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Research Article

Formulation and Evaluation of Bilayered Tablets Containing Immediate Release Layer of Glimepiride Complexed with *Mangifera indica* Gum and Sustained Release Layer Containing Metformin HCL by Using HPMC as Release Retardant

Hemalatha S[1], Srikanth P[2], Mounica Sai G[2]

[1]*Department of Pharmacognosy, Sri Venkateswara college of Pharmacy, RVS Nagar, Chittor, Andra Pradesh*
[2]*Department of Pharmaceutics, Sri Venkateswara college of Pharmacy, RVS Nagar, Chittor, Andra Pradesh*

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ABSTRACT

In present investigation an attempt has been made to design and develop the Bilayered tablet of Glimepiride and Metformin using *Mangifera Indica* Gum (MIG) and HPMC as Immediate Release and Sustained Release Layer polymers. Glimepiride and Metformin are oral-hypoglycaemic drugs which lower blood glucose level and have been selected to prepare Bilayered tablets. Glimepiride immediate release layer was prepared using MIG by wet granulation technique and Metformin sustained release layer was prepared using HPMC by dry granulation technique. Prepared Bilayered tablets were evaluated for parameters like thickness, diameter, weight variation, hardness, friability, disintegration and in-vitro release studies. All the prepared tablets were of smooth surface and elegant texture. The weights of the tablets were in the range of 540±0.551 mg. The thicknesses of the tablet were in the range of 4±0.05mm. The drug content uniformity study showed uniform dispersion of drug throughout the formulation in the range of 97.16±0.50%. The hardness was in the range of 4.0±0.5 kg/cm^2 and friability is in the range of 0.67±0.06%. The bilayered tablets were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulation by treating the data according to zero-order, first-order, Higuchi and peppas equations.The bioequivalence studies conducted between prepared and marketed (Glycomate) bilayered tablet showed the similarity factor value of 70.120 for IR layer and 57.689 for SR layer.

Keywords: Bilayered tablets, Glimepiride, Metformin, Mangifera Indica Gum, HPMC.

INRODUCTION

Dual release tablets are unit compressed tablet dosage form intended for oral application. It contains two parts in which one part having conventional or immediate release part another one is sustained or controlled release part[1].

Bilayer tablets[2]

Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles which improves patient compliance, prolongs the drug action. Two layer tablets may be designed for sustain release, one layer for the immediate release of the drug and second layer for extended release thus maintaining a prolonged blood level. Layers may be colored differently to identify the product

Types of Bilayer tablet press[3]

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring

Formulation of Bilayered tablets[4]

Tablet is an solid dosage form which consist of one or more active ingredient with excipients, excipients are very important part of the tablet formulation, Excipients are pharmacologically inactive substances included in the formulation which is used as a carrier of active ingredient. Need of Bilayer Tablets For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/muco adhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.

MATERIALS

Materials used to prepare Bilayered tablet are procured. Glimepiride gift sample from RINI life sciences, Metformin was gift sample from Wanbury limited HPMC Rolex chemical industry and Acetone, IPA, Sodium hydroxide, Magnesium stearate, Chloroform, Lactose, SSG, Bromo cresol Blue, Potassium dihydrogen phosphate, Hydrochloric acid are procured from Spectrum reagent and chemical pvt. Ltd

Formulation of Bilayered Tablets[5]

Preparation of sustained release layer of Metformin with HPMC

**Author for Correspondence: kavyasahana21@gmail.com*

Table 1: Composition of Metformin Layer for Sustained Release.

S.no	Ingredients	Mg/tablet
1	Metformin	250
2	Hydroxy Propyl Methyl Cellulose	150
3	Poly Vinyl Pyrrolidone	65
4	Iso Propyl Alcohol	2%
5	Magnesium stearate	2

Table 2: Composition of Glimepiride Layer For Immediate Release.

S. no	Ingredients	Mg/tablet
1	Glimepiride	2
2	Lactose	15
3	Sodium Starch Glucose	9
4	*Mangifera indica gum*	5%
5	Magnesium stearate	2
6	Distilled water	Q.S
7	Bromo cresol blue	0.1

Table 3: Physico-Chemical Properties of Mig.

S:no	Parameter	Observation
1.	Solubility	Soluble in water, practically insoluble in ethanol, acetone& chloroform
2.	Loss on drying	6.25%
3.	pH determination	7.7
4.	Angle of repose	26.75^{o}

Table 4: Precompression Parameters For Granules.

S:no	Parameter	Observation
1.	Angle of repose (Θ)	24.14^{0}
2.	Compressibility index or Carr's index (%)	16.42
3.	Hausner's ratio	1.19

The dose of Metformin HCI for sustained release was fixed as 250mg.

The sustained release layer of Metformin HCI was prepared by dry granulation technique.

Then Metformin, HPMC were sifted and mixed in mortar and pestle for 5 min.

PVP K-30 was dissolved in mixture of IPA.

Then above mixture with binder PVP K-30 solution was granulated. The granules were dried in tray dryer at 65°C.The granules were passed +through mesh no. 20#.

Finally mixture was lubricated with magnesium stearate for 2 min.

Preparation of immediate release layer of Glimepiride with Mangifera indica gum[6]

Procedure for Preparation of Mangifera indica gum

The mango gum was dried and hydrated in distilled water for one day with intermittent stirring; extraneous materials were removed by straining through a muslin cloth. The gum was precipitated from solution using absolute acetone. The precipitate was separated and dried on water bath at 50°C. The dried gum was pulverized using a laboratory blender and stored in tightly closed container.

Procedure for preparation of immediate release layer

Glimepiride and other excipients mentioned in table no:5 were passed through sieve no. 20 # and thoroughly mixed in a blender approximately for 5 min.

The Bromo cresol Blue was passed through sieve No. 20 # and added to above mixer.

The whole blend was lubricated for 2 min with Magnesium Stearate which was already passed through sieve no. 20 #.

Sodium starch glycolate was used as super disintegrant.

After preparing the granules for Metformin and Glimepiride layers are punched into a Bilayered tablet using 16 stationed Single Rotary Tablet press (Karnavathi model).

Preparation of Calibration Curve

Preparation of standard graph of Metformin using distilled water

Beer's law is obeyed in the concentration range of 5-25mcg/ml

Method

100 mg of Metformin was accurately weighed into 100ml volumetric flask and dissolved in distilled water. The volume was made up to 100 ml to get a concentration of (1mg/ml) stock solution-I from this 10ml was withdrawn and diluted to 100ml to get a concentration of (100µg/ml) stock solution-II. From stock solution- II prepare concentrations of 2, 4, 6, 8, 10 µg/ml by taking 0.2, 0.4, 0.6, 0.8 and 10 ml from above stock respectively and make up to 10ml.

Scanning of drug

UV scan range was taken between the wavelengths 200-400 nm. It gave a peak at 231nm and calibration curve was plotted between drug concentration and absorbance value.

Preparation of standard graph of Glimepiride using chloroform[7]

10mg of Glimepiride drug is taken into 100ml volumetric flask and ur chloroform solvent up to the mark. This stock solution concentration is 100µg/ml.

To prepare 5,10, 15, 20, 25 µg/ml concentration. Take o.5, 1, 1.5, 2, 2.5 ml into 10ml volumetric flask and make up to mark with chloroform.

Scanning of drug

UV scan range was taken between the wavelengths 200-400 nm. It gave a peak at 249nm and calibration curve was plotted between drug concentration and absorbance value

Evaluation of Characteristics of Mangifera Indica Gum[8]

Solubility test

The separated gum was evaluated for solubility in water, acetone, chloroform and ethanol in accordance with the B.P. specifications.

Loss on drying

The method adopted was that specified in the B.P. for acacia. 1.0 g of the sample was transferred into each of several Petri dishes and then dried in an oven at 105°C until a constant weight was obtained. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage.

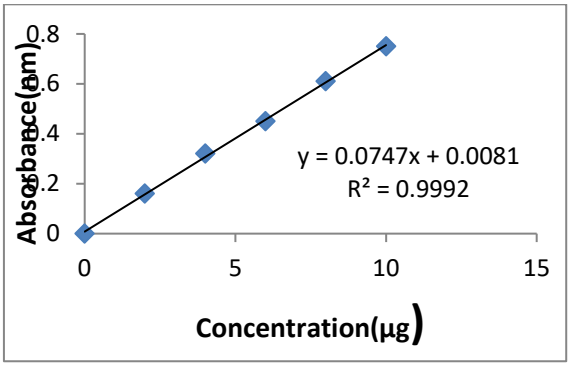
pH determination

Table 5: Surface Characteristics Of Bilayered Tablets.

S:no	Test	Observation	Inference
1.	Surface roughness	Smooth	Passes the test
2.	Crack	Absent	Passes the test
3.	Depression	Absent	Passes the test
4.	Pin holes	Absent	Passes the test
5.	Colour	Uniform	Passes the test
6.	Polish	Uniform	Passes the test

Table 6: Evaluation of Bilayered Tablets of Glimepiride and Metformin HCl.

S.no:	Parameters	Observation	Inference
1.	Thickness (mm)	4±0.05	Passes the test
2.	Diameter (mm)	12±0.04	Passes the test
3.	Hardness (kg/cm^2)*	4.0±0.5	Passes the test
4.	Friability (%)	0.67±0.06	Passes the test
5.	Weight variation test (mg)**	540±0.55	Passes the test
6.	Content uniformity test (%)$^@$	97.16±0.50	Passes the test
7.	Disintegration time for IR layer (min)*	<15	Passes the test
8.	Disintegration time for SR layer (min)*	112	Passes the test



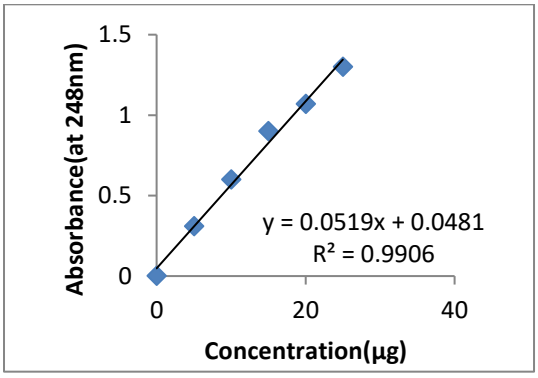


Figure 1 a) Calibration curve of Metformin 1b) Calibration curve of Glimepiride.

Table 7: Bioequivalence Data for IR Layer.

S:no	Time	%Cumulative drug release	
		Prepared(a)	marketed(b)
1.	0	0	0
2.	5	51.8	49.2
3.	10	85.8	78.6
4.	15	98.54	98..23

$F_2 = 50x\log\{[1+(1/n)\Sigma_{t=1}\ n(a-b)^2]^{-0.5}x100\}$
=70.120

This was done by shaking a 1% w/v dispersion of the sample in water for 5 min and the pH determined using a digital pH meter.

Angle of repose

The static angle of repose (θ), was measured according to the fixed funnel and free standing cone method. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the equation: tan θ= 2h/D

Phytochemical examination

Preliminary tests were performed to confirm the nature of gum obtained. The chemical tests that were conducted are: Ruthenium red test, Molisch tests, test for reducing sugars.

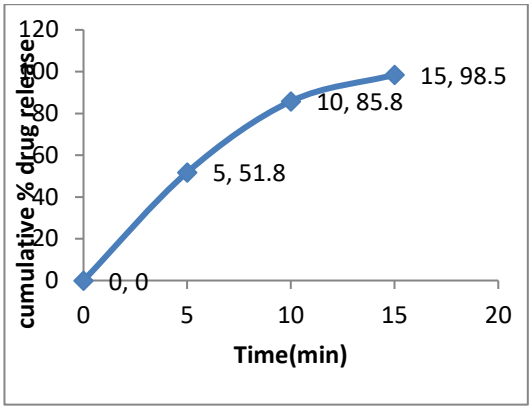
RESULTS AND DISCUSSION

Standard Calibration curve of Metformin

Standard calibration curve of Metformin was drawn by plotting absorbance v/s concentration. The absorbance values were tabulated in table. Standard calibration curve of Metformin in the Beer's range between 2-10 µg/ml is shown in Fig.1 a

Standard Calibration curve of Glimepiride

Standard calibration curve of Glimepiride was drawn by plotting absorbance v/s concentration. The absorbance values were tabulated. Standard calibration curve of



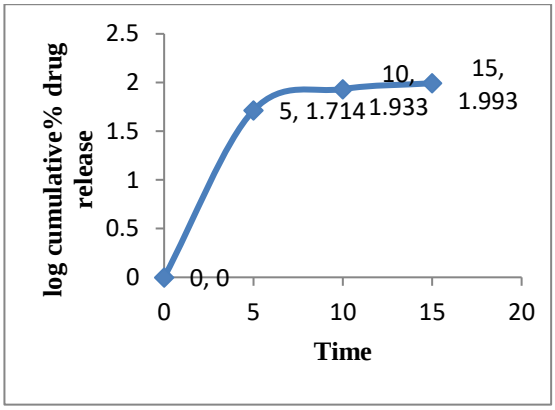
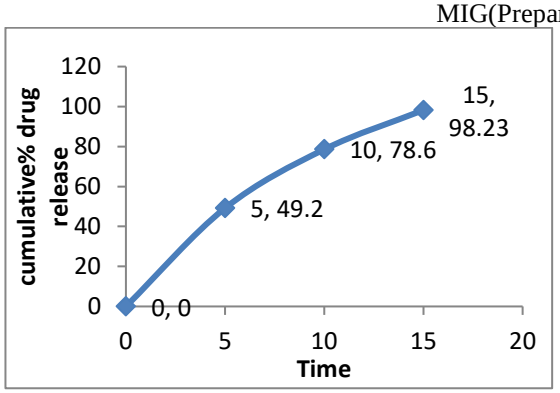


Figure 2 a) :Zero order release of IR layer with MIG(Prepared Bilayered Tablet) b) First order release of IR layer with MIG(Prepared Bilayered Tablet)



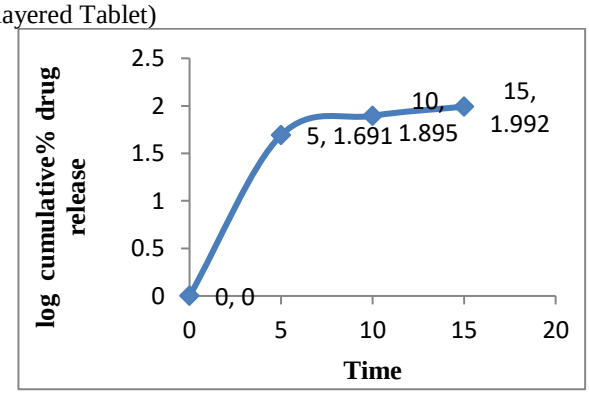
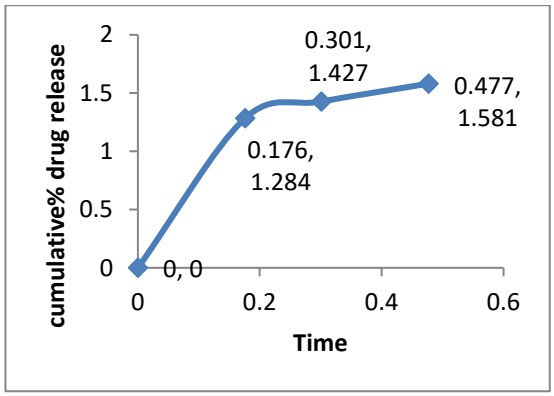


Figure 3 a): Zero Order Release Of IR Layer Of Marketed Preparation b) first Order Release Of IR Layer Of Marketed Preparation.



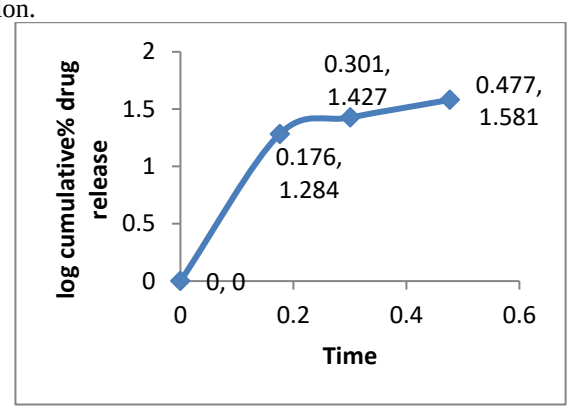


Figure 4 a): First Order Release Of Sr Layer Of Laboratory Preparation b) First Order Release Of Sr Layer Of Laboratory Preparation.

Glimepiride in the Beer's range between 5-25 µg/ml is shown in Fig.1b

Evaluation of Characteristics of Mangifera Indica Gum

Phyto-chemical screening of MIG

Phytochemical tests carried out on *Mangifera indica gum* confirmed the absence of alkaloids, glycosides and tannins. On treatment of mucilage with ruthenium red, it showed red colour confirming the obtained product as gum. A violet ring was formed at the junction of two liquids on reaction with Molisch's reagent indicating the presence of carbohydrates. Gum could reduce Fehling's solution, so the sugars present were reducing sugars. The results of phytochemical screening of gum are summarized in Table No.3

Table 3: Phytochmeical Screening of MIG

Physico-chemical properties of MIG

The MIG is soluble in water and practically insoluble in ethanol, acetone and chloroform. The pH , loss on drying and Angle of repose were also determined and tabulated.

Evaluation of Pre Compression Parameter

The Blend was evaluated for % Compressibility index, Hausner's ratio and Angle of repose and tabulated.

Evaluation of Bilayered Tablets For Physico-Chemical Characteristics

Appearance

The surface Morphology was inspected visually and its characteristics were tabulated below.

Tablet dimensions

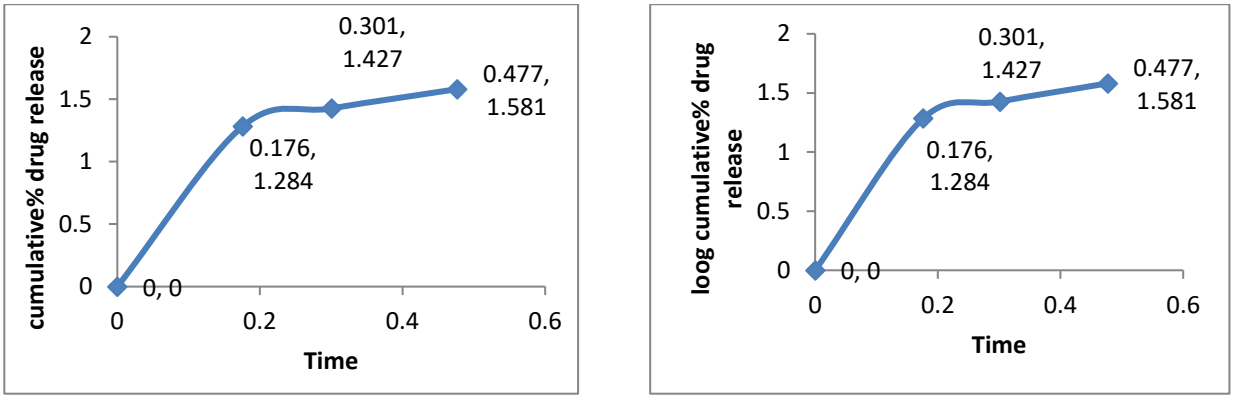


Figure 5 a): Zero Order Release of SR Layer Of Marketed Preparation b) First Order Release Of SR Layer Of Marketed Preparation.

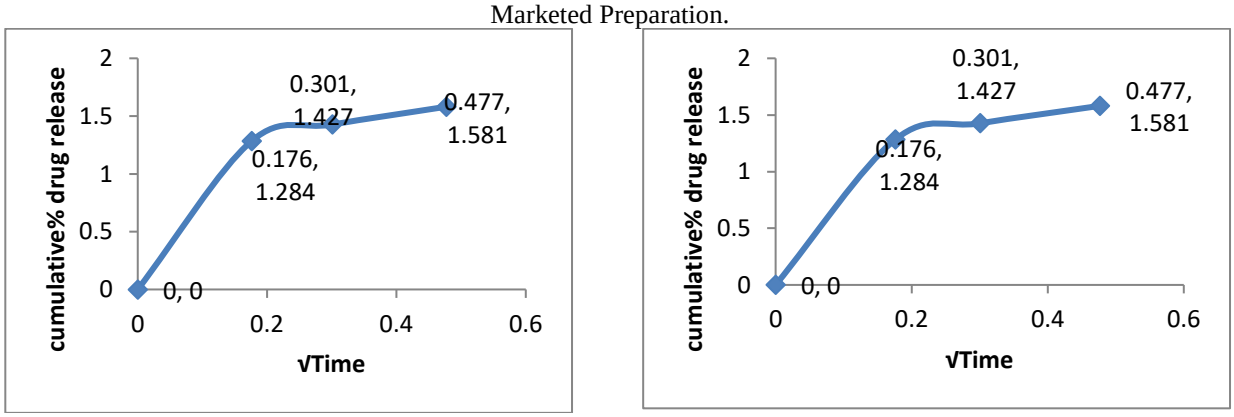


Figure 6 a): Higuchi Kinetics for SR Layer Of Prepared Bilayered Tablet b) Higuchi Kinetics For SR Layer Of Marketed tablet.

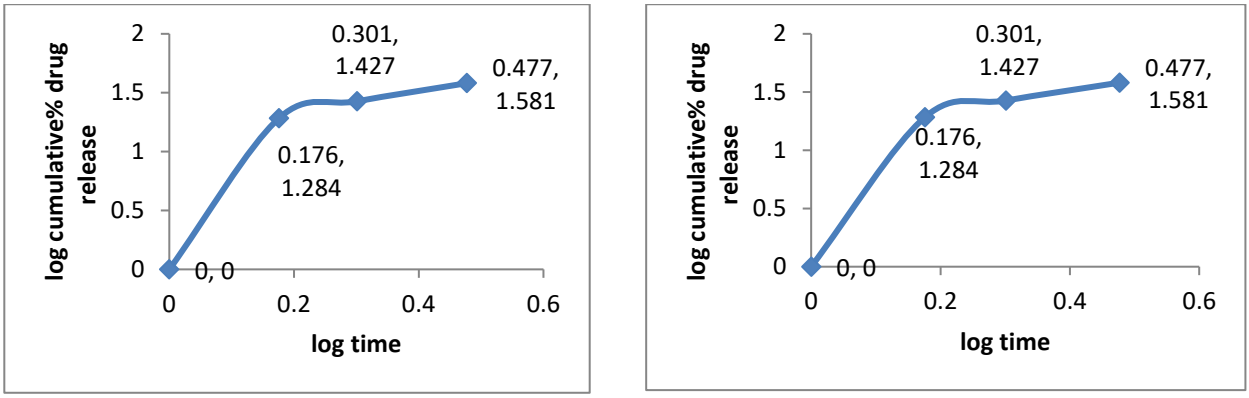


Figure 7 a): Korsemeyer peppas kinetics for prepared Bilayered tablet b) Korsemeyer Peppas Kinetics Of SR Layer Of Marketed Tablet.

The tablet dimensions were calculated and found to be within the I.P. limits using Vernier calliper's and values obtained are tabulated.

Hardness

The hardness of the tablet formulations was found to be in the range of 4.0±0.5kg/cm^2 using Pfizer hardness tester and values obtained are tabulated.

Friability

The friability values were found to be in the range of 0.67±0.06% using Roche friabilator and values obtained are tabulated.

Weight variation test

The prepared Bilayer tablets of Glimepiride and Metformin HCl were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±5% and values are tabulated.

Content uniformity test

Percent drug content of the bilayered tablet was found to be 98.24%(which was within the acceptable limits of ±5%) and values are tabulated.

Disintegration test

The disintegration test was performed accordingly by maintaining pH 0.1N Hcl for first 15 minutes and pH 6.8 phosphate buffer for rest of the test and the values were found to be within the range of I.P. limits and values are tabulated.

*n=6,**n=20, @n=3

In vitro dissolution study In vitro dissolution studies were performed for IR, SR layers. In the dissolution studies the

Table 8: Bioequivalence Data For SR Layer.

S:no	Time	%Cumulative drug release	
		Prepared(a)	marketed(b)
1.	1.5	20.16	19.27
2.	2	32.64	26.74
3.	3	46.47	38.13
4.	4	58.72	46.16
5.	6	68.22	57.18
6.	8	79.34	75.20
7.	10	88.92	87.74
8.	12	98.73	98.18

$F_2 = 50x\log\{[1+(1/n)\Sigma_{t=1}\ n(a-b)^2]^{-0.5}x100\}$
=57.689

MIG showed a better drug release within 15 min while HPMC showed a better drug release upto 12 hrs.

The above Zero order drug release pattern (Fig no: 2a) for Immediate release layer of Glimepiride with MIG of prepared tablet was plotted in above graphical representation and found to be within limits. The above First order drug release pattern(Fig no:- 2b) for Immediate release layer of Glimepiride with MIG of prepared Bilayered tablet was plotted in above graphical representation and found to be within limits.

Invitro drug release profile of Glimepiride IR layer of marketed preparation

The above Zero order drug release pattern (Fig no:- 3a) for Immediate release layer of Marketed Bilayered tablet was plotted in above graphical representation and found to be within limits.The above First order drug release pattern (Fig no:- 3b)for Immediate release layer of Marketed Bilayered tablet was plotted in above graphical representation and found to be within limits

Invitro drug release profile of Metformin with HPMC

The above Zero order drug release pattern (Fig no:- 4a) for Sustained release layer of Prepared Bilayered tablet was plotted in above graphical representation and found to be within limits.The above First order drug release pattern Fig no:- 4a) for Sustained release layer of Prepared Bilayered tablet was plotted in above graphical representation and found to be within limits.

Invitro drug release profile of Metformin SR layer of Marketed preparation

The above Zero order drug release pattern(Fig no:- 5a) for Sustained release layer of Marketed Bilayered tablet was plotted in above graphical representation and found to be within limits.The above First order drug release pattern(Fig no:- 5b) for Sustained release layer of Marketed Bilayered tablet was plotted in above graphical representation and found to be within limits.

Model-Dependent Approaches Release Kinetics

To know the drug release kinetics from the prepared formulation, the dissolution data was subjected to different kinetic model such as Higuchi's square root kinetics model and Korsemeyer peppas model

Higuchi Model For Sr Layer

Higuchi model for prepared Bilayered tablet

The dissolution data was subjected to Higuchi's square root kinetics model and the above graphical representation (Fig no:- 6a) of sustained release layer of prepared Bilayered tablet shows better invitro drug release pattern.The dissolution data was subjected to Higuchi's square root kinetics model and the above graphical representation(Fig no:- 6b) of sustained release layer of Marketed Bilayered tablet shows better invitro drug release pattern.

Korsemeyer Peppas Model for Sr Layer

Korsemeyer peppas model for prepared Bilayered tablet

The Korsemeyer peppas kinetics model was plotted between log cumulative% drug release and log time (Fig no:- 7a) of sustained release for prepared Bilayered tablet and was found to be within the limits. The Korsemeyer peppas kinetics model was plotted between log cumulative% drug release and log time (Fig no:- 7b) of sustained release for Marketed Bilayered tablet and was found to be within the limits

Bioequivalence

To determine the bioequivalence between prepared tablet and marketed preparation, the similarity factor was determined accordingly and the similarity between the IR layer was found to be more such that the MIG achieved a better performance in its dissolution profile.

DISCUSSION

The standard calibration curve for Metformin and Glimepiride was calibrated and the regression value was within the limits and it obey the Beer's law.

The phyto-chemical and physico-chemical properties of Mangifera indica gum shows presence of Mucilage, Carbohydrates, Reducing sugar and its solubility is good in water and insoluble in ethanol, acetone, and chloroform.

The pre-compression parameters were within the limits.

The surface characteristics of prepared Bilayered tablets were evaluated visually found to be elegant and no cracks were found.

The thickness, diameter, hardness, friability, weight variation, content uniformity, and disintegration test were found to be within the limits according to I.P.

The dissolution profile of Glimepride IR layer and Metformin SR layers was given in graphical representation, which showed maximum drug release.

The drug release kinetics was graphically represented from above Invitro dissolution data were subjected to different kinetic model such as Zero order and Higuchi's square root kinetics and Kosemeyer's peppas model and release

kinetics was interpreted for both prepared and marketed Bilayered tablets.

The Bioequivalence was determined for Immediate release layer and Sustained release layer of Prepared and Marketed Bi-layered tablets, the data was tabulated and the similarity factor was within the range of 50-100. Therefore results confirm the presence of bioequivalence between the analyzed brand and Prepared product

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