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EVALUATION OF SUSTAINED RELEASE BILAYER TABLETS OF METFORMIN HYDROCHLORIDE AND GLIMEPRIDE

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ABSTRACT

The present research work was aimed to establish bi layer tablets containing Metformin HCl as sustained release and Glimepiride as immediate release layer for diabetes therapy. Sustained layer of the tablet were prepared by wet granulation method using different polymers of HPMC K 100M and ethylcellulose as bio adhesive polymers and immediate release layer were prepared by direct compression using super disintergrants such as sodium starch glycolate. Tablets were evaluated for both pre compression and post compression parameters. In-vitro drug release from the formulations was studied by dissolution method. The result showed that optimization of polymers namely HPMC and Ethyl cellulose in sustained layer can control the release of drug. The physico – chemical property of the finished product complies with the standard limit. The obtained were fitted into higuchi's models, zero order, first order and korrsmeyer-peppas. The present study concluded that bi-layer of Glimepride and Metformin HCL can have a good to extent metabolism and as an alternative to the conventional dosage form.

KEYWORDS: Metformin HCl, Glimepiride, bi layer tablets, super disintergrants.

INTRODUCTION

Now a days various developed and developing countries move towards combination therapy for the treatment of various diseases and disorders requiring long term therapy such as diabetics. Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects is minimized, a low dose combination of two different effects of the other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet.[1]

Bi layer tablets are novel drug delivery system where combination of two or more drugs in a single unit having different release profiles which improves patient compliance, prolongs the drug(s) action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug levels.[2]

Diabetes mellitus is probably one of the oldest diseases for clinicians since centuries. It was first reported in Egyptian manuscript about 3000 years ago.[3] In 1936, the distinction between type I and type II diabetes mellitus was clearly made.[4] Type II diabetes mellitus was first described as a component of metabolic syndrome in 1988.[5] diabetes mellitus is the most common form which is characterize ed by hyperglycemia, insulin resistance, and relative insulin deficiency.[6] Type II diabetes results from interaction between genetic, environment and behavioural risk factors.[7,8]

Because of the chronic nature of diabetes, the relentlessness of its complications and the means required to control both diabetes and its complications; this disease is very costly not only for affected individuals and families but also for the healthcare systems. Studies done in India estimates that for a low income family with an adult having diabetes, as much as 25% of the family's income may need to be devoted to diabetes care.[9]

Metformin hydrochloride is an oral biguanidine one of the most frequently prescribed oral antidiabetic drugs for the treatment of Type 2 diabetes mellitus. It is recommended as the first line choice in overweight Type 2 diabetic mellitus patients who have failed diet control. Metformin hydrochloride lowers fasting and postprandial plasma glucose levels primarily by reducing elevated rates of hepatic gluconeogenesis in patients with type 2 diabetes and also by reducing intestinal glucose absorption. Glucose disposal in peripheral tissues may also be increased with metformin, resulting in improve insulin sensitively. Metformin hydrochloride may also protect β-cell function.[10]

Metformin hydrochloride has a oral bioavailability of 50-60% under fasting conditions, and is absorbed slowly, Peak plasma concentrations (C_{MAX}) are reached within 4

to 8 hours with extended – release formulations. The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution (300-1000 L after a single dose). Steady state is usually reached in one or two days, Metformin hydrochloride is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine. The average elimination half life in plasma is 6.2 hours.[10]

Glimepiride is a prescription drug of the class sulfonylureas increases insulin sensitivity. It has poor solubility, and half life is about 5-8 hours which is extensively metabolized in liver and having extensive protein binding (>99.5%).

Metformin hydrochloride is a biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, reduces hepatic gluconeogenesis and improves peripheral glucose uptake. It is slowly and incompletely absorbed from GI Tract, with its absolute bioavailability reported to be about 50 to 60%. It is freely soluble in water. A traditional oral multiple release formulation releases the drug with undesired peaks and troughs. These drawbacks can be overcome by designing a suitable sustained release metformin preparation.

Both the agents reduce hyperglycemia and hyperinsulinemia, and appear to protect ß cell function. Their similar pharmacokinetic time profiles have facilitated a co- formulation bioequivalence to their separate administration.

Based on the consideration the present study purposed to formulate bi-layer of metformin hydrochloride as sustained release layer and glimepiride as immediate release layer using hydrophilic polymers and superdisintegrants for oral immediate and sustained delivery with improved bioavailability for diabetes therapy.

MATERIALS AND METHODS

Glimepiride and Metformin were received as gift samples from Syskeme pharmacocrats. Hydroxy propyl methyl cellulose, Ethyl cellulose, Polyvinylpyrolidone, Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, Lactose, Isopropyl alcohol and other chemicals were obtained from Loba chemie Pvt.Ltd, Mumbai.

Pre- formulation studies

Fourier transformer infrared spectrometric method (FTIR)

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients, drug excipients mixture was subjected to FTIR studies using Schimadzu FTIR spectrometer model to investigate the Drug – excipient interaction. The IR spectra of the test samples were obtained by pressed pellet technique using potassium bromide and the ratio of sample 1: 100.[11,12]

Construction of standard curve for Glimepiride

10mg of pure glimepiride was accurately weighted and transferred to 100ml volumetric flask, 30ml of 0.1 M sodium hydroxide was added, and the mixture was sonicated it dissolve and make up the volume with methanol. Aliquots of these standard solution was transferred using A- grade bulb pipette into 100ml volumetric flaks and made up to volume with methanol to get final concentration of 6.0 – 14.0 µg/ml. The absorbance of above solution was measured at 225nm using methanol as blank and plotted to get the calibration curve.

Construction of standard curve for Metformin HCL

20mg of metformin was dissolved in 100ml phosphate buffer pH6.8. From the stock solution aliquots of 1, 2, 3,4,5,6 ml were pipette out and made up to 100ml with buffer. The absorbance of above solution was measured at 233nm using phosphate buffer as blank and plotted to get the calibration curve. Correlation coefficient value indicates there is a linear correlation between concentration and absorbance. Metformin obeys the beers law in concentration range of 2- 12 µg/ml.

Preparation of bi-layer tablets

Formulation of immediate release Glimepiride

Immediate releasing layer containing 1mg of drug is prepared by direct compression method employing sodium starch glycolate as superdisintegrants.

Direct compression method

1. Glimepiride and other excipients sifted through sieve no 40# and thoroughly mixed in a blender approximately for 5min.
2. Above mixer was lubricated for 2min.with magnesium stearate which was already passed through sieve 60
3. For all formulations sodium starch glycolate was used as superdisintegrants.

Formulation of sustained release Metformin Hydrochloride

sustained layer containing 500mg of drug is prepared by wet granulation method employing HPMC and ethyl cellulose as rate controlling polymers, lactose and microcrystalline cellulose as diluent, magnesium stearate as glidant and lubricant and PVP as binder.

Wet granulation method

1. Metformin HCl, microcrystalline cellulose, lactose, HPMC and ethyl cellulose were sifted through sieve no40#. Then the above sifted materials were mixed in rapid mixer granulator for 5mins.
2. PVP was dissolved in mixtures of isopropyl alcohol. Then above mixture with binder PVP was granulated at impeller at 200rpm.
3. one to two minute binder addition and three min kneading without chopper was used to get desired granules.

4. Drying of wet granules was carried out in rapid dryer at temperature 50^0C and air flow at 60%.
5. Final dried granules were passed through screen 20.
6. Finally mixture was lubricated with magnesium stearate for 2 min.

Preparation of bi-layer tablets formulation

Final bi-layer tablets were compressed by as one layer only for glimepiride and second layer for metformin. The tablet was compressed as a bi-layer tablet using both glimepiride and metformin granules. In this glimepiride were introduced first into the die cavity and a slight precompression was made so that layer was uniformly distributed after that metformin granules were added and final compression was made.

Table 3: Composition of Glimepiride as immediate release layer.

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1.	Glimepiride	1	1	1	1	1	1	1	1
2.	Sodium starch glycolate	6	8	10	12	6	8	10	12
3.	Microcrystalline Cellulose	65.5	52	79	42	67	49	82	47
4.	Lactose	75.5	89	62	99	73	91	58	93
5.	Povidone	6	6	6	6	6	6	6	6
6.	Magnesium stearate	2	2	2	2	3	3	3	3
	Total weight	150	150	150	150	150	150	150	150

Table 4: Composition of Metformin as sustained release layer.

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1.	**Metformin hydrochloride**	500	500	500	500	500	500	500	500
2.	**Microcrystalline Cellulose**	200	168	136	104	200	168	136	104
3.	**Ethyl cellulose**	68	100	132	164	-	-	-	-
4.	**HPMC K100M**	-	-	-	-	68	100	132	164
5.	**Povidone**	24	24	24	24	24	24	24	24
6.	**Magnesium stearate**	8	8	8	8	8	8	8	8
7.	**Isopropyl alcohol**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total weight	800	800	800	800	800	800	800	800

Physico- Chemical Evaluation of Bi-Layer Tablets

Pre-compression parameters[13,14,15,16]

Angle of repose

The flow property was determined by measuring the angle of repose. It is the maximum angle that can be obtained between the freestanding surface of powder heap and the horizontal plane. Values of θ are rarely less than 20^o, and values of upto 40^o indicate reasonable flow potential. Above 50^o, however, the powder flows only with difficulty if at all.

$$\Theta = Tan^{-1} (h/r)$$

Where,
h = height the pile
r =radius of the pile
θ =angle of repose

5 grams of the sample was taken in a funnel fixed in a holder, 6cm above the surface at an appropriate height and a graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined using the above formula. This was repeated 3 times for a sample.

Determination of bulk density and tapped density

A quantity of 20 g of the powder (W) from each formula was introduced into a 100ml measuring cylinder. After the initial volume was observed, the cylinder was a allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density and tapped density were calculated using the following formulas:

Bulk density = W/V_0

Tapped density = W/V_f

Where,

W =weight of the powder
V_0 = initial volume
V_f = final volume

Compressibility index

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having a value less than 18% is defined as the free flowing material.

$$C_1 = 100 (V_0 - V_f)/V_0$$

Where, C_1 = compressibility index

Table 4: Standard values of compressibility index.

% Comp. Index	Properties
5-12	Free flowing
12-18	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's ratio[17,18,19]

It indicated the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's ratio = $(W/V_f)/ (W/V_0)$

Where,

W/V_f = tapped density

W/V_0 = bulk density

Thus, Hausner's ratio = tapped density/bulk density.

Table 5: Standard values for Hausner's Ratio.

S.No	Hausner's ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive powder

Post –Compression Parameters

Hardness test

Hardness test was carried out by using vankel (VK 200) hardness tester. Three tablets were used for each formulation in the hardness test.

Thickness

Ten tablets were selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurements.

Friability

Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. Compressed tablets that loose less than 0.5% to 0.1% in weight are generally considered acceptable.[55,67]

Method: 6.5 gm of tablets were transferred into friabilator and subjected to 100 revolutions in 4 minutes. Dedusted tablets were reweighed (final wt). Friability was calculated as below formula.

$$\text{Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablet}}{\text{Final weight of the tablets}} \times 100$$

Weight variation test

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights should deviate from the average weight by more than the percentage deviation shown in tablet and none should deviates by more than twice the percentage.[20,21]

Table 6: Weight variation tolerances for uncoated tablets.

S. No	Average weights of tablets	Maximum percentage difference allowed
1.	130 or less	10
2.	130 to 324	7.5
3.	More than 324	5.0

% Maximum positive deviation = $(W_H - A/A) \times 100$

% Minimum negative deviation = $(A - W_L/A) \times 100$

Where,

W_H = highest weight in mg

W_L =lowest weight in mg

A = average weight of tablet in mg.

Drug content uniformity[22,23]

Drug content of bi-layer tablet for glimepiride

Preparation of buffer

Dissolve 1.5gm of potassium di hydrogen phosphate in 500ml of distilled water. Adjusted the pH with phosphoric acid.

Preparation of mobile phase

Prepare a mixture of buffer and acetonitrile in the ratio of 800: 200 respectively. Degas for 15minutes and filter the mobile phase through 0.22µ filter.

Diluents: 0.1 M Methanolic hydrochloride.

Chromatographic conditions

Column: waters symmetry C_8 (100mm X4.0mm), 5 µ or Equivalent

Flow rate: 1.0ml/minute

Wavelength: 276nm

Injection volume: 20 µl

Column temperature: 40^0C

Standard preparation

Weigh accurately about 50mg of glimepiride to 100ml volumetric flask, add 50ml of diluent to dissolve with the aid of ultrasound and make volume with diluents. Transfer 10ml of this solution to 50ml volumetric flask and make volume with diluents.

Sample preparation

Crush the content of 20 tablets to a fine powder and weigh accurately quantity of powder equivalent to about 5 avg weight (equivalent to 5mg of glimepiride) of tablet to a 50ml volumetric flask, add 25 ml of diluents to dissolve with the aid of ultrasound and make volume with diluents. Filter the solution through whatmann filter paper no.1.

Calculation

The percentage of glimepiride present in the tablet can be calculated by using the formula

At / As × Ws/100 × 5/50 × 5/10 × 250/Wt × 100/5 × 10/5 × Purity/100

x1115.32/1155.4

Where,
A_t =absorbance of sample preparation
A_s = absorbance of standard preparation
W_s = weight of pure glimepiride taken
W_t = weight of tablets taken

Drug content of bi-layer tablet for metformin HCL
Preparation of phosphate buffer pH 6.0
Weigh accurately about 6.8 gm of potassium di hydrogen orthophosphate in 1000ml beaker, add sufficient water to dissolve and make up the volume with water. Adjust pH 6.0 with 1M sodium hydroxide.

Standard preparation
Weigh accurately about 50mg of metformin HCL in 100ml volumetric flask, add 50ml of phosphate buffer pH-6 to dissolve with the aid of ultrasound and make volume 100ml with phosphate buffer pH-6. Transfer 1ml of this solution to 100ml volumetric flask and make volume 100ml with phosphate buffer pH-6.

Sample preparation
Crush the content of 20 tablets to a fine powder and weigh equivalents to 50 mg of metformin HCL to 100ml volumetric flask, add 50ml of phosphate buffer pH-6.0 to dissolve with the aid of ultrasound and make the volume 100ml with phosphate buffer pH-6.0. Filter the solution through whatmann filter paper no (1). Transfer 1ml of this solution to 100ml volumetric flask and make volume 100ml with phosphate buffer pH-6. Measure the absorbance of standard and sample solution at about 254nm using phosphate buffer pH 6.0 as a blank in the reference cell.

Disintegration test
The disintegration time was measured by using USP disintegration test apparatus. Six tablets were placed in tubes and the basket was kept positioned in a 1litre beaker of pH 1.2 phosphate buffer maintained at 37^0C ± 0.5^0C. The tablet remain 2.5cm from the bottom of medium, a standard motor driven move the basket containing tablet up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute.

***In-Vitro* Release Studies for Bi-Layer Tablet of Glimepiride and Metformin**
Glimepiride
Dissolution parameter

- **Buffer phase:** 900ml, pH1.2
- **RPM :** 50 rpm
- **Apparatus:** USP XXIII paddle type
- **Time point(min):** 5,15,30,45
- **Temperature:** 37^0C
- **Estimation:** UV spectrophotometer.

Metformin hydrochloride
Dissolution parameters

- **Buffer phase:** 900ml 6.8 pH buffer
- **RPM:** 50RPM
- **Apparatus:** USP XXIII paddle type
- **Time point(hrs):** 1- 12 hrs
- **Temperature:** 37^0C
- **Estimation:** UV spectrophotometer

Procedure
The release of glimepiride from the bi-layer tablet was studied upto 45 mins in 900ml 0f 0.1 N HCL as dissolution medium and the release of metformin hydrochloride from bi-layer tablet was studied in 900ml of phosphate buffer pH 6.8 as dissolution medium up to 12hrs using a USP dissolution paddle assembly at 50rpm and 37^0±0.5^0C. An aliquot (5ml) was withdrawn at specific time intervals, filtered and replaced with equal volume of dissolution medium. Samples were suitably diluted and drug content was determined by chromatogram.[24,25]

Kinetic Analysis of *In-Vitro* Release Rates of Sustained Release Layer of Metformin
The results of in-vitro release profile obtained for sustained release layer were plotted in modes of data treatment as follows:

1. Zero order kinetic model- cumulative percentage drug released versus time.
2. First order kinetic model- log cumulative percentage drug remaining versus time
3. Higuchi's model-cumulative percentage drug released versus square root of time
4. Korsmeyer equation/ peppa's model- log cumulative percentage drug remaining versus log time

Zero order kinetics
Zero order release would be predicted by the following equation:

$$A_T = A_0 - K_0t$$

Where,
A_T = drug release at time 't'.
A_0 = initial drug concentration.
K_0 = zero- order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero – order kinetics and its slope is equal to zero order release constant K_0.

First order kinetics
First – order release would be predicted by the following equation:

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where,
C = amount of drug remained at time 't'.
C_0 = Initial amount of drug.
K = first- order rate constant (hr^{-1}).

When the data plotted as log cumulative percent drug remaining versus time, yields a straight line, indicating that the release follow first order kinetics. The constant 'k_1' can be obtained by multiplying 2.303 with the slope value.[26,27]

Koresmeyer equation / peppa's model

To study the mechanism of drug release from the sustained –release layer of metformin, the release data were also fitted to the well- known exponential equation (koresmeyer equation/ peppa's law equation), which is often used to describe the drug release behaviour from polymeric systems.

$M_t / M_\alpha = Kt^n$

Table 7: Mechanism of drug release as per koresmeyer equation / peppa's model.

S.No	n value	Drug release
1.	< 0.45	Fickian release
2.	0.45< n < 1.0	Non- fickian release
3.	>1.0	Case II transport

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' for fickian release 'n' = 0.45 while for anomalous (non – fickian) transport 'n' ranges between 0.45 and 1.0. The drug release follows zero order drug release and Non-Fickian case II Transport if the value is 1. For the values of n higher than 1, the mechanism of drug released is regarded as non- fickian case II transport.[28]

Higuchi model

The graph was plotted with % cumulative drug released Vs square root of time yields a straight line indicating that the drug was selected by diffusion mechanism.

$\mathbf{Q = Kt^{1/2}}$

Where,

K = constant reflecting design variable system

T = time in hours

The drug release rate is inversely proportional to the square root of time.[29,30]

Similarity factor (f2)

The resulting dissolution profile was compared to the targeted profile by means of the Food and Drug Administration (FDA) recommended modelindependent approach utilizing the similarity factor (f2) (Food and Drug Administration 1997 b). This similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles.

F2 = 50. Log {[1+ (1/n) Σ (=1 R t – T t)2]-0.5 . 100}

Where,

n = number of sample points

R t = percent of Reference release

T t = percent of test release

The FDA guidance stats that the two profiles are considered equivalent if the f2 score is greater than 50(Food and Drug Administration 1997 b).

Table 8: Similarity Factor Value and Its Significance.

Similarity factor (f2)	significance
<50	Test and Reference profiles are dissimilar
50 -100	Test and Reference profiles are similar
100	Test and Reference profiles are identical
>100	The equation yields a negative value

A value of 100% for the similarity factor suggests that the test and reference profiles are identical. F8 Values between 50 – 100, so the dissolution profiles are similar while smaller values imply an increase in dissimilarity between release profiles.[31,32]

RESULTS

Evaluation of immediate release layer

Pre compression parameters showed the **a**ngle of repose ranging from 24.54˚± 0.3282 to 30.79˚± 0.3087 (below 31˚). The LBD and TBD ranged from 0.32± 0.0022gm/cm^3 to 0.35± 0.0035 gm/cm^3 and 0.428 ± 0.0064 to 0.378± 0.0012 gm/cm^3. The compressibility index (%) ranged from 8.635± 0.0115 to 16.358 ± 0.1049. The hauser's ratio ranged from 1.105± 0.0081 to 1.191± 0.0049. The results indicate the free flowing properties of the blend.

Table 1: Pre compression parameters of immediate release layer.

F.Code	Angle of repose (in˚)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index	Hausner's ratio
G1	30.79±0.3087	0.34±0.0008	0.378±0.0012	8.6350.0115	1.10±0.0081
G2	27.60±0.1677	0.35±0.0029	0.428±0.0064	16.09±0.0163	1.19±0.0049
G3	27.72±0.2323	0.35±0.0035	0.388±0.0033	8.75±0.0167	1.10±0.0066
G4	25.24±0.1314	0.33±0.0009	0.408±0.0065	15.23±0.0957	1.17±0.0063
G5	25.18±0.9611	0.34±0.0012	0.415±0.0083	16.35±0.1049	1.19±0.0049
G6	25.24±0.1314	0.35±0.0008	0.416±0.0032	15.54±0.1860	1.18±0.0037
G7	24.77±0.8196	0.34±0.0022	0.400±0.0039	15.07±1.1828	1.18±0.0165
G8	24.54±0.3282	0.32±0.0022	0.378±0.0008	12.97±0.7685	1.15±0.0101

Evaluation of sustained release layer

The angle of repose ranged from 27.28˚±0.7546 to 29.95˚±0.0648. The LBD and TBD ranged from 0.278±0.0057 to 0.442±0.016 gm/cm^3 and 0.317±0.0035 to 0.628±0.0029 gm/cm^3 respectively. The compressibility Index (%) ranged from 11.81± 0.1779 to 20.46± 0.3895. The Hausner's ratio ranged from 1.130±0.0047 to 1.247±0.0123. The results indicate the free flowing properties of the granules.

Table 2: Pre compression parameters of sustained release layer.

F.Code	Angle of repose (in˚)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index	Hausner's ratio
G1	29.94±0.7546	0.432±0.076	0.33±0.0047	13.33±0.9024	1.154±0.0134
G2	29.15±0.1228	0.286±0.0040	0.319±0.0029	11.99±0.8147	1.137±0.0116
G3	27.32±0.2334	0.285±0.0022	0.317±0.0035	11.81±0.1779	1.13±0.0047
G4	28.52±0.3821	0.412±0.0118	0.543±0.0076	20.46±0.3895	1.256±0.0047
G5	29.95±0.0648	0.442±0.0106	0.628±0.0029	18.78±1.2539	1.23±0.0216
G6	27.28±0.7546	0.412±0.0118	0.526±0.0082	16.08±0.9841	1.19±0.0163
G7	29.15±0.7176	0.278±0.0057	0.514±0.0127	19.92±0.7408	1.247±0.0123
G8	28.18±0.2361	0.51±0.0082	0.542±0.0012	20.24±0.7408	1.246±0.0094

Post compression parameters of bi-layer tablets

The prepared tablets were evaluated for various physical parameters and the hardness of all batches ranged from 9.7±0.0816 to 10.1±0.0471kg/cm^3. The percentage friability of all batches ranged from 0.04% to 0.07%. All the formulations passes weight variation test as per the pharmacopoeial limit of 10%. Tablets mean thickness was found to be in the range of 6.72 ±0.012 to 6.81±0.012mm. (Table 3).

Drug content was found to be uniform among all formulations and ranged from 97.46±0.3793 to 99.65±0.2577 (Table 4) and 98.14±0.3756 to 99.65±0.2577 (Table 5) for glimepiride and metformin hydrochloride respectively. The disintegration time of Bi-layer tablets (immediate release layer) ranged between 54 to 97seconds.

Table 3: Post compression parameters of bi-layer tablets.

Formulations	Hardness	Friability	Weight variation	Thickness	Disintegration time
G1+M1	9.7±0.0816	0.05±0.0048	948.3±0.471	6.72±0.016	97±0.816
G2+M2	9.73±0.0471	0.04±0.0008	948.3±0.471	6.81±0.012	95.66±0.471
G3+M3	9.93±0.1247	0.04±0.0022	948.3±0.471	6.79±0.015	94.66 ±0.816
G4+M4	9.7±0.0471	0.05±0.0022	946 ±1.4142	6.79±0.067	89±0.9428
G5+M5	9.9±0.1247	0.04±0.0012	949.3 ±0.942	6.77±0.020	81.66±1.247
G6+M6	10.1±0.0471	0.05±0.0048	947.6 ±1.699	6.79±0.009	74±1.633
G7+M7	9.93±0.01247	0.07±0.0012	950 ±0.8164	6.72 ±0.012	62.67±0.942
G8+M8	9.8±0.0942	0.04±0.0022	946.3 ±1.247	6.76 ±0.012	54±1.4142

Table 4: Drug content uniformity of glimepiride.

S.No	Formulations	Trial I	Trial II	Trial III	Mean ±SD
1.	G1	97.08	97.33	97.98	97.46±0.3793
2.	G2	98.36	98.14	98.29	98.26±0.0925
3.	G3	98.98	98.50	98.34	98.6±0.02724
4.	G4	98.33	98.98	99.62	98.98±0.5256
5.	G5	99.16	99.64	99.00	99.27±0.2722
6.	G6	99.75	99.51	99.12	99.46±0.2610
7.	G7	99.29	99.89	99.76	99.65±0.2577
8.	G8	98.97	98.78	99.56	99.10 ±0.3320

Table 5: Drug content uniformity of metformin hydrochloride.

S.No	Formulations	Trial I	Trial II	Trial III	Mean ±SD
1.	M1	98.6	98.14	97.68	98.14±0.3756
2.	M2	99.52	99.06	98.83	99.14±0.2868
3.	M3	99.76	99.29	99.89	99.65±0.2577
4.	M4	99.09	99.57	99,25	99.3±0.1995
5.	M5	99.69	99.29	99.62	99.53±0.1744
6.	M6	99.06	99.89	99.97	99.65±0.2577
7.	M7	99.29	99.76	99.89	99.65±0.2577
8.	M8	99.56	99.78	99.34	99.56 ±0.1796

In Vitro Drug Release for Bi-Layer Tablet

The release of glimepiride from the bi-layer tablet was studied in 900ml of 0.1N HCl for 45minutes as dissolution medium and for metformin HCl was studied in 900ml phosphate buffer pH 6.8 as dissolution medium for 12hrs using a USP XXIII dissolution paddle assembly at 50 rpm and 37˚± 0.5˚C.

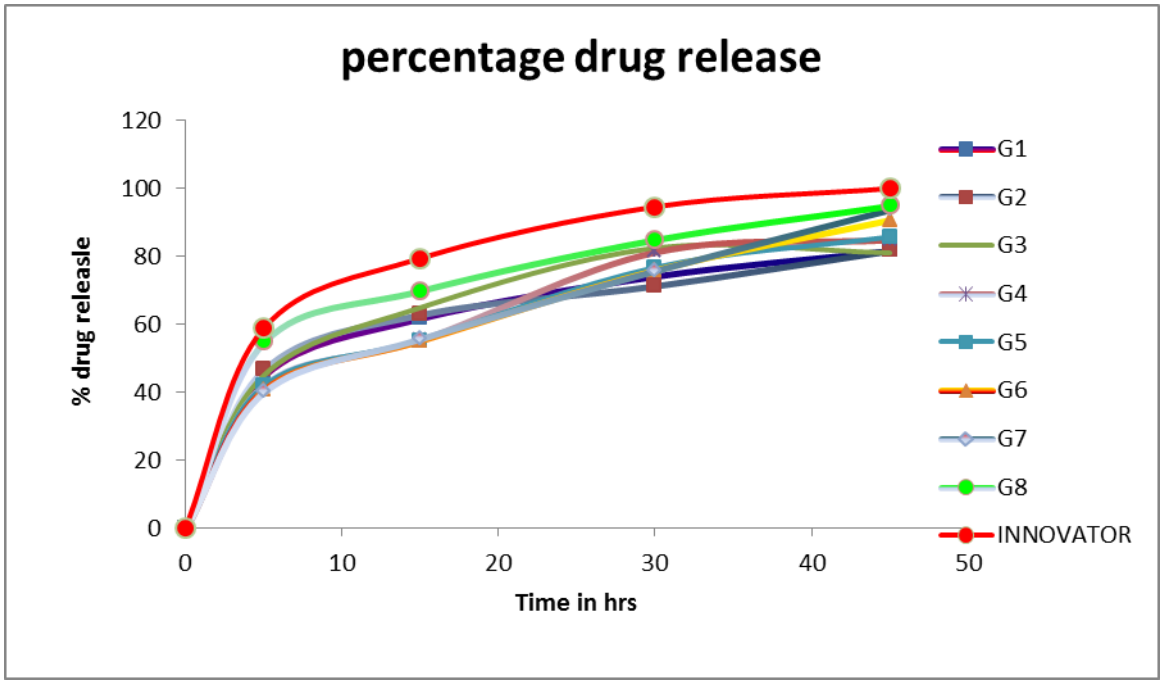

Fig. 1: Comparative *In-vitro* drug release profile of glimepiride immediate release layer at pH 1.2.

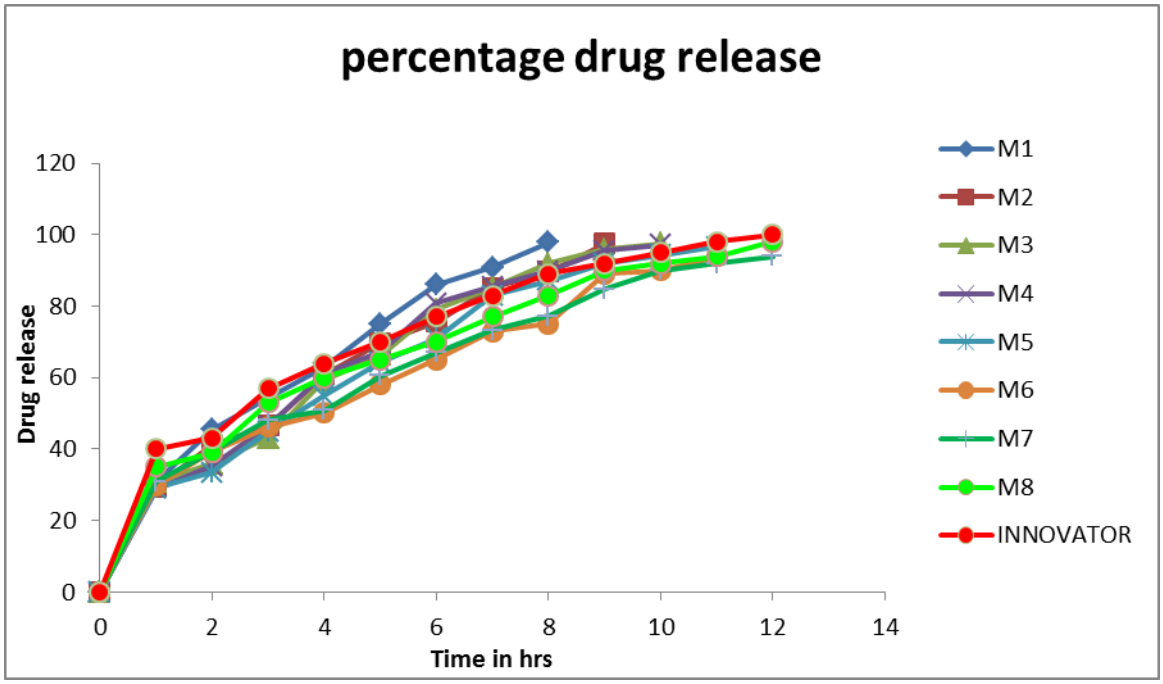

Fig. 2: Comparative *in- vitro* drug release profile of Metformin HCl sustained release layer at pH 6.8.

Table 6: Similarity factor for bi layer tablet in different formulation.

Drug	F1	F2	F3	F4	F5	F6	F7	F8
Glimepiride & Metformin	51.72	51.62	51.47	51.26	51.63	51.79	51.44	51.18

DISCUSSION

The study attempted to prepare and evaluate the combination of glimepiride as immediate release and metformin hydrochloride as sustained release formulation for the treatment of patients with Type II diabetes mellitus.

Estimation of pre and post compression parameters shows that the prepared powders were having good flow properties and the results were within the acceptable limits. Post compression parmaeters such as content uniformity, hardness, friability and weight variation were within the official limits. It indicates all the prepared tablets were good in their physico-chemical properties.

Formulations G1 to G8 were prepared with different concentration of sodium starch glycolate (SSG) to find out the effect of super disintegrants on release pattern and disintegration time. In formulations G1 to G4 sticking was observed during compression, so the concentration of lubricant was increased in formulations G5 to G8 which showed better disintegration time and drug release. Increasing the amount of SSG in formulation F8 brought rapid disintegration and a drug release of 97.84% within 45 minutes.

The effect of different polymers like HPMC K100M, Ethyl cellulose in sustained layer and effect of super disintegrants in different concentration was studied. Results indicated that all the formulation meet the requirements of physico- chemical and In-vitro release characteristics.

The results suggested that for highly water soluble drug like Metformin HCl, it is desirable to use optimized concentration of HPMC for sustained release layer and incorporation of super disintegrants such as sodium starch glycolate in immediate release layer. The release data further indicates that HPMC K100M can give the sustained release effect followed by the initially burst release effect due to the super disintegrants in immediate release layer. The formulations F1-F8 were compared with marketed tablets containing the same strength of glimepiride and metformin hydrochloride.[33]

HPMC K100M polymer controlled the release of Metformin HCl upto 12 hrs intended for once daily administration whereas Ethyl cellulose controlled the drug release up to 8 -10 hrs. The release data of *In-vitro* study indicates that formulation follows zero order kinetic release. The results of the in-vitro release data were fitted to the korsemeyer peppa's equation, the value of 'n' was found to be more than 1, indicating the drug release follows Case II transport mechanism. The drug release of all the formulations was found to be similar with that of the marketed product.

CONCLUSION

The present research work was carried out to develop a bi layer tablet of glimepiride as immediate release layer using super disintegrants such as sodium starch glycolate and metformin hydrochloride as sustained release layer using HPMC K100M and Ethyl cellulose. Formulation F8 shows better dissolution. So it is suggested that for highly water soluble drug like Metformin HCl, it is desirable to use HPMC K100M for sustained release and incorporation of super disintegrants like sodium starch glycolate in immediate release layer. HPMC K100M polymer controlled the release of Metformin HCl upto 12 hrs intended for once daily administration whereas Ethyl cellulose controlled the drug release up to 8 -10 hrs. Finally it may be concluded that glimepiride as immediate release and Metformin HCl as sustained release in the form of bilayer tablets serves to be a promising potential as an alternative to the conventional dosage form.

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