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

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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/cm² 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.

INTRODUCTION
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 part¹. Bilayer tablets²

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 press³

2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring Formulation of Bilayered tablets⁴

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 Tablets⁵
Preparation of sustained release layer of Metformin with HPMC

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The mango gum was dried and hydrated in distilled water with Mangifera indica gum. Then above mixture with binder PVP K30 was dissolved in mixture of IPA. Then above mixture with binder PVP K30 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**

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 5-25 mcg/ml

**Method**

100 mg of Metformin was accurately weighed into 100 ml 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 10 ml was withdrawn and diluted to 100 ml 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 10 ml.

**Scanning of drug**

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

*Preparation of standard graph of Glimepiride using chloroform*

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

To prepare 5, 10, 15, 20, 25 µg/ml concentration. Take 0.5, 1, 1.5, 2, 2.5 ml into 10 ml 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 249 nm and calibration curve was plotted between drug concentration and absorbance value.

**Evaluation of Characteristics of Mangifera Indica Gum**

*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**
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:  
\[
\tan \theta = \frac{2h}{D}
\]

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 7. Standard calibration curve of Metformin in the Beer’s range between 2-10 µg/ml is shown in Fig.1a

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...
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: Phytochemical 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**

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![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)](image)

![Figure 3 a): Zero Order Release Of IR Layer Of Marketed Preparation b) first Order Release Of IR Layer Of Marketed Preparation.](image)

![Figure 4 a): First Order Release Of Sr Layer Of Laboratory Preparation b) First Order Release Of Sr Layer Of Laboratory Preparation.](image)
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/cm² 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

![Figure 5 a): Zero Order Release of SR Layer Of Marketed Preparation b) First Order Release Of SR Layer Of Marketed Preparation.](image5.png)

![Figure 6 a): Higuchi Kinetics for SR Layer Of Prepared Bilayered Tablet b) Higuchi Kinetics For SR Layer Of Marketed tablet.](image6.png)

![Figure 7 a): Korsemeyer peppas kinetics for prepared Bilayered tablet b) Korsemeyer Peppas Kinetics Of SR Layer Of Marketed Tablet.](image7.png)
MIG showed a better drug release within 15 min while HPMC showed a better drug release up to 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 Glimepride 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:- 4b) 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**

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**

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 Ko semeyer’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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