Metformin hydrochloride was milled through 0.5 mm screen. Rosiglitazone maleate, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and polyvinyl pyrrolidone were sifted through ASTM 60 mesh. Milled metformin hydrochloride was mixed with specified amount of rosiglitazone maleate, polyvinyl pyrrolidone and a part of microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate in rotating mixer granulator. The blend was granulated with solution of hydroxypropyl methyl cellulose and maleic acid in purified water. The wet mass was dried and sized through about 1.0 mm screen. The dried granules were lubricated with a blend of specified amounts magnesium stearate and remaining portion of of microcrystalline cellulose, sodium starch glycolate and colloidal silicon dioxide. The lubricated granules were compressed into tablets. The compressed tablets were coated with Opadry II coating to a weight gain of 2.91 %.

The tablets according to the comparative example III were stored in (HDPE) containers at a temperature of 40^0 C $\pm$ 2^0 C and 75 % $\pm$ 5 % relative humidity for a period of one month. The tablets were analyzed for the content of rosiglitazone, known and unknown impurities with the analytical method described above. Results are represented in table no 8.

COMPARATIVE EXAMPLE IV

Solid dosage form was prepared according to the formula given in table 7

Table 7

Ingredients	mg per tablet	% by weight of the coated tablet
metformin hydrochloride	1000	80.23
rosiglitazone maleate	2.65	0.213
microcrystalline cellulose	79	6.34
sodium starch glycolate	55.5	4.45
polyvinyl pyrrolidone K 30	36.3	2.91
colloidal silicon dioxide	6.35	2.80
hydroxypropyl methyl cellulose	18.15	1.46
magnesium stearate	6.05	0.485
Opadry coating	36.3	2.91

Specified amount of metformin hydrochloride was milled through 0.5 mm screen. Rosiglitazone maleate, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and polyvinyl pyrrolidone were sifted through ASTM 60 mesh. Milled metformin hydrochloride was mixed with specified amount of rosiglitazone maleate, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and polyvinyl pyrrolidone in rotating mixer granulator. The blend was granulated with solution of hydroxypropyl methyl cellulose in purified water. The wet mass was dried and sized through about 1.0 mm screen. The dried granules were lubricated with a blend of specified amounts of microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate. The lubricated granules were compressed into tablets. The compressed tablets were coated with Opadry II coating to a weight gain about 3.0 %.

The tablets according to the comparative example IV were stored in (HDPE) containers at a temperature of 40^0 C ± 2^0 C and 75 % ± 5 % relative humidity for a period of three months. The tablets were analyzed for the content of rosiglitazone, known and unknown impurities. Results are represented in table no 8.

Table 8

	Comparative Example							
Storage condition and Duration	I		II		III		IV	
	at R.T 10 M	40^0 C 75 % RH 3 M	at R.T 12 M	40^0 C 75 % RH 3M	initial	40^0 C 75 % RH 1M	initial	40^0 C 75 % RH 3 M
Assay	93.26	87.74	93.48	90.9	96.0	94.4	94	94.3
Related substances (% w/w of rosiglitazone)								
Impurity B	ND	ND	ND	ND	ND	0.01	ND	0.01
% unknown impurity	0.52	1.13	0.25	0.51	0.03	0.19	0.03	0.28
% total impurity	1.93	3.83	0.9	1.9	0.07	1.38	0.09	1.00

ND: not detectable, RH: Relative humidity, M: Month, R.T: room temperature

claim:

1. A stable, oral, solid dosage form comprising uncoated rosiglitazone acid addition salt, uncoated biguanide (s), citric acid and other pharmaceutically acceptable excipients.

2. A stable, oral, solid dosage form as claimed in claim 1 wherein uncoated rosiglitazone acid addition salt and citric acid are in homogeneous admixture with other pharmaceutically acceptable excipients.

3. A stable, oral, solid dosage form as claimed in claim 1 wherein uncoated rosiglitazone acid addition salt, uncoated metformin and citric acid are in homogeneous admixture with other pharmaceutically acceptable excipients.

4. A stable, oral, solid dosage form as claimed in claim 1 wherein the rosiglitazone acid addition salt is maleate salt and the biguanide is metformin or its pharmaceutically acceptable salt.

5. A stable, oral, solid, dosage form as claimed in claim 4 wherein rosiglitazone maleate is present in amount of about 0.5 % and citric acid is present in amount of about 2.5 % by the total weight of the dosage form.