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(54) Title: DUAL RELEASE BILAYER TABLETS COMPRISING METFORMIN

(57) Abstract: The present invention discloses dual release bilayer pharmaceutical formulation in unit dosage form comprising met-
formin or its acid addition salt. The formulation has an advantage of achieving the minimum effective concentration (MEC) rapidly
along with maintaining therapeutic plasma concentration in effective range for several hours, thus controlling blood glucose
throughout the length of time.



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“DUAL RELEASE BILAYER TABLETS COMPRISING METFORMIN”**Technical field of the invention:**

The present invention relates to dual release bilayer pharmaceutical formulation in unit dosage form comprising metformin or its acid addition salt. The formulation has an advantage of achieving the minimum effective concentration (MEC) rapidly along with maintaining therapeutic plasma concentration in effective range for several hours, thus controlling blood glucose throughout the length of the time.

Background of the invention:

Metformin is a widely prescribed drug for people with type 2 diabetes and is available commercially in two different formulations; as sustained or extended release formulation and is marketed as Metformin 500mg SR, Metformin 850mg SR and Metformin 1000mg SR; as instant release (IR) formulation as Metformin 500mg, Metformin 750mg etc.

In instant release formulation, Metformin is used in the dose range of 0.5-2.0 gm. In this dose strength, Metformin has an absolute oral bioavailability of 40 – 60%. Further, Metformin IR formulation achieves minimum effective concentration (MEC) of 500ng/ml quickly within a time period of less than one hour and displays a relatively lesser lag time. Though onset of action is relatively faster than SR formulation, Metformin IR formulation is able to maintain the plasma concentration within the effective range of 500-1000ng/ml just for a period of 2-3 hours. This implies to its limited duration of action. Further, food also causes a reduction in the bioavailability of Metformin IR. Moreover, the plasma half-life of Metformin is very short, requiring multiple dosing. High dose of Metformin viz. 500mg-1500mg- in IR formulation is reported to cause incidences of gastro-intestinal disturbances like nausea or vomiting hence affecting patient compliance.

The sustained release (SR) formulation of metformin although maintains the plasma concentration in effective range relatively longer than the IR formulation, suffers from the disadvantage that it takes considerably longer time to achieve MEC of 500ng/ml. This lag time significantly delays the onset of glucose lowering effect of Metformin. In such case, despite the therapeutic intervention the subject is expected to spend a considerable length

of time in Hyperglycaemic state after dosing. This hyperglycaemic lag time, may further damage vital organs like eyes, nerves, kidney, coronary arteries etc. and in long run puts the patient on a high risk of developing micro- and macro vascular complications related to diabetes.

The sustained release (SR) formulation is further disadvantageous to patients, since the patients generally take metformin just before his meal. If there is considerable lag time in achieving the MEC level of 500ng/ml, this may shoot up the levels of post prandial hyperglycemia, have inadequate control over blood glucose profile and hence elevate the risk for developing cardiovascular disorders related to diabetes. Thus, large patient population who suffer from Type 2 diabetes and treated with Metformin SR, face the risk of inadequate control of blood glucose profile and related cardiovascular disorders due to the above said shortcomings of Metformin SR.

The sustained release (SR) tablets are formulated because of the short half-life of metformin. However, since the absorption of metformin is limited to small intestine and the sustained release dosage forms release a significant proportion of medication beyond small intestine, in colon, where the absorption is minimal, the traditional SR dosage form of metformin limits its effect to a considerable extent. In addition the high water solubility of Metformin means that large amounts of polymer are required to control its release from conventional modified-release formulations. This makes the application of many existing extended release technologies inappropriate for Metformin.

Moreover, since the various pharmacological effects displayed by Metformin like reduction of blood glucose levels and HbA1c, reduction of triglycerides, stimulation of GLP-1 release – all depend on the plasma concentration of Metformin, there remains a need in the art to formulate a composition which carry the benefits associated with immediate release formulation such as attaining minimum effective concentration (MEC) rapidly, providing a rapid onset of action and together with it, maintaining therapeutic concentration in the range of 500-1000ng/ml over longer duration and thus controlling blood plasma, blood glucose levels throughout the length of time to cater to the large number of population with diabetes around the globe.

This is intended as the array of pharmacological effects displayed by Metformin like reduction of blood glucose levels and HbA1c, reduction of triglycerides, stimulation of GLP-1 release – all depend on the plasma concentration of Metformin and hence, achieving MEC as fast as possible after taking Metformin orally and maintaining the plasma concentration in therapeutic range for a longer period of time becomes an important and crucial part in delivering an effective treatment of Metformin.

In light of the above, there remains a need in the art to develop a pharmaceutical composition comprising metformin wherein the lag time to achieve Minimum Effective Concentration (MEC) of 500ng/ml is significantly reduced and which maintains plasma concentration in an effective range over a longer period of time which is highly desirable to patients with Type II Diabetes.

Summary of the invention:

The primary object of the present invention is to provide Metformin formulation, which overcomes the pharmacokinetic limitations of Metformin IR and Metformin SR alone, and which achieves minimum effective concentration in reduced lag time as well as which maintains therapeutic concentration in blood serum over longer period of time for better control of blood glucose level throughout the length of time.

The above objectives of the present invention are realised by providing dual release bilayer pharmaceutical formulation in a single unit dosage form, preferably tablets, comprising metformin, wherein significant proportion of metformin is released instantly followed by release of the remaining dose of metformin in a sustained manner.

In an aspect, the present invention provides dual release bilayer Metformin tablet formulation comprising;

- a. Instant release layer which releases significant amount of Metformin or its acid addition salt immediately; and
- b. Sustained release layer of metformin or its acid addition salt, matrixed with release retarding polymer;

wherein the controlled release of metformin or its acid addition salt thereafter maintains the plasma concentration in therapeutic range for longer period of time providing better control of fasting blood glucose level throughout length of the time.

In another aspect, the present invention provides a process for preparation of such dual release bilayer tablet formulation. The instant/immediate release layer and the sustained release layer are prepared by wet granulation method and the granules obtained are compressed to form the bilayer tablets.

In an aspect, the instant release layer is a rapid disintegrating layer and releases Metformin or its acid addition salt immediately as soon as it comes in contact with gastric fluid. Metformin absorbed helps in attaining minimum effective concentration (MEC) of 500ng/ml in reduced lag time in comparison to the Metformin SR known in the art as shown in **Table 1** herein below.

In another aspect, the sustained release layer which is matrixed in rate controlling/retarding polymer ensures that the active ingredient, metformin or its acid addition salt is released in a controlled and extended manner so as to maintain the plasma concentration in the therapeutic range for a considerable longer period of time.

Description of figures:

Fig 1 depicts plasma concentration time profile, where,

T0 : Time taken by formulation to achieve MEC. It suggests onset of action,

T1: Time by which plasma drug concentration fall below minimum effective concentration (MEC). It indicates that therapeutic efficacy decreases after T1,

T1-T0: It is time for which formulation maintains plasma concentration in therapeutic range.

Fig 2 depicts the *in vivo* metformin plasma profile of the formulation described in example 1.

Abbreviations:

C_{max} is the maximum (or peak) concentration the drug achieves in plasma. It is expressed as ng or µg.

T_{max} is the time taken by drug to reach maximum (or peak) plasma concentration. It is expressed in minutes or hours.

ROA is Rate of absorption. It is a mathematical expression of the ratio of C_{max}/T_{max}. It is expressed in µg/min or ng/min.

AUC - Area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug. It is expressed in mg*h/L. It is the measure of extent of absorption.

MEC- Minimum Effective Concentration – It is the minimum concentration of a drug in serum required to produce a desired pharmacological effect. It is basically the threshold level of drug below which the efficiency of the drug falls sharply.

MTC-Maximum Tolerated Concentration – It refers to the highest dose of pharmacological treatment that will produce the desired effect without causing unacceptable toxicity.

Definition: Onset of action: It is the time taken by drug to reach minimum effective concentration (MEC).

Detailed Description of the invention:

The invention will now be described in detail in connection with certain preferred and optional embodiments; so that various aspects thereof may be more fully understood and appreciated.

The present invention relates to dual release bilayer pharmaceutical formulation in unit dosage form, preferably tablets, comprising metformin or its acid addition salts, wherein a part of Metformin dose is released immediately while the remaining proportion is released in a sustained manner.

By using the tablets of the invention, it becomes possible to optimize the supply of the active ingredient i.e. metformin or its acid addition salts in the body while taking into account both the subject's tolerance to the active ingredient and the pharmacokinetic and metabolic profiles of the metformin.

In an embodiment, the present invention discloses a dual release bilayer Metformin tablet formulation comprising;

- a. an instant release layer of Metformin or its acid addition salt in an amount 10-55% of total weight of the composition; and
- b. sustained release layer of metformin or its acid addition salt in an amount 45-90% of total weight of the composition matrixed with release retarding polymer in an amount of 5-20% by weight of the composition;

wherein the instant release of metformin attains minimum effective concentration 500ng/ml in reduced lag time and the sustained release layer maintains the therapeutic concentration in plasma in the range 500-1000 ng/ml for a period of 7-8 hours as depicted in Table 3/Fig. 2 providing control of fasting blood glucose level throughout the length of the time.

In an embodiment, the release retarding/controlling polymer for sustained release layer is selected from hypromellose (HPMC) high viscosity grades K100M, K200M polymers such as hydroxypropyl methyl cellulose of grade K-200M (Methocel K-200M), derivatives of high and low molecular weight cross linked polyacrylic acid polymers (Carbopol polymers) and various grades of copolymer of ethyl acrylate, methyl acrylate and low content of methacrylic acid ester with quaternary ammonium groups (Eudragit sustained release polymers) in an amount of 5-20% by weight of the composition. Preferably, the release retarding polymer is selected from hypromellose (HPMC) high viscosity grades K100M, K200M polymers such as hydroxypropyl methyl cellulose of grade K-200M (Methocel K-200M) in an amount of 5-20% by weight of the composition.

In an embodiment, the ratio of metformin or its acid addition salt to the release retarding polymer in the sustained release layer is 5:1.

The bilayer Metformin tablet formulation of the present invention further comprises binders, fillers or diluents, lubricants and other pharmaceutically acceptable excipients such as granulating aids, colorants, flavorants, surfactants, pH adjusters, anti-adherents and glidants etc.

Binders usually are low viscosity polymers or non-polymeric materials and therefore they do not extend the release of a drug. Although binders improve appearance, hardness and friability of the preparation they are usually not intended to influence the disintegration or dissolution roles of active substance. The binders suitable for use herein include but are not limited to copovidone or polyvinyl pyrrolidone (PVP) with grade values (k) of 29-32, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxy ethyl cellulose, polyvinyl alcohol, sodium carboxy methyl cellulose, starches such as corn starch, modified corn starch, sugars, gum acacia and the like and mixtures thereof in the range of 1-15% w/w.

The fillers or diluents include but are not limited to mannitol, lactose monohydrate, microcrystalline cellulose, silicon dioxide, sorbitol, powdered cellulose, cellulose acetate and the like and mixtures thereof in an amount of 1 – 20% w/w.

The lubricants are selected from but are not limited to talc, magnesium stearate, colloidal silicon dioxide, polyethylene glycol, cross carmellose sodium, sodium stearyl fumarate and the like and mixtures thereof in the range 1- 20% w/w.

In an embodiment, the single dual release metformin bilayer tablets are formulated containing total 750mg metformin or its acid addition salt wherein, the instant release layer comprises 75-410mg of metformin or its acid addition salt and the sustained release layer comprises 337-675 mg of metformin or its acid addition salt matrixed in release retarding polymer.

In another embodiment, the tablets of the current invention comprises sustained release layer arranged in contact with the immediate/instant layer which is either completely enveloped by the immediate/instant layer or only partially covered by it.

In an embodiment, the instant release layer of dual release bilayer tablets of the present invention comprises 75-410 mg of metformin or its acid addition salt and other pharmaceutically acceptable excipients. The active ingredient is released instantly in an

amount NLT 90% in 30min, as soon as it comes in contact with gastric fluid, gets absorbed and achieves minimum effective concentration (MEC) 500ng/ml in reduced lag time.

In yet another embodiment, the sustained release layer of dual release bilayer tablets of the present invention comprises 337-675 mg of metformin or its acid addition salt matrixed in release retarding polymer in an amount of 5-20%w/w and other pharmaceutically acceptable excipients. The active ingredient in the sustained release layer is released at a controlled rate in an amount of 15-20% in about 30min to 60-70% in about 10hour, that maintains the therapeutic concentration in range of 500-1000ng/ml for 7-8 hrs.

In yet another embodiment, the instant release layer of dual release bilayer tablets of the present invention comprises 250 mg of metformin or its acid addition salt and other pharmaceutically acceptable excipients. The active ingredient is released instantly in an amount NLT 90% in 30min; equivalent to 30% of total formulation strength as soon as it comes in contact with gastric fluid, gets absorbed and achieves minimum effective concentration (MEC) 500ng/ml in reduced lag time.

In yet another embodiment, the sustained release layer of dual release bilayer tablets of the present invention comprises 500 mg of metformin or its acid addition salt matrixed in release retarding polymer in an amount of 5-20%w/w and other pharmaceutically acceptable excipients. The active ingredient in the sustained release layer is released at a controlled rate in an amount of 15-20% in about 30 min to 60-70% in about 10hour which maintains the therapeutic concentration in range of 500-1000ng/ml for 7-8 hrs.

The dual release metformin bilayer tablets of the present invention is advantageous over the metformin IR and metformin SR tablets which are commercially available, as the formulation of the present invention provides minimum effective concentration (MEC) rapidly and therapeutic concentration in effective range for longer period of time thus controlling fasting blood glucose levels throughout the length of the time.

In another embodiment, the present invention relates to a process for preparation of dual release metformin bilayer tablet formulation. The tablet is prepared by wet granulation method and the granules obtained are compressed to form the tablets.

The solvents used for wet granulation method is selected from polar protic or aprotic solvents such as water, propylene glycol, isobutanol, ethyl acetate, methylene dichloride, or 1,1,1-trichloroethane or the like either alone or in combination thereof. Metformin granules so formed are uniformly dispersed in controlled release matrix comprising of rate controlling polymers.

Accordingly, the process for preparation of dual release metformin bilayer tablets of the present invention comprises:

Part I: Wet granulation of Instant Release Layer

Metformin HCl in the range of 10-55% w/w, selected diluents in the range of 1-20% w/w, binders in the range of 1-15% w/w, and other suitable pharmaceutically acceptable excipients were dry mixed and passed through the mesh size 80 for appropriate size reduction. The contents were added in Rapid Mixture Granulator (RMG). To the mixture was further added solution of suitable binder in water and wet granulated to form granules. The granules were dried on Fluidized Bed dryer (FBD) followed by addition of pre-lubricants in the range of 1-15%w/w. The sample was tested for its assay and potency. When the quantitative test was observed to be positive, the granules were further lubricated using selected lubricant in the range of 1-15%w/w to obtain the metformin composition fit for instant release.

Part B – Wet Granulation of Metformin Sustained Release layer

Metformin HCl in the range 45-90%w/w and selected binder in the range of 1-15% w/w were dry mixed and passed through the mesh size 80 for appropriate size reduction. The contents were then added in Rapid Mixture Granulator (RMG). To the mixture was further added solution of selected binders in the range of 1-15% w/w in mixture of polar solvents and wet granulated to form granules. The granules so formed were dried on

Fluidized Bed dryer (FBD) followed by addition of release retarding polymer in the range of 5-20%w/w and selected lubricant in the range of 1-10%. The sample was tested for its assay and potency. When the quantitative test was observed to be positive, the granules were further lubricated using selected lubricant in the range of 1-10%w/w to obtain the metformin composition fit for sustained release.

The release retarding/controlling polymer is selected from hypromellose (HPMC) high viscosity grades K100M, K200M polymers such as hydroxypropyl methyl cellulose of grade K-200M (Methocel K-200M), derivatives of high and low molecular weight cross linked polyacrylic acid polymers (Carbopol polymers) and various grades of copolymer of ethyl acrylate, methyl acrylate and low content of methacrylic acid ester with quaternary ammonium groups (Eudragit sustained release polymers) in an amount of 5-20% by weight of the composition. Preferably, the release retarding polymer is selected from hypromellose (HPMC) high viscosity grades K100M; K200M polymers such as hydroxypropyl methyl cellulose of grade K-200M (Methocel K-200M) in an amount of 5-20% by weight of the composition.

Part C: Tablet manufacturing:

Each of the granules was then filled separately in the hopper of tablet compression machine and further the granules were compressed to form the dual release bilayer tablets.

The binders suitable for the formulation are selected from copovidone or polyvinyl pyrrolidone (PVP) with grade values (k) of 29-32, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxy ethyl cellulose, polyvinyl alcohol, sodium carboxy methyl cellulose, starches such as corn starch, modified corn starch, sugars, gum acacia and the like and mixtures thereof in the range of 1-15% w/w.

The fillers or diluents include but are not limited to mannitol, lactose monohydrate, microcrystalline cellulose, silicon dioxide, sorbitol, powdered cellulose, cellulose acetate and the like and mixtures thereof in an amount of 1 – 20% w/w.

The lubricants are selected from but are not limited to talc, magnesium stearate, colloidal silicon dioxide, polyethylene glycol, cross carmellose sodium, sodium stearyl fumarate and the like and mixtures thereof in the range of 1- 20% w/w.

The tablet may optionally be coated with a thin layer of a film forming polymer or moisture barrier polymer. The sustained/ controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. The film coating protects the tablet from hygroscopicity thus preventing the tablet from disintegrating and increasing the stability.

The tablets are made of acceptable sizes such that they can be taken orally without causing any uneasiness to the patient.

In an embodiment, dual release metformin bilayer tablets of 750mg strength are administered twice daily.

In an embodiment, the characteristic feature of the tablet is that the part of it disintegrates rapidly as soon as it comes in contact with gastric fluid, gets absorbed and achieves the desired minimum effective concentration (MEC). In contrast, the other segment of the formulation layer which has Metformin matrixed with sustained release polymers releases metformin at a controlled rate, hence maintaining the plasma concentration in the effective range for a longer period of time (**Table 4**).

In a preferred embodiment, formulation of the present invention attains the plasma concentration of 500ng/ml rapidly in 0.9 hrs (T_0) and subsequently maintains the plasma concentration in therapeutic range of 500ng/ml-1000ng/ml for 7-8 hrs. The same is revealed graphically in **Fig. 2** where T_1 -Time by which plasma drug concentration falls below MEC indicating therapeutic efficacy decreases after T_1 (T_1 is 8.7hrs). The pharmacokinetic comparison of different formulations of Metformin vis-à-vis the current invention is indicated in **Table 3** in the example below.

Fig. 2 is a graphical expression of pharmacokinetic profile of MaxforminTM 750mg. X – axis represents the Time in hours and Y-axis represents the mean plasma Metformin

concentration in 9 healthy volunteers after administering Maxformin™ 750mg tablets in fasting state (Metformin Dual Release Tablets 750mg). The X-axis represents time (in hours) and Y-axis represents the corresponding concentration of the drug (ng/ml) in plasma after oral administration.

Fig.1 is a schematic representation of a typical concentration vs. Time profile a drug in plasma upon its absorption after oral administration. The X-axis represents time (in hours) and Y-axis depicts the corresponding concentration of drug in plasma after oral administration.

T₀ is the time (in hours) metformin achieves a plasma concentration of 500ng/ml while T₁ is the time (in hours) after which plasma metformin concentration decreases below 500ng/ml. Hence, T₁-T₀ is the time period in which plasma concentration remains in active window i.e. therapeutic window. Primary pharmacological action of metformin is to decrease the glucose production from liver (hepatic gluconeogenesis). This action is best achieved when the plasma concentration of metformin is in the therapeutic range i.e. between 500ng/ml–1000ng/ml. Hence, the formulations maintaining the plasma concentration in therapeutic window for the maximum time are considered to be the best effective. This time period is directly related to clinical efficacy of drug.

The active ingredient of the present formulation is better absorbed as compared to the formulation for Metformin IR or Metformin SR alone and is evident from AUC- Area under the plasma drug concentration-time curve (AUC) in **Table 3**. Although the onset of action (T₀) is better for Metformin IR formulation in certain cases, however, the rate and extent of absorption after administration is lower than the present composition. It can therefore be inferred that the present formulation is advantageous over the formulation of prior art since it has enhanced bioavailability and maintains the plasma concentration in the effective range for a longer period of time.

In another embodiment, the present invention relates to the therapeutic use of the present formulation for oral administration for treatment of Diabetes Type II.

In yet another embodiment, the present invention discloses a method for treatment of Diabetes Type II in a subject comprising administering an effective amount of active ingredient content included in the tablet formulation as described herein.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the invention. The description and the examples provided are merely an illustration of the particular aspects of the disclosure and do not limit the scope of the present invention.

Examples:

Example 1: Composition of Dual Release Metformin Bilayer Tablets:

Table 1:

Contents of immediate release Metformin layer	
Ingredient	Qty(mg)
Dry Mixing	
Metformin HCl IP	250
Lactose Monohydrate	51.5
Microcrystalline Cellulose Plain IP	20
Cross Carmellose sodium	10
Lake Tartarazine	0.5
Binder	
PVPK-30	15
Purified Water	-
Pre-lubricants	
Cross Carmellose sodium	10
Colloidal Silicon dioxide	3
Post-Lubrication	
Magnesium Stearate IP	5
Contents of sustained release Metformin layer	
Ingredient	Qty(mg)

Dry Mixing	
Metformin HCl IP	500
Microcrystalline Cellulose Plain IP	51.5
Binder	
Ethyl Cellulose IP	25
Methylene dichloride	-
Iso Propyl Alcohol	-
Pre-Lubricants	
Methocel K-200M	101.7
Colloidal Silicon dioxide	5.33
Post-Lubrication	
Magnesium Stearate IP	5.33

Table 2:

Contents of immediate release Metformin layer	
Ingredient	Qty(mg)
Dry Mixing	
Metformin HCl IP	350
Lactose Monohydrate	55.5
Microcrystalline Cellulose Plain IP	21
Cross Carmellose sodium	14
Lake Tartarazine	0.5
Binder	
PVPK-30	15
Purified Water	-
Pre-lubricants	
Cross Carmellose sodium	12
Colloidal Silicon dioxide	3
Post-Lubrication	

Magnesium Stearate IP	5
Contents of sustained release Metformin layer	
Ingredient	Qty(mg)
Dry Mixing	
Metformin HCl IP	350
Microcrystalline Cellulose Plain IP	48.5
Binder	
Ethyl Cellulose IP	19
Methylene dichloride	-
Iso Propyl Alcohol	-
Pre-Lubricants	
Methocel K-200M	90.1
Colloidal Silicon dioxide	5.33
Post-Lubrication	
Magnesium Stearate IP	5.33

Example 2: Process for preparation of Dual Release Metformin Bilayer Tablet**Table 3:**

Contents of IR layer	
Ingredients	Prep. range
Metformin HCl IP	10-55%
Lactose Monohydrate	1-20%
Microcrystalline Cellulose Plain IP	1-15%
Cross Carmellose sodium	1-20%
Lake Tartarazine	1-10%
PVPK-30	1-15%
Purified Water	-
Cross Carmellose sodium	1-15%
Colloidal Silicon dioxide	1-15%
Magnesium Stearate IP	1-15%

Contents of SR layer	
Metformin HCl IP	45-90%
Microcrystalline Cellulose Plain IP	1-15%
Ethyl Cellulose IP	1-15%
Methylene dichloride	-
Iso Propyl Alcohol	-
Polymer (Methocel K-200M)	5-20%
Colloidal Silicon dioxide	1-10%
Magnesium Stearate IP	1-10%

Example 2(a):**Part A – Wet Granulation of Metformin Immediate Release layer.**

The ingredients required were weighed as per the weight mentioned above in **Table 1**. Accordingly, the weighed amount of Metformin HCl IP, Lactose Monohydrate, Microcrystalline Cellulose, Cross Carmellose sodium and Lake Tartarazine were dry mixed and passed through the mesh size 80 for appropriate size reduction. The contents were further added in Rapid Mixture Granulator (RMG). To the mixture was added solution of PVPK-30 in water and wet granulated to form granules. The granules were dried on Fluidized Bed dryer (FBD) followed by addition of Cross Carmellose sodium and Colloidal Silicon dioxide. The sample was tested for its assay and potency. When the quantitative test was observed to be positive, magnesium stearate was added to the mixture to yield metformin composition fit for instant release layer.

Part B – Wet Granulation of Metformin Sustained Release layer

The weighed amount of Metformin HCl and Microcrystalline Cellulose were dry mixed and passed through the mesh size 80 for appropriate size reduction. The contents were added in Rapid Mixture Granulator (RMG). To the mixture was added solution of Ethyl Cellulose in mixture of methylene dichloride and isopropyl alcohol and wet granulated to form granules. The granules were dried on Fluidized Bed dryer

(FBD) followed by addition of Methocel K-200M and silicon dioxide. The sample was tested for its assay and potency. When the quantitative test was positive, magnesium stearate was added to the mixture to yield metformin composition fit for sustained release layer.

Part C-Tablet manufacturing:

Each of the granules was then filled separately in the hopper of tablet compression machine and further the granules were compressed to form dual release bilayer tablet of appropriate size and texture.

Example 3: Pharmacokinetic comparison of different formulations of Metformin

Table 4:

Table 4 represents a comparative pharmacokinetic profile of various formulations of Metformin upon administration to healthy human volunteers in fed or fasted state. The

Brand Name	Generic Name	Strength	Type of dosage form	Fasting/Fed State	T0	T1	T0-T1	Cmax	Tmax	AUC
Glucophage	Metformin	750mg	SR	Fasted	2.3	6.4	4.1	787.7	4.4	5855
Glucophage	Metformin	750mg	SR	Fed	3.5	9.2	5.7	764	6.5	8445.8
<i>Maxformin</i>	<i>Metformin</i>	<i>750mg</i>	<i>Dual Release</i>	<i>Fasted</i>	<i>0.9</i>	<i>8.7</i>	<i>7.8</i>	<i>1223.3</i>	<i>4.5</i>	<i>9803.8</i>
	Metformin + Glimepride	500mg + 1mg	SR	Fasted	3.6	5.9	2.3	593.2	4.4	4940.9
	Metformin + Glimepride	500mg + 2mg	SR	Fasted	3.4	5.8	2.4	591.2	4.4	4935.5
Glucophage	Metformin	500mg	IR	Fasted	0.6	6.6	6	937.3	3	7138.2
	Metformin	500mg	IR	Fasted	0.4	7.8	7.4	1223.8	3	8371.9
	Metformin	500mg	IR	Fasted	0.6	6.5	5.9	963.9	3.1	7425.9
Glucophage	Metformin	500mg	IR	Fasted	0.7	5.2	4.5	901.6	2.5	5567.6
Glucophage	Metformin	500mg	IR	Fasted	0.7	5.1	4.4	901.6	2.5	5534
Glucophage	Metformin	1000mg	IR	Fasted	0.4	7	6.6	1475.8	2.5	9322.9
Glucophage	Metformin	1000mg	IR	Fasted	0.4	7	6.6	1449.3	2.5	8983

formulations were in the form of immediate release (IR) or sustained release (SR) as mentioned in table.

- T0: The time at which plasma Metformin concentration increases more than 500ng/ml. This time depicts the onset of action for metformin formulation.

- T1: Time by which plasma drug concentration falls below minimum effective concentration (MEC). After time T1 the therapeutic efficacy of formulation decreases.
- T1-T0: It is time for which formulation maintains plasma concentration in therapeutic range.
- Cmax is the maximum (or peak) concentration the drug achieves in plasma. It is expressed as ng or ug.
- Tmax is the time taken by drug to reach maximum (or peak) plasma concentration. It is expressed in minutes or hours.
- AUC: Area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug. It is expressed in mg*h/L. It is the measure of extent of absorption.

Example 4: Release profile

The tablet of example 1 was tested in simulated intestinal fluid (pH 6.8) according to the procedure mentioned in IP 14 and found to have the following release profile:

Table 5:

TESTS	SPECIFICATIONS	ANALYSIS(n=6)
For instant release layer		
After 30 minute	NLT 30 %	Min. 47.2% ; Max. 51.2% ; Avg. 49.3%
For sustained release layer		
After 1 hour	40 % to 65%	Min. 57.1% ; Max. 61.2% ; Avg. 59.2%
After 3 hour	60 % to 90%	Min. 83.0% ; Max. 86.1% ; Avg. 84.4%
After 10 hour	NLT 80 %	Min. 96.6% ; Max. 100.6% ; Avg. 99.1%
Assay (Metformin Hydrochloride IP)	675-825 mg (90.0-110.0% of label claim)	757.87 mg (101.05% of label claim)

We claim,

1. A dual release metformin bilayer tablet formulation comprising;
 - a. an instant release layer of Metformin or its acid addition salt in an amount 10-55% of total weight of the composition; and
 - b. sustained release layer of metformin or its acid addition salt in an amount 45-90% of total weight of the composition matrixed with release retarding polymer selected from hydroxypropyl methyl cellulose (K-200M) in an amount of 5-20% by weight of the composition;

wherein the instant release of metformin attains minimum effective concentration 500ng/ml in reduced lag time and the sustained release layer maintains the plasma concentration in therapeutic range 500ng/ml-1000ng/ml for a period of 7-8 hours as depicted in Table 3/Fig. 2 providing control of blood glucose level throughout the length of time.

2. The bilayer tablet formulation according to claim 1, wherein the ratio of metformin or its acid addition salt to the polymer in the sustained release layer is 5:1.
3. The bilayer tablet formulation according to claim 1, wherein said formulation, comprises binders, diluents, lubricants and other pharmaceutically acceptable excipients.
4. The bilayer tablet formulation according to claim 1, wherein the sustained release layer is arranged in contact with the instant release layer which is either completely enveloped by the immediate layer or only partially covered by it.
5. The bilayer tablet formulation according to claim 1, wherein the tablet is optionally coated.
6. The bilayer tablet formulation according to claim 1, wherein the instant release layer is a rapid disintegrating layer.

7. The bilayer tablet formulation according to claim 1, wherein the instant release layer comprises 75-410mg Metformin or its acid addition salt and other pharmaceutically acceptable excipients.
8. The bilayer tablet formulation according to claim 7, wherein the instant release layer comprises 250mg Metformin or its acid addition salt and other pharmaceutically acceptable excipients
9. The bilayer tablet formulation according to claim 1, wherein the sustained release layer comprises 337-675mg Metformin or its acid addition salt matrixed in release retarding polymer selected from hydroxypropyl methyl cellulose (K-200M) in the range of 5-20%w/w and other pharmaceutically acceptable excipients.
10. The bilayer tablet formulation according to claim 9, wherein the sustained release layer comprises 500 mg Metformin or its acid addition salt matrixed in release retarding polymer selected from hydroxypropyl methyl cellulose (K-200M) in the range of 5-20%w/w and other pharmaceutically acceptable excipients.
11. A process for preparing dual release metformin bilayer tablet formulation according to claim 1 comprising;
 - i. wet granulating metformin or its acid addition salt in the range of 10-55% of total weight of the composition along with pharmaceutically acceptable excipients in a solvent to obtain metformin granules for instant release layer;
 - ii. wet granulating metformin or its acid addition salt in the range of 45-90% of total weight of the composition matrixed with release retarding polymer selected from hydroxypropyl methyl cellulose (K-200M) in an amount of 5-20% by weight of the composition along with pharmaceutically acceptable excipients in a solvent to obtain metformin granules for sustained release layer; and
 - iii. ~~compressing the granules of step (i) and (ii) to obtain bilayer tablet.~~

12. The process according to claim 11, wherein the tablets are optionally coated.
13. The process according to claim 11, wherein the solvent is selected from polar protic or aprotic solvents.
14. A bilayer tablet formulation according to any of the preceding claims for therapeutic use for oral administration for treatment of Diabetes Type II.

I/II

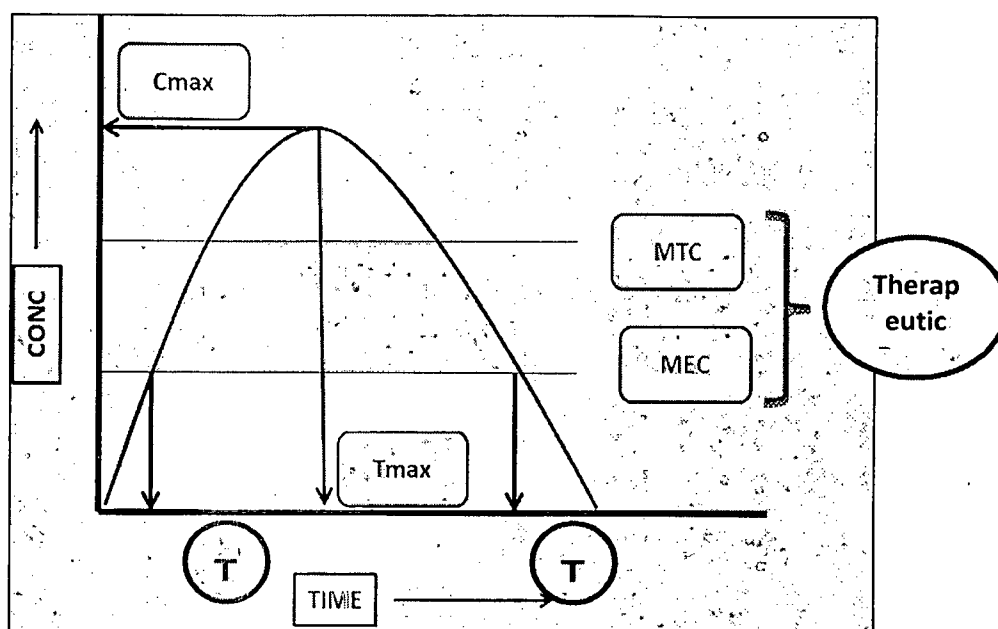


Fig 1

II/II

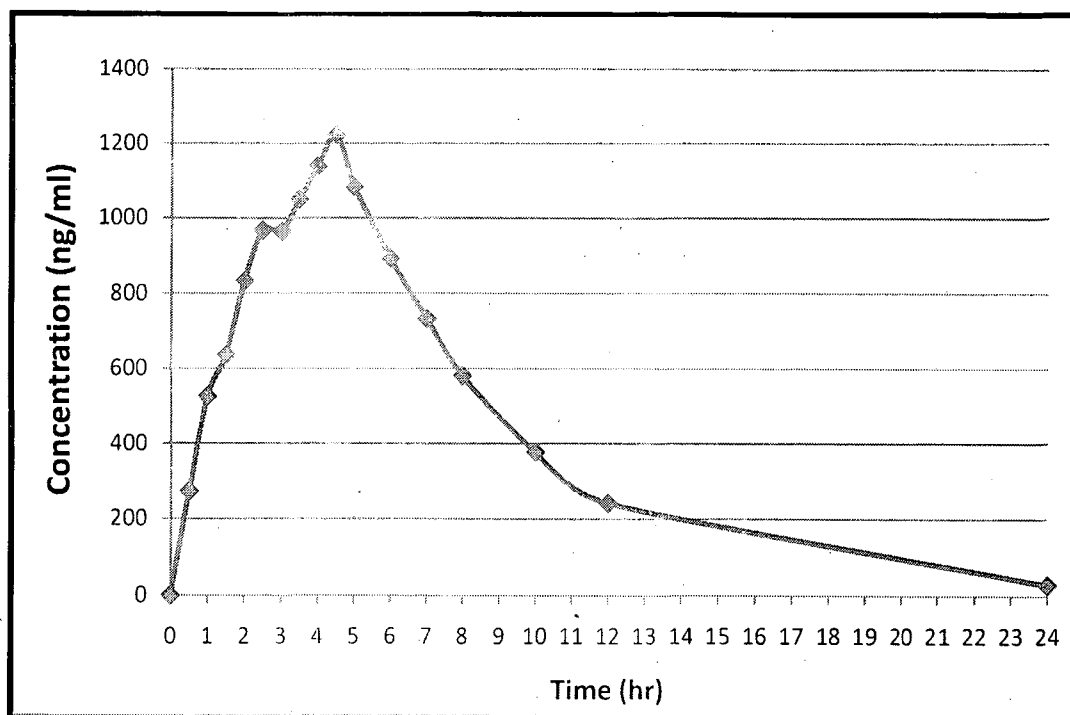


Fig 2