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Gastroretentive System of Metformin: An Approach to Enhance Its Oral Bioavailability

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ABSTRACT

After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and prolonged manner, so that the drug is supplied continuously to its absorption sites in the upper gastrointestinal tract. In the present study an attempt was made to formulate Metformin as floating drug delivery system in order to enhance its bioavailability and to localize drug at the absorption site significance in controlling release rate for drugs having site specific absorption. Floating tablets of Metformin were formulated using sodium bicarbonate as gas generating agent and HPMC K4M as water swellable polymer by wet granulation method. These formulations were subjected to various evaluation parameters like hardness, friability, tablet density, floating test, swelling index, drug content, *in vitro* release studies, comparative evaluation with marketed products and stability studies. The results of all these parameters are tabulated and depicted graphically in the result and discussion section. IR spectral studies revealed that the drug, polymer and excipients used were compatible. Evaluation parameters viz. tablet dimensions, hardness, weight variation, friability and drug content were within acceptable limits for all three formulations. Batches F1, F2 and F3 showed satisfactory results for tablet density, floating test, and swelling studies.

Keywords: Metformin hydrochloride; Absorption window; Effervescent floating matrix tablet; Controlled release; Bioavailability.

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INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation[1]. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery[2]. These systems achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. This results in significant fluctuation in drug levels[3].Gastroretentive drug delivery systems have shown to be of better significance in controlling release rate for drugs having site specific absorption. The present study was an attempt to develop floating tablets of Metformin hydrochloride which on oral administration prolongs its gastric residence time thereby increasing bioavailability, diminishing side effects and enhanced patient compliance. Metformin an oral antidiabetic having narrow absorption window in the upper part of gastrointestinal tract, was formulated as floating matrix tablet using gas generating agent sodium bicarbonate and hydrophilic polymer hydroxypropyl methyl cellulose by wet granulation technique. All three formulations possessed good floating properties with total floating time more than 12 hours. The effect of stearic acid on drug release profile and floating properties were investigated, and results revealed better control on drug release with increase in the concentration of stearic acid. Studies on dissolution methods showed, the modified dissolution method as a better alternative to conventional method as it mimics the physiological conditions existing in gastrointestinal tract. Hence it is evident from this study that effervescent floating matrix tablet could be a promising delivery system for Metformin with controlled release action and improved drug availability. Now-a-days most of the pharmaceutical scientists are involved in developing an ideal drug delivery system (DDS). An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period[4]

MATERIAL AND METHODS

The following materials that were either AR/LR grade or the best possible pharma grade available were used as supplied by the manufacturer.

Sr. No.	Materials	Grade	Manufacturer
1	Metformin HCl	IP	Ajanta Pharma Ltd., Mumbai.
2	HPMC K4M (Methocel K4M	USP/EP	Colorcon Asia Pvt. Ltd., Goa.

	Premium)		
3	Stearic acid	L.R.	S.D. Fine Chem. Ltd., Mumbai.
4	Citric acid (anhydrous)	L.R.	S.D. Fine Chem. Ltd., Mumbai.
5	Sodium bicarbonate	L.R.	S.D. Fine Chem. Ltd., Mumbai.
6	Purified Talc	I.P.	Swastik Pharmaceuticals, Mumbai.
7	Magnesium stearate	A.R.	Loba Chemie Pvt. Ltd., Mumbai.
8	Chloroform	L.R.	Ranbaxy Fine Chemicals Ltd., New Delhi.
9	Isopropyl alcohol	A.R.	S.D. Fine Chem. Ltd., Mumbai.

DETAILS OF EQUIPMENTS USED:

Sr. No.	Instruments	Manufacturer
1	Electronic Balance	Afcoset, Mumbai.
2	Monsanto Hardness Tester	Ketan, Mumbai.
3	Roche Friability test apparatus	Secor, India.
4	Hydraulic Press	Kimaya Engineers, Mumbai.
5	Dial Caliper	Mitutoyo, Japan.
6	Tablet Dissolution Tester (USP XXIII) TDT-06P	Electro Lab
7	UV-Vis Spectrophotometer (UV-1201)	Shimadzu, Japan.
8	FTIR Spectrophotometer	Thermo Nicolet, USA.
9	Oven	PSM Industries, Bangalore.
10	Distillation unit	Bhanu Scientific Industries Co. Pvt. Ltd., Bangalore.
11	Magnetic Stirrer	Remi Equipments, Mumbai.
12	Test Sieve (No.60)	Filterwel, India.

METHODS

I) Preformulation Studies: It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility studies and compatibility studies.

a) **Determination of Melting Point:-** Melting point of Metformin was determined by capillary method.

b) **Solubility:-** Solubility of Metformin was determined in Water, 0.1N HCl, phosphate buffer pH 6.8 and Chloroform.

c) **Compatibility Studies:-** The compatibility of the drug and polymer under experimental conditions is an important prerequisite before formulation. It is necessary to confirm that the drug does not react with the polymer or excipients and affect the shelf life of the product. This can be confirmed by carrying out infrared spectroscopy studies.

Procedure:- The obtained drug, polymer and formulation F3 were subjected to IR studies. In the present study potassium bromide disc (pellet) method was employed and the obtained IR spectra were analysed comparatively, with reference spectrum of Metformin[5,6].

II) Preparation of Standard Calibration Curve of Metformin:

Preparation of Simulated Gastric Fluid TS (without enzyme): 2 gm Sodium chloride was dissolved in 7 ml of Concentrated Hydrochloric acid and the resulting solution diluted to 1000 ml with distilled water. This test solution had a pH of about 1.2.

Standard stock solution of Metformin:- 50 mg of Metformin HCl was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and diluted to volume with simulated gastric fluid (SGF) to give stock solution containing 500 µg/ml.

The standard stock solution was then serially diluted with SGF to get 5, 10, 20, 30 and 40 µg/ml of Metformin HCl. The absorbance of the solutions were measured against SGF as blank at 230 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve[7].

III) Formulation of Floating Tablets of Metformin:

Floating tablets of Metformin hydrochloride were prepared by wet granulation method using sodium bicarbonate as gas generating agent and water swellable polymer (HPMC K4M) as hydrophilic matrix in each formulation. The composition of each formulation is given in Table 1.

Metformin HCl was dispersed in chloroformic solution of the required quantity of Stearic acid. The dispersion was stirred using a magnetic stirrer and chloroform was evaporated to form Metformin HCl – Stearic acid mixture. This mixture was then blended with the remaining ingredients by geometric mixing. 1% w/v solution of HPMC K4M in isopropyl alcohol was used as the granulating agent. The granules (60 mesh) were dried in an oven at 45°C for 2 hours. The dried granules were then lubricated

with magnesium stearate (1% w/w) and purified talc (1% w/w) and compressed with a compression force of 2 ton (2000 kg) on a hydraulic press using 13 mm flat punch[8,9]. .

The composition of the various formulations prepared is listed in the table given below:

Table 1: Composition of Floating tablets of Metformin HCl with varying quantities of stearic acid

Ingredients (mg/tablet)	Batch Code		
	F1	F2	F3
Metformin HCl	500	500	500
Stearic acid	-	8	30
HPMC K4M	134	134	134
$NaHCO_3$	75	75	75
Citric acid (anhydrous)	15	15	15
All batches contained 1% w/w talc, and 1% w/w Magnesium stearate. HPMC K4M – Hydroxypropyl methyl cellulose, NaHCO3 – Sodium bicarbonate			

IV) Evaluation Parameters:

a) Pre-compression Parameters:

i) **Bulk Density:-** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of sample (5 gm) was transferred into a 25 ml measuring cylinder. The volume of packing was recorded. The measuring cylinder was then tapped 100 times on a plane hard wooden surface and the tapped volume of packing was recorded. LBD and TBD were calculated by the following formula:

$$LBD\ (Loose\ bulk\ density) = \frac{Weight\ of\ granules}{Volume\ of\ packing}$$

$$TBD\ (Tapped\ bulk\ density) = \frac{Weight\ of\ granules}{Tapped\ volume\ of\ packing}$$

ii) **Compressibility Index:-** Percent compressibility of granules as determined by Carr's compressibility index was calculated by the following formula:

$$Carr's\ Index = \frac{TBD - LBD}{TBD} \times 100$$

iii) **Angle of Repose (θ):-** The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r, \ \theta = \tan^{-1} (h/r)$$

Where θ = Angle of repose, h = height, r = radius

Values of angle of repose ≤30° indicate free flowing granules and ≥40° suggest poorly flowing material[10].

b) Post-Compression Parameters: The tablets were evaluated for the various parameters enlisted below:-

Appearance:- The compressed tablets were examined under the magnifying lens for its appearance.

Thickness and Diameter:- The tablet dimensions were measured using a calibrated dial caliper. 5 tablets of each batch were picked randomly and its thickness and hardness were measured individually. Tablet thickness should be controlled within ±5% variation of a standard value[11].

Weight Variation:- The procedure described in IP 1996 was employed to determine the weight variation of the tablets. Ten tablets were randomly selected from each batch and weighed on a electronic balance and the mean weight taken. Each tablet was then weighed individually and the standard deviation in weight was calculated for each batch[12].

Hardness:- Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets were determined using Monsanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked from each batch and the hardness of the tablets were determined. The mean and standard deviation values were calculated for each batch.

Friability:- Friability of the tablets were determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions, and then the

tablets were weighed again (W_{final}). The loss in tablet weight due to abrasion or fracture was the measure of tablet friability. % Friability was then calculated by :-

$$F = \frac{W(initial) - W(final)}{W(initial)} \times 100$$

% Friability of less than 1% is considered acceptable.

Tablet Density:- Tablet density is an important parameter for floating tablets. The tablet will only float when its density is less than that of gastric fluid (1.004g/cm^3). The density was determined using following relationship.

$$V = \pi r^2 h \quad d = m/V$$

V = volume of tablet (cc), r = radius of tablet (cm), h = crown thickness of tablet (cm)
m = mass of tablet (g), d = density of tablet (g/cc)[13]

Floating Test:- The tablets were placed in a 100 ml beaker containing simulated gastric fluid. The time between introduction of dosage form and its buoyancy on simulated gastric fluid, and the time during which the dosage form remains buoyant were measured. The time taken for the dosage form to emerge on surface of medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time during which the dosage form remains buoyant is called Total Floating Time (TFT)[14].

Swelling Study:- The swelling behaviour of a dosage form is measured by studying its weight gain or water uptake (WU). The study was done by immersing the dosage form in SGF at 37°C and determining these factors at regular intervals up to a period of 5 hours. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$WU = (W_t - W_o) \times 100 / W_o$$

W_t = Weight of the dosage form at time t. W_o = Initial weight of the dosage form[15].

Determination of Drug Content:- The assay method described in IP 1996 for Metformin tablets was employed to determine the drug content of Metformin floating tablets.

Procedure: Tablet powder containing 0.1g of Metformin HCl was shaken with 70 ml of water for 15 minutes, diluted to 100 ml with water and filtered, discarding the first 20 ml. 10 ml of the filtrate was diluted to 100 ml with water, and from the resulting solution 10ml was further diluted to 100 ml with water. The absorbance of the resulting solution was measured at the maximum at 232 nm

and the content of Metformin HCl was calculated taking 798 as the value of A(1%,1cm) at the maximum at 232 nm.

1) **In vitro Dissolution Studies:-** In vitro drug release of Metformin floating tablets was determined by 2 methods.

a) USP dissolution apparatus 2:

In vitro drug release profile of Metformin HCl was evaluated using USP dissolution apparatus 2 (paddle, 900 ml simulated gastric fluid (without enzyme), 37±0.5°C, 75 rpm). One tablet was placed in each of the six dissolution vessels and the system was run.

Aliquots of samples were withdrawn after 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 10^{th} and 12^{th} hour. Fresh dissolution medium was replaced to maintain the original volume. The withdrawn aliquots were filtered, suitably diluted with SGF to obtain concentration of 20 µg/ml, and its absorbance measured spectrophotometrically at 230 nm to determine drug release.

Kinetic Treatment:- The data obtained from in vitro dissolution studies was subjected to kinetic treatment in order to determine release kinetics of the formulations[16].

b) Modified Dissolution Method :-

The proposed method is essentially a modification of the Rossett-Rice test, which is a popular in vitro test for evaluating the acid neutralization efficiency of antacids. In the proposed method, a gastric emptying phenomenon is mimicked by providing a delivery tube at the bottom of the inverted bottle. The test also tries to simulate the conditions of a flow-through cell with respect to availability of fresh dissolution medium around the dosage form. In short, the modified test tries to mimic the gastric volume (70 ml), gastric acid secretion rate (2ml/min) and emptying of liquid through pylorus opening.

Procedure: 150 ml capacity plastic bottle was modified by cutting the base of the bottle and securing tightly its mouth by means of cork; so that the bottle can hold 70 ml of dissolution medium. A plastic tube was inserted into the mouth of the bottle such that the medium comes out from the end of the tube at a rate of 2ml/min. The reservoir containing dissolution medium was mounted at a level higher than the dissolution assembly, so as to deliver the medium at the same flow rate.

The modified assembly was placed into the dissolution vessel. Metformin floating tablet was introduced in the modified bottle containing 70 ml of SGF. When the tablets floated, the contents were stirred at a speed of 75 rpm using USP apparatus I without the wire mesh. Temperature of the dissolution medium was maintained at 37±0.5°C.

In order to maintain sink conditions for study, SGF was added at rate of 2ml/min to 70 ml of dissolution medium, simultaneously withdrawing 2ml/min from the bottom outlet. The modified dissolution assembly is shown in Plate 2. Aliquots were collected after 1st, 2nd, 4th, 6th, 8th, 10th and 12th hour. The aliquots were filtered, diluted with SGF to obtain concentration of 20 µg/ml and its absorbance measured spectrophotometrically at 230 nm to determine drug release.

12) Stability Studies:

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and pack profile.

The prepared floating tablets of Metformin were placed in plastic tubes containing dessicant and stored at ambient humidity conditions, at room temperature, oven temperature (40±2°C) and in refrigerator (2-8°C) for a period of 30 days.

The samples kept for stability were evaluated for the following physicochemical parameters after 7, 15 and 30 days[17,18,19].

RESULTS AND DISCUSSION

Hydrodynamically balanced tablets of Metformin were prepared and evaluated for their use as gastroretentive drug delivery systems to increase its bioavailability. In the present study, three formulations were prepared and the composition of all the batches are shown in Table 1. The formulated tablets are shown in Plate 1. The tablets were characterized for various physicochemical parameters.

I) PREFORMULATION STUDIES:

a) **Melting point determination:** Melting point of Metformin was found to be in the range of 223 – 225°C, which complied with IP standards, indicating purity of the drug sample.

b) **Solubility:** Metformin was found to be freely soluble in water, 0.1N HCl, phosphate buffer pH 6.8 and practically insoluble in chloroform.

c) **Compatibility Studies:** Compatibility studies were performed using IR spectrophotometer and the IR spectrum of the obtained drug, polymer and formulation F3 were studied. The characteristic absorption peaks of Metformin obtained at 1495cm^{-1}, 1028cm^{-1} were seen in the IR spectrum of F3, indicating compatibility of drug with formulation components. The IR spectrum of the drug, polymer and F3 formulations are shown in Spectra No.1, 2 and 3 respectively.

II) STANDARD CALIBRATION CURVE OF METFORMIN:

The λmax of Metformin HCl in simulated gastric fluid was found to be 230 nm. The absorbance values are tabulated in Table 2. Metformin obeyed Beer's law in the concentration range of 5-40 µg/ml with regression coefficient of 0.9994.

III) EVALUATION OF HYDRODYNAMICALLY BALANCED TABLET FORMULATIONS OF METFORMIN:

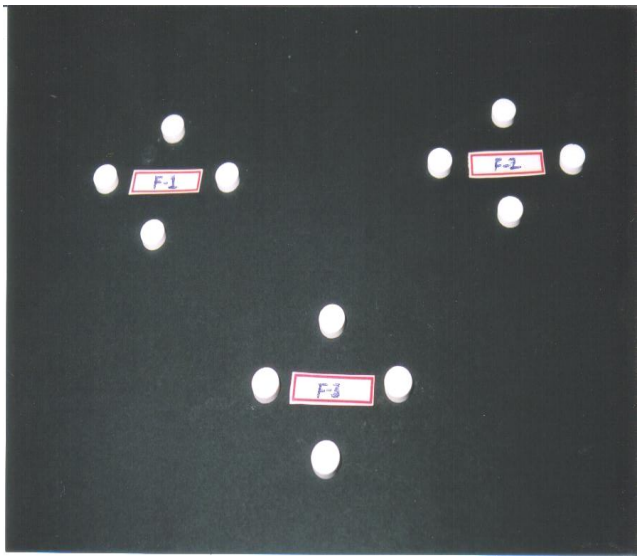

Plate No.1: Tablet Formulations

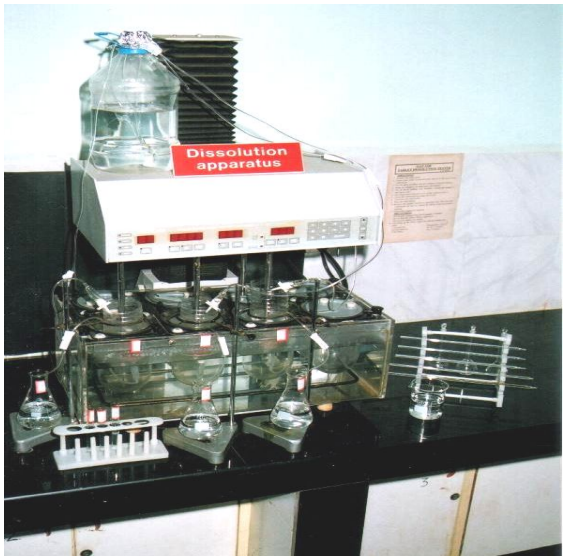

Plate No.2: Modified Dissolution Assembly

***IN VITRO* BUOYANCY STUDY**

Plate No.3: At Initial Time

Plate No.4: After 3 Minutes

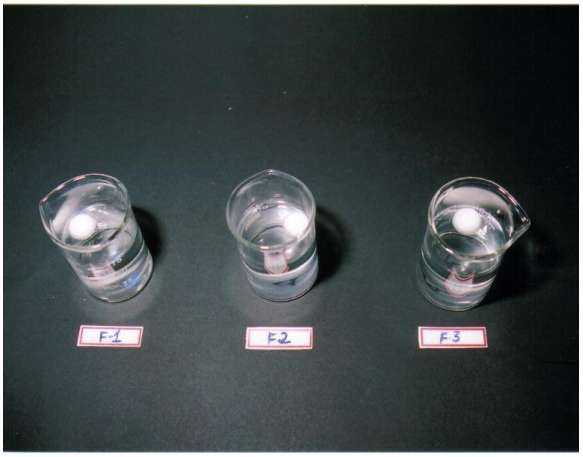

Plate No.5: After 4 Hours

Table No.2: Absorbance of standard solutions of Metformin HCl in SGF at 230 nm

Sr. No.	Concentration (µg/ml)	Absorbance
1	5	0.151
2	10	0.296
3	20	0.571
4	30	0.841
5	40	1.166

Table No.3 Micromeritic Evaluation of Granules

Sr. No.	Formulation	Mass of granules (gm)	Volume of packing (ml)	Tapped volume of packing (ml)	LBD (g/ml)	TBD (g/ml)	Compressibility Index (%)	Angle of Repose (θ)
1	F-1	5	11	8	0.454	0.625	27.36	37°69’
2	F-2	5	10.5	7.5	0.476	0.666	28.53	35°21’
3	F-3	5	12.5	9	0.4	0.555	27.93	38°33’

Table No.4 Physicochemical Properties of Metformin Floating Tablets Batches F1 to F3

Batches	Diameter (mm) Mean±SD (n=5)	Thickness (mm) Mean±SD (n=5)	Hardness (kg/cm^2) Mean±SD (n=5)	Friability (%)	Weight Variation (gm) Mean±SD (n=10)	Drug Content (%)	Compressibility Index (%)	Angle of Repose (θ)
F1	13.13 ±0.027	4.43 ±0.027	3.2 ±0.45	1.35	0.7392 ±0.008	99.54	27.36	37°69’
F2	13.11 ±0.022	4.45 ±0.021	4.6 ±0.55	0.96	0.7463 ±0.002	99.28	28.53	35°21’
F3	13.13 ±0.027	4.45 ±0.021	7.0 ±0.71	0.72	0.7649 ±0.002	98.12	27.93	38°33’

Table No.5 Tablet Density, Buoyancy Lag Time, Total Floating Time

Batch	Tablet Density (g/cc)	Buoyancy Lag Time (Sec)	Total Floating Time (hrs)
F1	1.22	55 sec	>12 hrs
F2	1.24	110 sec	>12 hrs
F3	1.27	240 sec	>12 hrs

Table No.6 Swelling Index of Tablets of Batches F1 to F3

Time (hrs)	Swelling Index (%)		
	F1	F2	F3
1	40.7	39.2	30.2
2	51.4	44.9	40.8
3	62.3	50.7	46.4
4	73.4	59.2	53.8
5	89.9	68.4	60.1

Table No.7 Cumulative % Drug Released from Tablet Formulations F1 to F3 using Modified Dissolution Apparatus

Time (hrs)	Cumulative % Drug Released		
	F1	F2	F3
1	15.1	13.6	12.2
2	35.9	34.9	32.7
3	50.6	53	51
4	62.9	68.5	65.2
6	74.7	80.7	75.6
8	85.7	89.6	84.1
10	93.1	94.5	90.5
12	97.6	96.3	93.5

Table No.9Model Fitting of Release Profile of batches F1 to F3 using Different Models

Dissolution Method	Batch No.	Mathematical Models (r-values)			
		First order	*Higuchi matrix*	*Peppas*	Zero order
USP dissolution apparatus 2	F1	0.9958	0.9851	0.9911	0.9517
	F2	0.9961	0.991	0.9948	0.9659
	F3	0.9948	0.9903	0.993	0.9644
Modified dissolution apparatus	F1	0.9883	0.9838	0.9674	0.9458
	F2	0.9983	0.964	0.9514	0.9135
	F3	0.9971	0.9682	0.95	0.9204

Table No.10 Cumulative % Drug Released from Marketed Conventional Tablet of Metformin

Time (mins)	Cumulative % Drug Released (Gluformin-500)
15	41.4
30	79.2
45	95.5

Table 11: Formulations F1 to F3 stored at Room Temperature

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test		Drug Content %	Cum. % Drug Released
				BLT (sec)	TFT (hrs)		
F1	7	3.3	1.37	53	>12 hrs	99.26	94.4
	15	3.3	1.36	58	> 12 hrs	98.79	93.9
	30	3.6	1.36	63	> 12 hrs	98.22	93.1
F2	7	4.7	0.96	114	> 12 hrs	99.04	92.1
	15	4.7	0.98	112	> 12 hrs	98.89	91.6
	30	4.7	0.98	115	> 12 hrs	98.56	90.8
F3	7	7	0.74	236	> 12 hrs	98.07	86.4
	15	7	0.74	242	> 12 hrs	97.93	85.5
	30	6.7	0.78	244	> 12 hrs	97.86	87.1

Table No.12 Formulations F1 to F3 stored in Refrigerator (2-8°C)

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test		Drug Content %	Cum. % Drug Released
				BLT (sec)	TFT (hrs)		
F1	7	3.3	1.36	54	> 12 hrs	99.49	94.7
	15	3.3	1.38	56	> 12 hrs	99.12	93.8
	30	3.6	1.38	59	> 12 hrs	98.95	93.5
F2	7	4.6	0.96	112	> 12 hrs	99.13	92.5
	15	4.7	0.97	113	> 12 hrs	99.02	91.5
	30	4.7	0.98	115	> 12 hrs	98.89	91
F3	7	7	0.73	239	> 12 hrs	98.1	86.6
	15	7.3	0.74	241	> 12 hrs	98.03	85.9
	30	7.3	0.74	244	> 12 hrs	97.91	85.1

Table No.13 Formulations F1 to F3 stored at 40°C

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test		Drug Content %	Cum. % Drug Released
				BLT (sec)	TFT (hrs)		
F1	7	3.7	1.38	56	>12 hrs	99.34	94
	15	3.7	1.39	59	> 12 hrs	98.42	93.2
	30	3.7	1.4	65	> 12 hrs	98.01	92.9
F2	7	4.7	0.98	115	> 12 hrs	99.07	91.9
	15	5	0.99	118	> 12 hrs	98.55	91.3
	30	5	0.99	118	> 12 hrs	98.11	90.4
F3	7	7	0.74	245	> 12 hrs	98.09	86.1
	15	7	0.76	248	> 12 hrs	97.74	85.8
	30	6.7	0.8	250	> 12 hrs	97.23	86.9

CONCLUSION:

Hydrodynamically balanced tablets of Metformin can be formulated with an approach to increase gastric residence and thereby improve drug bioavailability. An attempt to develop floating tablets of Metformin, using sodium bicarbonate as gas generating agent and HPMC K4M as hydrophilic polymer by wet granulation method was achieved. The formulated tablets showed compliance for various physiochemical parameters viz. tablet dimensions, total floating time, tablet density and drug content. Incorporating higher amount of stearic acid showed a better control of drug release in formulation F3 followed by F2 and F1. The modified dissolution method is a better alternative to the conventional method as it mimics the physiological conditions existing in GIT. Data obtained from kinetic treatment revealed all three formulations follow first order release. The results of stability studies indicated that the most suitable storage temperature was 2-8°C for a period of 30 days. The present work can be investigated further to assess the long term stability of Metformin floating tablets, determination of gastric residence time using gamma scintigraphy, *in vivo* evaluation of Metformin floating tablet and establishment of *in vitro – in vivo* correlation.

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