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Formulation and evaluation of bilayered gastro retentive floating tablets containing metformin HCl and glipizide

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ABSTRACT

Bilayer tablets of Metformin hydrochloride and Glipizide were formulated. Glipizide is a poor water soluble (BCS class 2) antidiabetic drug. The present study aims to increase the solubility of Glipizide by solid dispersion technique using sodium starch glycolate and crospovidone as super disintegrants. Metformin hydrochloride was formulated by using Hydroxy Propyl Methyl Cellulose as the matrix forming polymer and was directly compressed. The compressed bilayer tablets were evaluated for all required parameters. It was found that the optimized formulation showed 99% release for Metformin hydrochloride in 24 hours. However, Glipizide released 97% at the end of 60 minutes. The IR spectrum studies revealed that there is no disturbance in the principal peaks of pure drugs alone as well as with the excipients. The stability studies were carried out for the optimized batch for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows Korsemeyer- peppas diffusion model.

Keywords: Metformin hydrochloride, Glipizide, HPLC

INTRODUCTION

In the recent times, multi-layer matrix tablets are gaining importance in the design of oral controlled drug delivery systems. Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit. They are preferred for the following reasons:To co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for staged drug release, IR and SR in the same tablet, for chronic condition requiring repeated dosing. Metformin hydrochloride, chemically N,N-Dimethylimidodicarbonimidic diamide, is a biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose uptake. Metformin is the only oral antihyperglycemic agent that is not associated with weight gain. Metformin may induce weight loss and is the drug of choice for obese NIDDM patients. When used alone, metformin does not cause hypoglycemia; however, it may potentiate the hypoglycemic effects of sulfonylurea's and insulin. The half-life of metformin is 6.2hours.[1-3] It is freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.[4-6]It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability of a single 500 mg dose is reported to be 50% to 60%. This indicates the need to develop dosage forms that can retain the drug in the stomach for better absorption. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occur during the initial weeks of treatment. The compound also has relatively short plasma elimination half life1.5 to 4.5 hr. Sustained release formulations may be administered once or twice

daily. A sustained release formulation that would maintain plasma levels of the drug for 10 to 16 hr might be sufficient for once daily dosing of metformin. So SR formulations that release metformin for 24hr may be suitable for once daily dosing. SR products are needed for metformin to prolong its duration of action and improve patient compliance

Glipizide is an oral antidiabetic drug of the sulfonylurea class that is used together with diet and exercise to reduce blood glucose in patients with type 2 diabetes. It stimulates the release of insulin from the pancreas, directing the body to store blood sugar. Glipizide and metformin combination is used to treat high blood sugar levels that are caused by type 2 diabetes. Normally, the pancreas releases insulin after eating to help the body store excess sugar for later use. This process occurs during normal digestion of food. In type 2 diabetes, the body does not work properly to store the excess sugar and the sugar remains in the bloodstream. Chronic high blood sugar can lead to serious health problems in the future. [7] With two different modes of action, the combination of glipizide and metformin help the body cope with high blood sugar more efficiently.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. **[8]** Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.**[9]** Comprehensive knowledge about GI dynamics such as gastric emptying, small intestine transit, colonic transit, etc. is the key for the optimum design of oral controlled release dosage forms. The rate and extent of drug absorption from different sites of GI tract and factors that govern the absorption further assist the design of dosage form.

MATERIALS AND METHODS

Materials: Metformin hydrochloride, Glipizide was received as a gift sample from Matrix pharma. Pvt. Ltd. Hyderabad, HPMC (K100M & K15),Carbopol, sodium bicarbonate, microcrystalline cellulose, magnesium stearate, hydrochloric acid and polyethylene oxide were obtained from Neha Pharmaceuticals Pvt. Ltd. Crospovidone and sodium carboxymethyl cellulose were obtained from Kevin Pharmaceuticals Pvt.Ltd. Sodium starch glycolate, Poly vinyl pyrrolidine K30 and Talc were obtained from Spectra Pharmaceuticals Pvt.Ltd. All other ingredients were of analytical grade.

Calibration curve for the estimation of Metformin: *[10]* The standard solution was prepared by dissolving 100 mg of Metformin using 0.1N hydrochloric acid of pH 1.2 in a 100 ml volumetric flask and the volume was made up to mark with the same medium. The standard solution was subsequently diluted with the same medium to obtain a series of dilutions containing 10, 20, 30, 40 and 50 µg/ml of drug. The absorbance of these dilutions was measured using UV spectrophotometer at 234 nm against blank. The resultant calibration curve was shown in Fig. 1.

Calibration curve for the estimation of Glipizide: *[11]* The standard solution was prepared by dissolving 100 mg of glipizide using small amount of methanol and dilute in 0.1N hydrochloric acid of pH 1.2 in a 100 ml volumetric flask and the volume was made up to mark with the same medium. The standard solution was subsequently diluted with the same medium to obtain a series of dilutions containing 10, 20, 30, 40 and 50 µg/ml of drug. The absorbance of these dilutions was measured using UV spectrophotometer at 276 nm against blank. The resultant calibration curve was shown in Fig.2.

Preparation of bilayer floating tablets *[12]*

Sustain release layer: For the preparation of sustain release layer, the active ingredient was thoroughly mixed with polymer(s), diluent (MCC) and gas forming agent (sodium bicarbonate) using a mortar and pestle for 10 min; magnesium stearate and aerosil were added to the above blend as flow promoters. In all the formulations, the amount of Metformin hydrochloride was kept constant at 500 mg and different polymers like HPMC K100M , Carbopol71G, HPMC K 15M, PEO were used in different ratios.

Immediate release layer: IR layer containing drug, super disintegrating agent, diluent and lubricants were mixed in adsorption technique uniformly and compressed over SR layered tablet with hardness 5 to 8 kg cm^2 to obtain bilayer floating tablets. The formulation details are given in Table 1 and 2.

Preparation of Glipizide immediate release layer: IR layer containing active ingredient, super disintegrating agent, diluents and lubricants were mixed in adsorption technique uniformly and

compressed over SR layered tablet with hardness 5 to 8 kg cm^2 to obtain bilayers floating tablets.

Tablet compression:The bilayer tablet compression was made using 15/10 mm punch in a 27 station rotary tablet machine with double feed. In this, sustained release metformin hydrochloride granules were introduced first in to the die cavity and a slight precompression was made so that the layer was uniformly distributed. After that immediate release Glipizide granules were added through the other feed and a final compression was made.(table 3)

Evaluation of floating tablets

Melting Point: Melting point of the drug was determined by Thiele's melting point apparatus and the melting point was noted. Average of three readings was taken.

Solubility studies [13]: It is important to know about solubility characteristic of a drug in aqueous system. Since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia, 2007.

Angle of repose [14] Angle of repose was determined using fixed funnel method. Bulk density and tapped density were determined by cylinder method.

Compressibility index [15]

Based on the apparent bulk density and the tapped density, the percentage compressibility of the powder mixture was determined by the following formula.

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped volume}} \times 100$$

Hardness: [16]

The hardness of the tablet was determined using a Pfizer hardness tester. It was expressed in Kg / cm^2.

Weight variation: [17]

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. The weight variation was determined by the following formula.

$$\text{Percent deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Thickness: [18] The thickness of the tablets was measured by vernier calliper scale. It is expressed in mm.

Friability: [19]Friability of the tablets was determined using Roche friabilator (Electrolab, Mumbai). The friability (F) it was calculated by the following formula $F = (1- W_0 / W) \times 100$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

Drug Content: [20]

Metformin: The drug content was carried out by weighing five tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which is equivalent to 100 mg of metformin and dissolved in a 100 ml volumetric flask containing 50 ml of 0.1N HCl and volume was made up to 100 ml with same solvent. The volumetric flask was shaken using sonicator for 1 hrs and after suitable dilution with 0.1N HCl, the drug content was determined using UV-Visible Spectrophotometer at 234 nm.

Glipizide: The drug content was carried out by weighing five tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which is equivalent to 100 mg of glipizide and dissolved in a 100 ml volumetric flask containing 10ml of methanol 40 ml of 0.1N HCl and volume was made up to 100 ml with same solvent. The volumetric flask was shaken using sonicator for 1 hrs and after suitable dilution with 0.1N HCl, the drug content was determined using UV-Visible Spectrophotometer at 276 nm.

Buoyancy lag time determination and Total floating time: [21] The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation.

In Vitro Dissolution Studies: [22]

Metformin SR Floating tablets: The release rate of Metformin from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 234 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

Glipizide IR tablets: The release rate of glipizide from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium.

The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 276 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

In Vitro Dissolution Studies of bilayers floting tablet by HPLC method: The release rate of metformin glipizide floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter. The sample solution was placed in HPLC (waters-2695) (EMPOWER 2) .Absorbance of these solutions was measured isobesitic point at 225 nm using a HPLC (waters-2695) (EMPOWER 2) . The percentage drug release was plotted against time to determine the release profile.

Chromatographic Parameters: Equipment: High performance liquid chromatography equipped with auto sampler and sampler and DAD or UV detector.

Column : Symmetry C18 (4.6 x 150mm, 5µm, Make: Thermosil) or equivalent.
Flow rate : 0.8 mL per min
Wavelength : 225 nm
Injection volume: 20 µl
Column oven : Ambient
Run time : 10min

Inject 20 µL of the standard, sample into the chromatographic system and measure the areas for the Metformin and Glipizide peaks and calculate the %Assay by using the formulae.

Calculation: (For Metformin)

$$\%\ \text{drug release metformin} = \frac{SA}{STD\ A} \times \frac{Wstd}{Dil\ std} \times Dilu\ sam\ x \times \frac{P}{100} \times \frac{900}{Label\ Claim} \times 100$$

Where:

SA = sample area of sample preparation.
STD A= standard area of standard preparation.
Wstd = Weight of working standard taken in mg.
Dilution std = dilution of std solution
LC = LABEL CLAIM OF Metformin mg/ml.
P = Percentage purity of working standard

$$\%\ \text{drug release glipizide} = \frac{SA}{STD\ A} \times \frac{Wstd}{Dil\ std} \times Dilu\ sam\ x \times \frac{P}{100} \times \frac{900}{Label\ Claim} \times 100$$

Where:

SA = sample area of sample preparation.
STD A= standard area of standard preparation.
Wstd = Weight of working standard taken in mg.
Dilution std = dilution of std solution
LC = LABEL CLAIM OF glipizide mg/ml.
P = Percentage purity of working standard

Fourier Transform Infrared Spectroscopy (FTIR) study

The compatibility between drug and polymer was detected by IR spectra obtained on (Shimadzu 8400). The pellets were prepared on sigma analytical testing house pvt ltd HYD. The spectra were recorded over the number range of 4000 to 400cm^{-1}.

Stability studies: [23]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product

degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. In the present study, stability studies were carried out at 40^{o}C / 75% RH ± 5% for 30 days by storing the selected formulations in stability chamber.

RESULTS & DISCUSSION

Development of oral controlled release systems has been a challenge to a formulator because of their inability to restrain and localize the system in the targeted area of the GIT. Various approaches that have been proposed to control the gastric residence of drug delivery systems in the upper part of the gastrointestinal tract include floating drug delivery systems (FDDS), high-density DDS, mucoadhesive systems, swelling and expanding DDS, modified shape systems, and other delayed gastric devises. Floating drug delivery systems (FDDS) also called hydrodynamically balanced system is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug.

A bilayer tablet is prepared to contain one immediate release and other sustained release layer. Immediate release layer delivers the initial dose whereas sustained release layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in system with bulk density lesser than that of gastric fluid and allows it to remain buoyant in the stomach for an extended period of time.

In the present study eight different immediate release formulations of Glipizide were prepared by maintain the drug weight constant and changing the polymers. Whereas sustained release Metformin were prepared in nine different formulae by keeping the drug constant and changing the polymer. The formulae were mentioned in table 1 & 2.

The two layers were optimized and for the final bilayer tablet IR5 was selected as immediate release layer and SR9 as sustained release layer. The final formula of bilayer tablet of Metformin and Glipizide (MG) was shown in table 3.

The melting point of the Metformin and Glipizide was found to be 224.3 ^{0}C and 208.3 ^{0}C respectively. This was in accordance with the reported value. Metformin (pure drug) exhibited angle of repose value of 42.55 ± 1.35^{0} indicating poor flow property. It was further supported by high compressibility index value (29.10±0.14%) and Hausner's ratio (1.41±0.13). Hence lubricants (Magnesium stearate) and directly compressible vehicles (MCC) were added to improve the flow property of drug. Table 4 shows the micromeritic property of precompressional mixture. Glipizide (pure drug) exhibited angle of repose value of 32.55 ± 1.23^{0} indicating poor flow property. Hence lubricants (Magnesium stearate) and directly compressible vehicles (MCC) were added to improve the flow property of drug. Table 5 shows the micromeritic property of precompressional mixture. All the formulations exhibited the angle of repose value of 20.17 – 29.29 %-metformin layer , 20.62 - 26.30% glipizide layer , which was further supported by good compressibility index value of 12.73-20.35% metformin layer , 14.46-30.10% glipizide layer and Hausner's ratio of 1.14 - 1.25 metformin layer ,1.16-1.32% glipizide layer , thus indicating the suitability of precompressional powder blend for direct compression. Optimized bilayers floating formulation exhibited the angle of repose value of 27.41 %, which was further supported by good compressibility index value of 13.8% and Hausner's ratio of 1.16, thus indicating the suitability of Precompressional powder blend for direct compression. The results are shown in Table 4, 5 &6.

The tablets prepared using different polymers like HPMC K100M and Carbopol 71 G, PEO ,HPMC K15 alone and in combination were found uniform with respect to thickness (5.13 – 5.22 mm metformin layer), (2.09 -2.23 mm glipizide layer)and hardness (6.7 to 7.5 kg/cm^2 metformin layer), (5.4-5.8kg/cm^2 glipizide layer). The friability (0.20 to 0.31% metformin layer), (0.22 – 0.35% glipizide layer) and weight variation (1.17 to 1.44% metformin layer), (1.42- 2.42% glipizide layer) of different batch of tablets were found within prescribed limits. Drug content (97.07 to 99.74%metformin layer),(97.26 – 100.20% glipizide layer) was found uniform within the batches of different tablets. Optimized bilayers floating formulation with respect to thickness (6.40 mm) and hardness (7.5 kg/cm^2). The friability (0.75 %) and weight variation (1.81 %) The results of physico-chemical evaluation of tablets are given in Table 6, 7 & 8. It was observed that, at optimum concentration of sodium bicarbonate (10%) all the floating tablets (SR4-SR9) batches had floating lag time below 180 seconds regardless the concentration of polymer used. No variation in floating lag time was observed with tablets prepared by using different concentration of polymer. The total floating time was found to be in the range of 16-28 hours for all the tablets prepared, which indicates a stable gel layer formation by HPMC and Carbopol and PEO that persists for a longer time. Fig. 3.

Since Metformin is freely soluble drug and Glipizide is a practically water insoluble drug, dissolution studies of prepared bilayer floating tablets were carried out in 0.1N HCl for a period of 24 hours. The samples were analyzed by UV-Spectrophotometer at 234 nm and 276nm. The results of *in vitro* drug release from tablet formulations are presented in Table 9 - 11 and Fig. 4 - 9. During

dissolution study, gel formation on tablet surface was observed macroscopically in all formulations which controlled the release of drugs from the tablet.

To investigate the mechanism of drug release, various kinetics models like zero order, first order, Higuchi's and Korsmeyer-Peppas equations were applied to the *in-vitro* release data obtained from the optimized floating tablets, (SR9, IR5 and MG). As observed from the Table 12, the values of correlation-coefficient (r^2) for all the formulations were high enough to evaluate the drug dissolution behavior. The value of release exponent (n) was found to be a function of polymer used and the physicochemical property of a drug molecule itself. The optimized floating bilayer tablet formulation MG showed the sustained drug release according to the Korsemeyer-peppas diffusion model.

The stability studies were conducted according to the relevant ICH guidelines. The optimized formulations (SR9, IR5 and MG) were stored for a period of 1month at 40^oC / 75% RH ± 5%. Table 13 & 14 shows the values of post-compressional parameters before and after stability studies. The results indicated that, the tablets did not show any physical changes (hardness and friability) during the study period. The drug content was found 98% and no significant variation was observed at the end of one month stability study. This indicates that, the prepared tablets remained fairly stable during storage conditions.

CONCLUSION

In this present study we have formulated a bilayer tablet containing Glipizide as immediate release layer and Metformin as sustained release layer. Preformulation studies of Metformin and Glipizide fairly corroborated with the reported literature limits. The adopted method of tableting yielded uniform and reproducible floating tablets. The hardness, friability, weight variation, drug content, floating lag time, total floating time, and *in vitro* release were uniform and reproducible. Floating time was largely dependent on gas generating agent concentration and found to be less than 180 sec at 10% sodium bicarbonate concentration for all the formulations. Irrespective of the polymers used, the rate of drug release was inversely proportional to the polymer concentration. Floating tablets of SR9 and MG gave controlled and complete drug release over a period of 24hrs and thus considered as optimized formulations. The mechanism of drug release was found to be non fickian, Korsemeyer – peppas diffusion model kinetics.FT-IR revealed the absence of any chemical interaction between drug and polymers used. Optimized bilayer floating tablet (MG) were found to be stable with respect to drug content, friability, weight variation and release profiles. Hence, floating bilayer tablet (MG) of showed promising results and there exist a scope for *in vivo* evaluation using suitable animal models.

Table 1: Formulae of different immediate release formulations of Glipizide

S. No.	Ingredients (mg)	Formulation code							
		IR1	**IR2**	**IR3**	**IR4**	**IR5**	**IR6**	**IR7**	**IR8**
1	**Glipizide**	10	10	10	10	**10**	10	10	10
2	**Lactose**	150	200	100	50	**100**	---	100	100
3	**PVP K30**	7.5	7.5	7.5	7.5	**7.5**	7.5	7.5	7.5
4	**SSG**	6	6	6	6	**10**	6	---	---
5	**MCC**	50	-	100	150	**100**	200	100	100
6	**Mg.St**	1.5	1.5	1.5	1.5	**1.5**	1.5	1.5	1.5
7	**Total**	225	225	225	225	**229**	225	229	225

Table 2: Formulae of different sustained release formulations of Metformin

S. No.	Ingredients(mg)	Metformin layer Formulation code								
		SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
1	Metformin	500	500	500	500	500	500	500	500	500
2	NaHco3	5	10	5	10	10	10	10	10	10
3	HPMC K 100m	100	150	-	100	200	150	150	150	--
4	Aerosil	1	1	1	1	1	1	1	1	-
5	Mg.st	1		1	1	1	1	1	1	5
6	lactose	25	25	25	25	-	-	-	-	-
7	Carbopol71	-	-	50	-	-	-	-	-	-
8	HPMC K15	-	-	100	-	-	-	-	-	-
9	Na.CMC	-	-	-	50	-	50	100	-	-
10	MCC	-	-	-	-	25	25	25	25	30
11	PEO	-	-	-	-	-	-	-	100	75
12	PVPK30	-	-	-	-	-	-	-	-	30

Table 3: Final Formulae of bilayer floating tablet of Metformin & Glipizide

Formulation code	Ingredients of IR layer 5 (229mg)						Ingredients of SR layer(725mg)							Total weight (mg)
	glipizide	lactose	MCC	Mg. stearate	Pvpk 30	crospovidone	metformin	HPMC K100M	$NaHCO_3$	PVP K 30	MCC	Mg. stearate	PEO	954
Mg	10	100	100	1.5	7.5	10	500	75	10	30	30	5	75	

Table 4: Micromeritic properties of Precompressional powder blends of different sustained release Metformin floating tablet formulations.

Formulation code	Angle of repose* (θ)	Carr's index* (%)	Hausner's ratio*
Pure drug	42.55±1.35	29.10±0.14	1.41±0.13
SR1	20.35±0.48	20.35±0.21	1.25±0.05
SR2	21.80±0.51	16.75±0.35	1.21±0.04
SR3	20.17±0.50	20.17±0.19	1.25±0.05
SR4	22.34±0.59	18.21±0.26	1.16±0.03
SR5	24.12±0.65	15.92±0.34	1.19±0.01
SR6	28.23±0.11	20.33±0.26	1.25±0.05
SR7	29.19±1.02	13.23±0.08	1.15±0.03
SR8	29.29±0.36	15.87±0.18	1.18±0.02
SR9	28.34±0.69	12.73±0.02	1.14±0.06

**Average of 3 determinations (±SD)*

Table 5: Micromeritic properties of Precompressional powder blends of different immediate release formulation of Glipizide layer.

Formulation code	Angle of repose* (θ)	Carr's index* (%)	Hausner's ratio*
Pure drug	32.55±1.23	27.10±0.18	2.41±0.18
IR1	25.74±0.78	20.35±0.14	1.25±0.01
IR2	24.28±0.43	24.60±0.35	1.32±0.02
IR3	26.06±0.60	18.43±0.18	1.22±0.13
IR4	27.40±0.25	16.39±0.26	1.19±0.08
IR5	26.30±0.36	14.46±0.02	1.16±0.01
IR6	23.65±0.48	20.17±0.33	1.25±0.03
IR7	20.62±0.93	30.10±0.12	1.24±0.05
IR8	22.62±0.83	16.36±0.62	1.19±0.04

**Average of 3 determinations (±SD).*

Table 6: Pre and Post compressional evaluation of optimized bilayer floating tablets

Preformulation studies	
Bulk density	0.589
Tapped density	0.684
Compressibility index	13.8±0.42
Hausner's ratio	1.16±0.03
Angle of repose	27.41±0.96
Post formulation results	
Friability	0.85±0.06
Drug content Metformin	
Weight variation (%)	1.81±0.59
hardness	7.5±0.23
Tablet thickness	6.40±0.03
Floating log time	117sec
Floating time	24hrs

Table 7: Post compression evaluation of sustained release Metformin floating tablets.

Formulation	Hardness*	Friability**	Thickness*	Weight variation***	Drug content*
SR1	6.7±0.32	0.26±0.04	5.22±0.01	1.22±0.11	98.74±0.93
SR2	6.8±0.52	0.28±0.02	5.19±0.03	1.17±0.32	97.00±1.02
SR3	7.3±0.23	0.22±0.05	5.21±0.09	1.37±0.33	98.18±0.57
SR4	6.8±0.23	0.31±0.01	5.18±0.05	1.41±0.69	98.28±0.66
SR5	7.5±0.44	0.27±0.08	5.26±0.07	1.44±0.18	97.76±0.34
SR6	6.9±0.49	0.20±0.06	5.25±0.03	1.38±0.43	98.34±0.89
SR7	7.4±0.38	0.32±0.03	5.28±0.04	1.22±0.16	97.26±0.34
SR8	7.2±0.31	0.22±0.04	5.13±0.06	1.23±0.03	98.36±0.89
SR9	7.5±0.17	0.29±0.04	5.19±0.05	1.33±0.22	99.94±0.21

**Average of 3 determinations (±SD).*

Table 8: Post compression evaluation of immediate release Glipizide tablets.

Formulation code	Hardness* Kg/cm^2	Friability** (%)	Thickness* (mm)	Weight variation*** (%)	Drug content*
IR1	5.3±0.32	0.32±0.04	2.09±0.10	2.42±0.21	98.27±0.57
IR2	5.2±0.52	0.31±0.02	2.16±0.03	1.42±0.32	98.54±1.02
IR3	5.6±0.33	0.27±0.05	2.12±0.15	1.14±0.33	99.34±0.59
IR4	5.4±0.32	0.35±0.06	2.17±0.07	1.93±0.43	100.20±0.48
IR5	5.5±0.21	0.28±0.08	2.25±0.14	1.67±0.28	99.82±0.19
IR6	5.8±0.42	0.26±0.04	2.20±0.10	1.72±0.33	98.42±0.32
IR7	5.6±0.34	0.22±0.03	2.15±0.15	1.68±0.17	97.38±0.28
IR8	5.4±0.45	0.33±0.04	2.23±0.13	2.02±0.14	97.26±1.24

Average of *3 determinations (±SD).

Table 9: In-vitro release of Metformin floating tablet from sustained release layer in 0.1N HCL.

Time (hrs)	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
1	25.2	24.0	25.0	27.0	23.0	17.0	29.0	24.3	13.0
2	38.0	36.0	35.3	41.0	38.0	38.0	31.0	37.0	38.0
4	61.0	58.0	60.0	56.0	48.0	60.0	48.0	51.0	61.6
6	79.0	74.0	81.0	75.0	56.0	77.0	67.0	67.0	75.0
8	80.0	77.0	85.0	80.0	79.0	83.0	74.0	81.0	89.0
10	87.0	84.0	91.0	83.0	89.0	84.0	81.0	90.0	92.0
12	88.0	87.0	92.0	89.0	93.0	90.00	87.0	90.3	95.0
16	89.0	87.5	95.0	93.0	94.0	94.0	93.0	91.0	96.0
24	93.0	92.0	97.0	95.0	95.0	95.0	96.0	93.0	99.0

Table 10: In-vitro release of Glipizide from immediate release layer in 0.1N HCl.

Time (min)	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8
10	28.0	51.0	54.0	34.0	62.0	36.0	62.0	53.0
20	39.0	64.0	67.0	47.0	74.0	52.0	72.0	69.0
30	49.0	77.0	79.0	53.0	78.0	63.0	80.0	78.0
45	62.0	83.0	87.0	70.0	81.0	73.0	90.0	86.0
60	70.0	93.0	92.0	79.0	97.0	81.0	93.0	93.0

Table 11: In vitro drug release profile of floating bilayer tablet (MG) by HPLC method

S.NO	TIME	METFORMIN AREAS	% C. D.R	GLIPIZIDE AREAS	%C.D.R
1	Std area	772485	---	33283	----
2	10 min	123478	2.8	2301	62.0
3	20min	245878	5.7	2754	74.3
4	30min	321487	7.4	2895	78.1
5	45min	485621	11.2	3012	81.2
6	1hr	576412	13.4	3598	97.0
7	2hr	1652487	38.4	3599	97.1
8	4hr	2647891	61.5	3606	97.3
9	6hr	3246481	75.4	3612	97.4
10	8hr	3846215	89.4	3618	97.60
11	10hr	3952315	91.9	3621	97.70
12	12hr	4102315	95.39	3623	97.77
13	16hr	4135987	96.18	3626	97.8
14	24hr	4295648	99.8	3629	97.9

Table 12: Kinetic analysis of *in-vitro* release data for optimized formulations of SR9, IR5, MG.

Code	Zero order		First order		Higuchi		Korsmeyer-peppas	
	n	r^2	n	r^2	n	r^2	n	r^2
IR5	1.265	0.681	0.021	0.872	11.69	0.908	1.118	0.878
SR9	3.938	0.652	0.213	0.966	23.380	0.876	0.161	0.597
MG	0.081	0.736	0.169	0.794	33.82	0.913	0.734	0.965

All values are expressed as mean ± SD. n=3

Table.13: Physico-chemical data of optimized formulations before and after stability studies at 40°C / 75% RH ± 5%.

Code	Hardness test[+] (kg/cm^2)		Friability[†] (%)		Weight variation* (%)		Thickness[†] (mm)		Drug content[**] (%)	
	Before	After	before	after	Before	After	Before	after	Before	After
IR5	5.50±0.44	5.2±0.86	0.28±0.08	0.33±0.03	1.67±0.28	1.65±0.09	2.25.±0.04	2.28±0.23	99.82±0.21	98.21±0.32
SR9	7.5±0.38	6.8±0.02	0.29±0.03	0.31±0.02	1.33±0.22	1.31±0.38	5.19±0.06	5.23±0.38	99.40±0.22	98.33.±0.09
MG	7.5±0.23	7.0±0.64	0.75±0.09	0.79±0.05	1.63±0.41	1.61±0.22	6.40±0.04	6.53±0.11	99.0±1.24	98.23±0.56

All values are expressed as mean ± SD [+]n=6, [†]n=10, *n=20, **n=3

Table 14: Physico-chemical data of optimized bilayer floating tablets before and after stability studies at 40°C / 75% RH ± 5%.

Code	FLT (Sec)		TFT (hrs)	
	Before	After	before	After
SR9	113	123	28	28
MG	120	128	24	24

All values are expressed as mean ± SD. n=3.

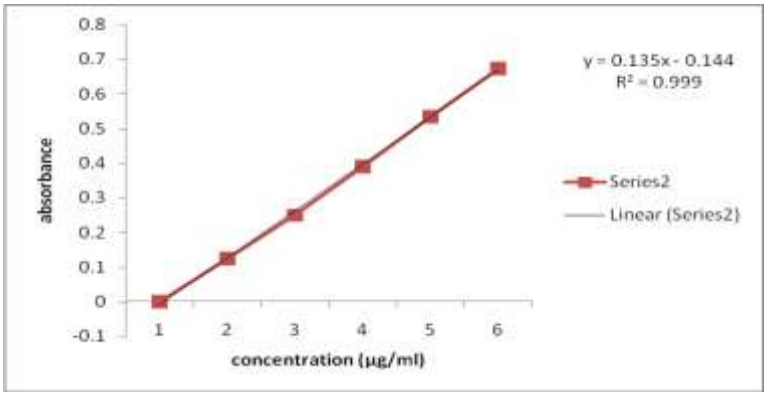

Figure 1: Calibration curve of metformin in 0.1 HCl.

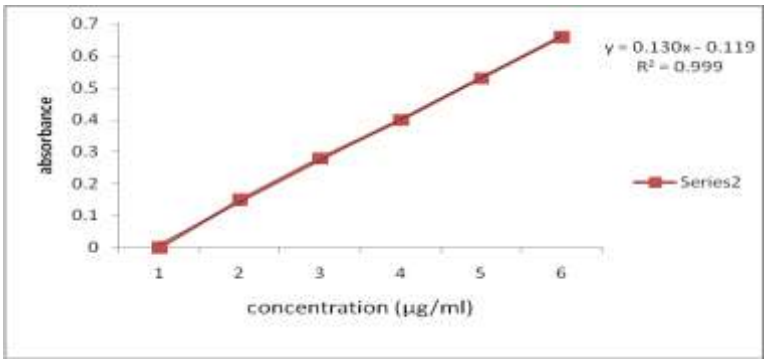

Figure 2: Calibration curve of Glipizide in 0.1 HCl.

Figure 3: Photographs indicating the floating lag time of optimized formulation (SR9)

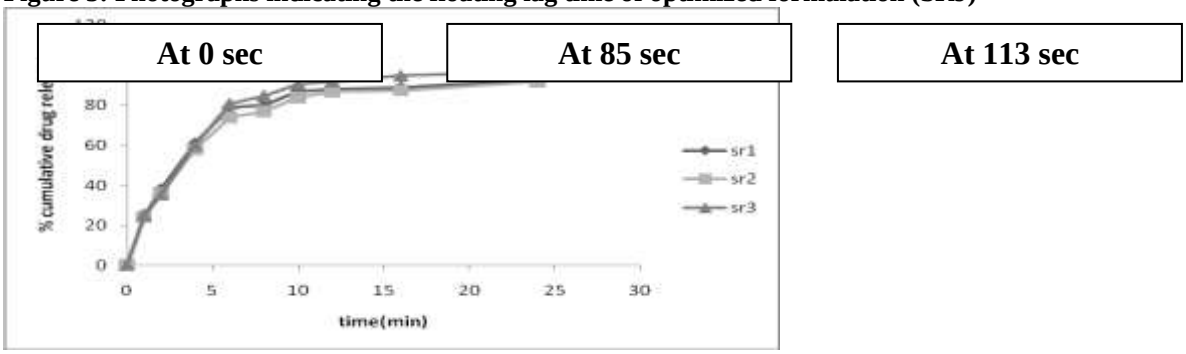

Figure 4: Comparative Drug release profile of SR1 to SR3formulation.

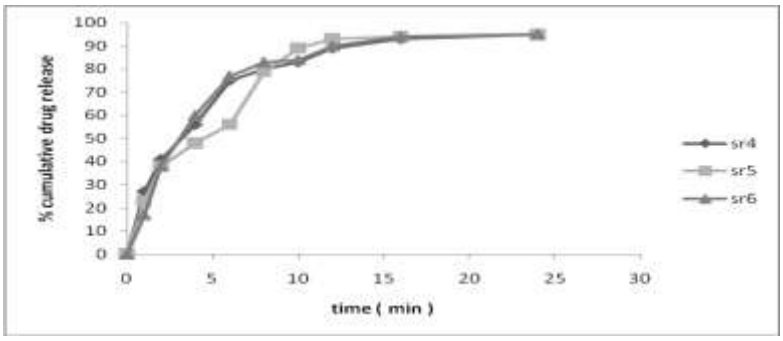

Figure 5: Comparative Drug release profile of SR4 to SR6 formulations.

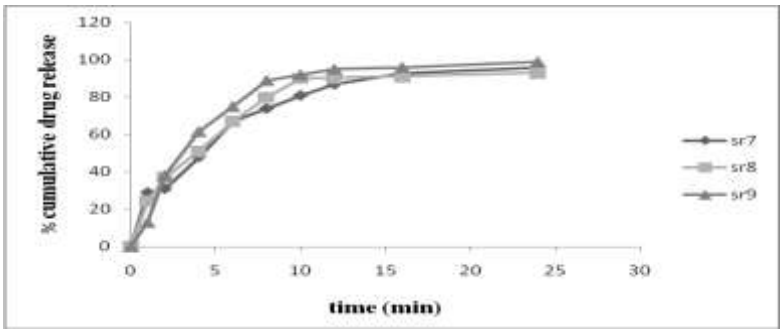

Figure 6: Comparative Drug release profile of SR7 to SR9 formulation

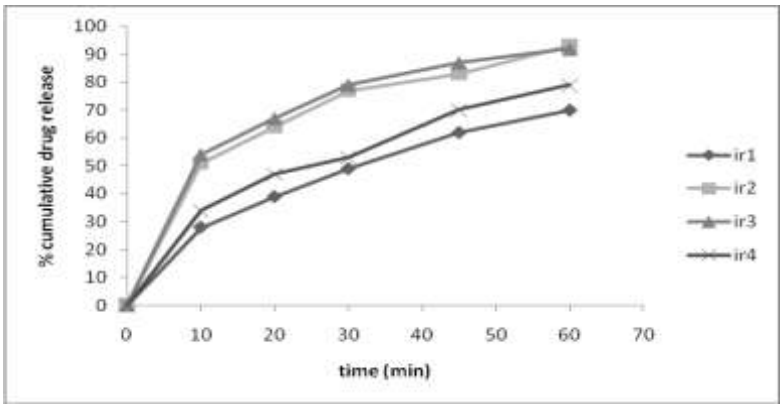

Figure 7: Comparative Drug release profile of IR1 to IR5 formulation

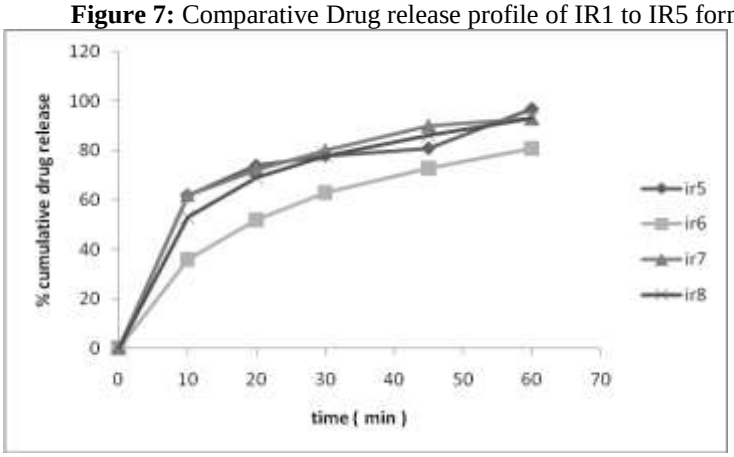

Figure 8: Comparative Drug release profile of IR5 to IR8 formulation

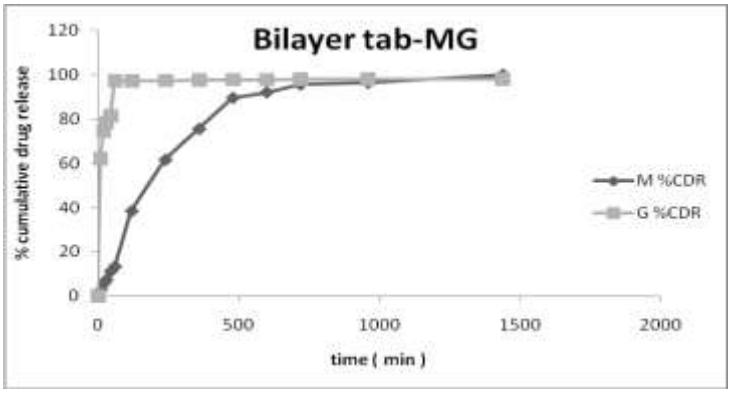

Figure 9: In-vitro release of optimized bilayer floating tablet (MG) in 0.1N HCl

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