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Research Article

INTRAGASTRIC FLOATING DRUG DELIVERY SYSTEM OF METFORMIN HYDROCHLORIDE AS SUSTAINED RELEASE COMPONENT AND GLIMEPIRIDE AS IMMIDIATE RELEASE COMPONENT: FORMULATION AND EVALUATION

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ABSTRACT

The aim of present investigation was to design the concept of bilayered tablet containing Glimepiride as immediate release using sodium starch glycollate as super disintegrant and Metformin Hydrochloride as sustained release floating delivery system. The purpose of this investigation was to prepare a gastroretentive bilayer drug delivery tablet. Floating layer of Metformin Hydrochloride were prepared employing different grades of gel forming agent and by various gas generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 6-10 hours. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Keywords: Bilayer tablets, Metformin Hydrochloride, Glimepiride, Floating.

INTRODUCTION

Among the various gastro retentive systems, gastric floating drug delivery systems (GFDDS) offer numerous advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach[1].

Metformin Hydrochloride is an orally administered biguanide derivative widely used in the treatment of non-insulin dependent diabetes mellitus. It improves glycaemic control by enhancing insulin sensitivity in liver and muscle. Metformin also has beneficial effects on several cardiovascular risk factor such as dyslipidemia, elevated plasma plasminogen activator inhibitors, other fibrinolytic abnormalities, and hyperinsulinemia and insulin resistance[2-3].

In humans, metformin is incompletely absorbed and predominantly excreted in urine with a half life of 4-6 hours[4]. Metformin has a property of a strong base (pKa = 11.5) and is protonated under physiological pH condition. The ionized metformin has a tendency to be absorbed to the negatively charged intestinal epithelium affecting the drug absorption pattern[5]. Thus, the absorption window is predominantly in small intestine and follows a saturable dose dependent mechanism[2,6]. Metformin absorption after oral absorption is therefore likely to be site specific.

A conventional oral sustained release formulation however, releases most of the drug content in a colon, which requires that the drug should have absorption window either in colon or throughout the GIT. Vidon et al. and Marathe et al. have indicated that metformin has poor colonic absorption in healthy human subjects[6,8]. Release of metformin after the small intestine is thus, of no therapeutic value. Marathe et al. have also strongly mentioned that the conventional strategies of prolonging the release of metformin from the dosage forms throughout the GIT would not be effective for metformin formulation as it is primarily absorbed from the small intestine. They have also indicated that the extent of metformin absorption is improved when the gastro intestinal motility is slow[7]. Thus, development of gastro retentive sustained release formulation for metformin hydrochloride would be a better alternative to the conventional sustained release formulations. Gusler et al. depicted that the mean bioavailability of gastro retentive metformin tablet was approximately 115% relative to the immediate release metformin product[8].

Glimepiride is one of the generation sulfonylurea drug useful for control of diabetis mellitus, type 2. Preclinical investigation of Glimepiride suggest a number of potential benefit over sulfonylurea currently available including lower dosage, rapid onset possibly due to less stimulation of insulin secretion and more pronounced extra pancreatic effects. Metformin and Glimepiride are used to treat high blood sugar level that is caused by type 2 diabetes. Normally, the pancreas release insulin after eating to help the body to 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 blood stream. Chronic high blood sugar can lead to serious health problem in the future. With two different mode of action, the combination of Glimepiride and Metformin HCl help the body cope with high blood sugar more efficiently. Immediate action of Glimepiride will be helpful to control excess sugar, which will be helpful to control excess sugar, which will be maintained by Metformin HCl action later on. Thus, the developed single tablet will be sufficient instead of two to three tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy[9].

Thus, controlled release gastro retentive tablet would be ideally suited to formulate metformin hydrochloride as floating drug delivery systems (FDDS) in the light of its PK/PD properties as already discussed. With these considerations in view, in the present investigation an attempt has been made to design, develop and evaluate GR-FDDS of metformin hydrochloride for better management of NIDDM. Our attempt has been to achieve a sufficiently prolong drug release at par with the existing clinically used single unit CR tablets while providing a floating time of more than 8 hours. So that the ample opportunity for the drug exists to get completely absorbed at predictable rate.

The aim of present study was to design the concept of Bilayer tablet containing Glimeperide for immediate release using sodium starch glycollate as super disintegrant and floating layer of Metformin hydrochloride using HPMC and carbopol as gel forming agent and sodium bicarbonate, a gas-generating agent. Thus, an effervescent floating tablet was developed and evaluated for floating lag time and in-vitro drug release study.

MATERIALS AND METHODS

The materials utilized in study with supplier name are shown in table 1.

Table 1: Materials

Materials	Supplier Name
Metformin hydrochloride	Wanbery laboratories
Glimepiride	Mederich laboratories Pvt.ltd.
Hpmc k4m	Colorcon asia pvt. Ltd., Goa
Hpmc k100m	Colorcon asia pvt. Ltd., Goa
Sodium bicarbonate	S.D.Fine-Chem Ltd., Vadodara
Stearic acid	S.D.Fine-Chem Ltd., Vadodara
Dicalcium phosphate dihydrate	Finar Chemicals Pvt. Ltd., Ahmedabad
Hydrochloric acid AR	S.D.Fine-Chem Ltd., Vadodara
Sodium hydroxide AR	S.D.Fine-Chem Ltd., Vadodara
Citric acid (anhydrous)	S.D.Fine-Chem Ltd., Vadodara
Calcium carbonate	S.D.Fine-Chem Ltd., Vadodara
Potassium carbonate	Nice Chemicals Ltd., Cochin
Sodium carbonate	S.D.Fine-Chem Ltd., Vadodara
Potassium dihydrogen orthophosphate	S.D.Fine-Chem Ltd., Vadodara
Sodium carboxymethylcellulose	Thomas Baker Chemicals Ltd., Bombay
Carbopol	Corel Pharma, Ahmedabad
Guar gum	National chemicals, Vadodara
Sodium alginate	S.D.Fine-Chem Ltd., Vadodara
Microcrystalline cellulose ph 102	Gujarat microvax pvt. Ltd.
Lactose DCL 15	DMV Fonterra
Talc	Luzenac
Magnesium stearate	Peter Greven
Sodium starch glycollate	Roquette
Red iron oxide	Rhodia
Barium sulphate (X-ray grade)	From clinic
Double distilled water	Prepared in laboratory

Table 2: Composition of Metfornin Hydrochloride and Glimepiride

Ingredients	Batch No.#																	
	A1	A2	A3	A4	B1	B2	B3	B4	C1	C2	D1	D2	D3	E1	E2	E3	E4	E5
Layer – 1																		
Metformin hydrochloride	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K 100M	125	250	-	-	125	125	125	125	125	125	-	-	-	125	125	125	125	125
HPMC K4M	-	-	125	250	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sodium bicarbonate	-	-	-	-	60	-	-	-	40	80	60	60	60	60	60	60	60	60
Sodium carbonate	-	-	-	-	-	60	-	-	-	-	-	-	-	-	-	-	-	-
Potassium carbonate	-	-	-	-	-	-	60	-	-	-	-	-	-	-	-	-	-	-
Calcium carbonate	-	-	-	-	-	-	-	60	-	-	-	-	-	-	-	-	-	-
Guar gum	-	-	-	-	-				-	-	125	-	-	-	-	-	-	-
Sodium Alginate	-	-	-	-	-	-	-	-	-	-	-	125	-	-	-	-	-	-
-Sodium carboxymethylcellulose	-	-	-	-	-	-	-	-	-	-	-	-	125	-	-	-	-	-
Stearic acid	-	-	-	-	-	-	-	-	-	-				8	16	24	-	-
Carbopol 934	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	40	-
Carbopol 940	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	40
Dicalcium phosphate dihydrate	159	34	159	34	99	99	99	99	119	79	99	99	99	91	83	75	59	59
Talc	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Magnesium stearate	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Avg. weight of layer 1	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800
Layer – 2																		
Glimepiride	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lactose DCL 15	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48
Microcrystalline cellulose pH 102	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90
Sodium starch glycollate	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Red iron oxide	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Average weight of layer 2	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Total weight	950	950	950	950	950	950	950	950	950	950	950	950	950	950	950	950	950	950

Methodology

Glimepiride granules are formulated as immediate release layer and Metformin HCl granules are formulated as extended release layer for bilayer tablets.

Blends of the IR layer

Composition of the IR layer is given in Table 2. The weight of the IR layer was fixed to 150 mg. Glimepride, sodium starch glycolate, and red iron oxide were passed through a mesh (100 #) and blended in a blender for 5 minutes at 24 RPM, so that the distribution of red iron oxide throughout the mass was uniform. Lactose DCL 15, Microcrystalline cellulose pH 102 were sifted through 30 # and added to above blend in blender and mix for 5 minutes at 24 RPM. Magnesium stearate was sifted through 40 # and mix to above blend in blender for 5 minutes at 24 RPM.

Granulation of the SR Layer

Composition of the SR layer is given in Table 2. The weight of SR layer was fixed to 800 mg. Different excipients like HPMC K4M, HPMC K100M, Sodium bicarbonate, Sodium carbonate, Potassium carbonate, Calcium carbonate, Guar gum, Sodium alginate, Sodium carboxy methyl cellulose, Stearic acid, Carbopol 934, Carbopol 940 were sifted through 40 # and mixed with Metformin HCl and stated quantity of Dicalcium phosphate dehydrate (previous sifted through 40 #) was mixed in blender for 5 minutes at 24 RPM. Sift talc through 40 # and mix with above blend for 5 minutes in blender at 24 RPM. Sift Magnesium stearate through 40 # and mix with above blend for 5 minutes in blender at 24 RPM. Composition of IR layer and SR layer is given in table 2.

Evaluation of Tablets

Weight Variation

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight, standard deviation and relative standard deviation were reported. The tablet compression machine was suitably adjusted to produce tablets of uniform weight. The results are included in table 3.

Tablet thickness

The thickness in millimetres (mm) was measured individually for 10 preweighed tablets by using a starrett portable dial hand micrometer. The average thickness, standard deviation and relative standard deviation were reported. The results are included in table 3.

Tablet hardness

Tablet hardness was measured using a Key hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (KP) and the average hardness. Tablets hardness was checked at the start and during the compression process to control an acceptable range of tablet hardness. The results are included in table 3.

Friability

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the VanKel tablet friabilator. The tablets were then will dust and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets. The results are included in table 3.

Floating lag time

The in vitro floating behavior was studied by placing them in 1000 ml glass beaker filled with 500 ml of 0.1 N HCl pH 1.2 temperature 37.5 ^{0}C ± 0.5 ^{0}C. The floating lag time is the time period between placing the tablet in medium and time of tablet floating in media. The results are included in table 4.

Dissolution

An *in vitro* drug release study from the prepared bilayered tablets was determined using the USP I (basket) apparatus (Lab India, DISSO2000). With 900 ml of pH of 1.2 with 0.1% w/v sodium lauryl sulphate and, followed by phosphate buffer pH 6.8 was used as dissolution media and maintained at 37±0.5ºC at a rotational speed of 100 rpm, for 45mins and 8hrs respectively. Dissolution Samples were analyzed by HPLC method.

HPLC Method

Chromatographic conditions

Column: C8 column (Phenominex) (250 × 4.6 mm, 5µm particle size)

Mobile phase: 10 m mol phosphate buffer of pH 2.5: Acetonitrile (50: 50 (v/v))

Detector: UV detection at 228 nm

Loop size: 20 µl

Stock solutions of Glimepride and Metformin HCl were prepared in 0.1 N NaOH as 1mg/ml. calibration curve was prepared for each of the analytes after appropriate dilution of stock solutions to obtain final concentrations of 0.1, 0.2, 0.5, 1, 2, 5, and 10 µg/ml for Glimepride and 0.1, 0.5, 1, 2, 5, 10, and 20 µg/ml for Metformin HCl. The calibration curve was prepared taking the peak area of the analytes (Glimepride/ Metformin HCl) versus the concentration (µg/ml) using a weighted (1/concentration2) linear least squares regression as the mathematical model. The regression equation of the calibration curve was then used to calculate the drug content and *in vitro* drug release. The lowest limit of quantitation for Glimepride and Metformin HCl was determined from the peak signal to noise level (S/N) as 10.

Table 3: Evaluation of tablets

Batch. No.	Weight variation	Tablet thickness	Tablet hardness	Friability
A1	944 mg to 954 mg	8.45 mm ± 0.2 mm	95 N to 104 N	0.11 % w/w
A2	939 mg to 951 mg	8.45 mm ± 0.2 mm	98 N to 103 N	0.19 % w/w
A3	938 mg to 957 mg	8.48 mm ± 0.2 mm	85 N to 94 N	0.13 % w/w
A4	941 mg to 960 mg	8.45 mm ± 0.2 mm	91 N to 97 N	0.17 % w/w
B1	950 mg to 957 mg	8.45 mm ± 0.2 mm	95 N to 109 N	0.17% w/w
B2	938 mg to 959 mg	8.42 mm ± 0.2 mm	92 N to 107 N	0.21 % w/w
B3	948 mg to 960 mg	8.46 mm ± 0.2 mm	98 N to 111 N	0.19 % w/w
B4	944 mg to 959 mg	8.45 mm ± 0.2 mm	95 N to 103 N	0.23 % w/w
C1	940 mg to 961 mg	8.47 mm ± 0.2 mm	96 N to 104 N	0.09 % w/w
C2	935 mg to 954 mg	8.45 mm ± 0.2 mm	98 N to 104 N	0.11 % w/w
D1	939 mg to 959 mg	8.45 mm ± 0.2 mm	89 N to 103 N	0.20 % w/w
D2	943 mg to 959 mg	8.45 mm ± 0.2 mm	93 N to 104 N	0.19 % w/w
D3	934 mg to 951 mg	8.51 mm ± 0.2 mm	92 N to 106 N	0.07 % w/w
E1	942 mg to 955 mg	8.45 mm ± 0.2 mm	90 N to 111 N	0.13 % w/w
E2	941 mg to 956 mg	8.45 mm ± 0.2 mm	92 N to 114 N	0.14 % w/w
E3	939 mg to 951 mg	8.43 mm ± 0.2 mm	88 N to 100 N	0.22 % w/w
E4	948 mg to 959 mg	8.49 mm ± 0.2 mm	91 N to 101 N	0.15 % w/w
E5	943 mg to 957 mg	8.42 mm ± 0.2 mm	96 N to 109 N	0.18 % w/w

In vitro Drug Release Study

Dissolution samples were analyzed by HPLC method. For Glimepride, the concentration range was 0.1 to 10 mcg/ml and the correlation coefficient was 0.99 (y = 80.271x +1.99). For Metformin HCl, the standard curves were linear over the concentration ranges of 0.1 to 20 mcg/ml and the correlation coefficient was 0.99 (y = 856.5x + 23.79). The lower limit of quantitation for Glimepride was 40ng/ml, and its precision (CV %) and accuracy (%RE) values being 5.27% and +2.40% respectively. The lower limit of quantification for Metformin HCl was 50ng/ml, its precision (CV %) and accuracy (%RE) values being 6.59% and +3.83%, respectively. The representative chromatogram of a dissolution sample shows separation of Glimepride at 5.11 minutes and Metformin HCl at 2.26. There is no interfering peak in the chromatogram and the resolution between the two analytes peaks is good. The results are included in table 4

Drug Content

Twenty tablets were taken and crushed to powder with a mortar and pestle. The exact amount of powder (around 1150 mg) was taken and diluted with 0.1 N sodium hydroxide (NaOH) up to 100 ml of volumetric flask. After sonication for 15 minutes, the solution was filtered through 0.45-µm filter paper. The total amount of drug within the tablets was analyzed after appropriate dilution of the test solution by using the modified HPLC method[10]. The results are included in table 5.

Table 4: Floating lag time and dissolution of Glimepiride and Metformin Hydrochloride

Test	Batch No																	
	A1	**A2**	**A3**	**A4**	**B1**	**B2**	**B3**	**B4**	**C1**	**C2**	**D1**	**D2**	**D3**	**E1**	**E2**	**E3**	**E4**	**E5**
Floating lag time (min)	No floating	No floating	No floating	No floating	3	49	23	57	12	2	8	Erosion and bursting	Erosion and bursting	2	3	3	2	3
Dissolution (cumulative % drug dissolved)																		
Glimepiride (45 minutes) Metformin Hydrochloride	97.3	98.1	97.9	100.1	100.0	99.0	96.8	99.0	97.9	98.7	99.3	-	-	98.8	98.5	99.4	99.7	97.9
1 Hr.	27.3	27.0	36.7	34.6	26.4	19.7	18.9	20.9	23.9	29.9	37.2	-	-	29.0	28.6	27.3	22.7	27.5
4 Hrs.	68.5	59.8	78.3	63.2	53.5	75.3	70.0	62.9	55.2	54.7	74.4	-	-	45.5	45.3	44.3	35.1	50.6
8 Hrs.	85.3	77.7	94.9	87.3	94.7	100.0	100.0	99.9	86.1	90.0	99.9	-	-	76.0	67.3	67.2	83.8	98.1

Table 5: Drug Content (% w/w)

Batch No.	Glimepiride	Metformin Hydrochloride
A1	98.7	99.6
A2	99.1	98.9
A3	97.3	99.5
A4	99.1	97.3
B1	100.1	100.6
B2	98.2	101.0
B3	98.3	100.6
B4	99.1	98.6
C1	98.6	98.1
C2	97.9	98.6
D1	98.1	99.0
D2	98.3	98.0
D3	99.0	99.9
E1	100.1	96.9
E2	100.9	98.9
E3	98.6	98.9
E4	97.1	99.6
E5	98.3	97.5

RESULT AND DISCUSSION

The tablets of different formulations were subjected to various evaluation tests such as weight variation, thickness, hardness, friability, floating lag time, dissolution and drug content. All the formulations showed uniform thickness. The average percentage deviation of all tablet formulations was found to be within the limit. Hence all the formulations passed the uniformity of weight. Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. Friability of the tablets was evaluated by using Roche friabilator, the percentage of friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits. Drug contents of all formulation are also within the limit and found satisfactory.

For floating lag time and dissolution as mentioned in table 4 there is no floating observed in B.No. A1, A2, A3, A4. Erosion and bursting observed in B.No. D2 and D3. For B.No. B2, B3, B4 floating lag time is more than 20 minutes. B.No. E1, E2, E3 does not show complete release in dissoluiton. B.No. C1 and C2 had been taken for optimization of Sodium bicarbonate. B.No. E4 had been taken with Carbopol 934 and B.No. E5 had been taken with Carbopol 940.

CONCLUSION

The present study was carried out to develop a bilayered matrix tablets containing 1mg of Glimepride as immediate release component and 500mg Metformin HCl as sustained release component. Sodium starch glycolate is taken as super disintegrant in immediate release layer.

For floating SR layer 60 mg Sodium bicarbonate is finalized based on optimization trial and floating time compare to other salt. Carbopol 940 is finalized based on complete release of Metformin HCl. HPMC K100M is used as rate controlling agent.

From all the above data it had been concluded that B.No. E5 is suitable and better intragastric floating drug delivery system of Metformin HCl as sustained release component and glimepiride as immidiate release component.

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