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RESEARCH ARTICLE

Formulation and Evaluation of Hydrodynamically Balanced Floating Tablet of Biguanide Class Anti-Hypertensive Drug

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ABSTRACT

Floating sustained release dosage forms present the most of the characteristics of hydrophilic matrices & are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates & builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3-4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Hydrodynamically balanced tablets of Metformin have been 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 and xanthin gum as hydrophilic polymer by wet granulation method was achieved. The formulated tablets showed compliance for various preformulation studies and various evaluation parameters like hardness, friability, tablet density, floating test, drug content and in vitro release studies.

KEYWORDS

Hydrodynamically Balanced Tablets, Metformin, HPMC K4M, Xanthin gum

INTRODUCTION

Metformin is a biguanide glucose-lowering agent that has been widely used in the management of NIDDM, whose hyperglycemia cannot be satisfactorily managed on diet alone. Metformin is incompletely absorbed from GI tract, with an absorption window confined to the upper part of GI tract. It also has a half life of about 2 hours and its absolute bioavailability is reported to be about 50-60% of the administered oral dose. An obstacle to the more successful use of Metformin therapy is the high incidence of GI symptoms seen in about 30% patients, especially during initial weeks of treatment.

Patient compliance decreases with frequent dosing regimen and side effects associated with the same. The above drawbacks provide a rationale for developing Metformin as a gastroretentive dosage form, which is retained in the stomach and produces a constant input of drug to the absorption site. This improves bioavailability of the drug, reduces frequency of dosing, thus minimizing side effects and enhances patient compliance. The present study outlines a systematic approach for the development of hydrodynamically balanced tablet of Metformin with a view to enhance its oral bioavailability and efficacy. [1-5]

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MATERIALS AND METHODS

Materials

Metformin as a gift sample from Strites Lab, Bangalore; HPMC K15 M & Xanthin Gum was obtained from Coral Pharmaceuticals, Ahmedabad; Sodium bicarbonate, Tartaric acid, Lactose, Talc & Magnesium stearate was obtained from S.D. Fine Chem. Ltd., Mumbai. All other chemicals & reagents used were of analytical grade.

Methods

Preformulation Studies [26,27]

Organoleptic Properties

Colour: A small quantity of Metformin Hydrochloride was taken in butter paper and viewed in well-illuminated place.

Taste and Odour: Very less quantity of Metformin Hydrochloride was used to get taste with the help of tongue as well as smelled to get the odour.

Physical Characteristics

Solubility Studies: The spontaneous interaction of two or more substances to form a homogenous molecular dispersion is called as solubility in that solvent**.** For the qualitative or crude solubility study, a known amount of drug (10 mg) was suspended in a series of different solvents (10 mL) at room temperature in tightly closed test tubes and shaken on wrist action shaker for 24 hrs. The crude solubility was observed only by visual inspection.

Partition Coefficient: Partition co-efficient of metformin in n-octanol-water was determined. Equal volumes of water and n-octanol (15 ml) were taken in separating funnel. To this known amount of metformin was added. The funnel was equilibrated for 4 hours at constant temperature with intermittent shaking at regular intervals. Then the aqueous and octanol layers were separated. The concentration of the solute in aqueous layer was determined by UV spectrophotometry after appropriate dilutions. The solvent in the organic layer was evaporated to obtain a residue. This residue was dissolved in a suitable solvent and then after appropriate dilution the concentration of the solute was determined by a UV spectrophotometry. The n-octanol – water partition coefficient of the drug was obtained using the following equation.

Loss on Drying: 1 gm of drug was weighed and kept for checking the loss on drying on a moisture sensitive balance at 105°C for 3 mins.

$$\text{Partition Co-efficient} = \frac{\text{Concentration of the drug in organic layer}}{\text{Concentration of the drug in aqueous layer}}$$

Percentage loss of moisture content is determined.

Melting Point Determination: Melting point determination of the obtained drug sample was done; as it is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by lowering as well as widening in the melting point range.

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 UV-Visible spectroscopy studies.100 mg quantities metformin, were weighted and each was dissolved in 100 ml of 0.1 N hydrochloric acid solution. Similarly 150 mg of powder blend containing 100 mg drug and 50 mg of powder blend containing no drug (placebo) were dissolved. All flasks were kept for 45 minutes in ultrasonic bath. Later solutions were filtered. Filtered solutions were diluted 100 times and the absorbances were measured at corresponding wavelength to verify the interference of additives.

Analytical Method Used in the Determination of Metformin Hcl[9,11,24,26]

Preparation of Reagent: Hydrochloric acid solution, 0.1 N: Concentrated hydrochloric (8.5 ml) acid was diluted with distilled water and volume was made up to 1000 ml with distilled

water. pH (1.2) was adjusted with dilute hydrochloric acid.

Preparation of Metformin Standard Stock Solution (1000 µg/ml) in 0.1 N HCl Solution: A standard stock solution of metformin hydrochloride was prepared by dissolving accurately weighed 100 mg of metformin in 0.1 N HCl solution in a 100 ml volumetric flask and the volume was made up to 100 ml with 0.1 N HCl solution to obtain a stock solution of 1000 µg/ml.

Determination of Analytical Wavelength: From the standard stock solution, 0.5 ml was pipetted into 100 ml volumetric flask. The volume was made up to 100 ml with 0.1 N HCl solution. The resulting solution containing 20 µg/ml was scanned between 200 and 400 nm. The λmax was found to be 201.5 nm. Since 201.5 nm cannot be considered as a λmax, 233 nm was considered as analytical wavelength.

Calibration Curve of Metformin Hydrochloride in 0.1 N HCl Solution: Accurately weighed quantity of metformin hydrochloride (50 mg) was dissolved in little quantity of 0.1 N HCl solution and volume was made up to 100 ml. Appropriate aliquots were taken into different volumetric flasks and volume was made up to 50 ml with 0.1 N HCl solution so as to get drug concentrations of5, 10, 15, 20, 25 µg/ml. The absorbencies of these drug solutions were estimated at λmax233 nm. This procedure was performed in triplicate to validate the calibration curve.

Method of Prepatration[6-9]

The composition of different formulations of metformin floating tablets is shown in Table No.1. The ingredients were weighed accurately and mixed thoroughly. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol. The granules (40 mesh) were dried in conventional hot air oven at 45°C. Drying of the granules was stopped when the sample taken from the oven reached a loss on drying (LOD) value of 1 to 3%, as measured by a moisture balance at 105°C.The dried granules were sized through 40/60 mesh, lubricated with magnesium stearate (2% w/w) and purified talc (1 % w/w) and then compressed.

Table 1: Formulation of Metformin Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Metformin	500	500	500	500	500	500
HPMC K 15 M	50	75	-	-	25	50
Xanthan gum	-	-	50	75	50	25
Sodium bicarbonate	20	20	20	20	20	20
Tartaric acid	10	10	10	10	10	10
PVP-K-30	10	10	10	10	10	10
Dicalcium phosphate	100	75	100	75	75	75
Magnesium Stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total weight	700	700	700	700	700	700

Evaluation Parameters

Pre-Compressional Parameters[11-16]

Bulk Properties: Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml gm/cc, by the formula:

Bulk density = Bulk Mass/ Bulk Volume

Compressibility Index (Carr's Index): Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. It can be calculated as per given formula:

$$C.I. = \frac{100\,(V_0 - V_f)}{V_0} \quad \text{OR} \quad C.I. = \frac{\text{Tapped density} - \text{Bulk densities}}{\text{Tapped density}} \times 100$$

Table 2: Carr's index range

S. no.	% Comp. Index	Properties
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair – passable
4	23-25	Poor
5	33-38	Very Poor
6	>40	Extremely poor

Hausner's Ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

Table 3: Hausner ratio and flow property characteristics

S. no.	Hausner Ratio	Property
1.	0.0 - 1.2	Free flowing
2.	1.2 - 1.6	Cohesive powder

*Standard value of Hausner ratio is 1.25.

Angle of Repose: The angle of repose is a relatively simple technique for estimating the flowability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resulting cone is measured and using the following equation, the angle of repose can be calculated.

$$\tan \theta = h/r$$

Where, h, r is the relatively height and radius of the powder cone. For most pharmaceutical powders, the angle of repose values range from 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose $\leq$ 30 usually indicate a free flowing material and angle $\geq$40 suggest a poorly flowing material.

Post-Compressional Parameters[17-22]

Shape and Color of Tablets: Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light.

Thickness Test: Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Weight Variation Test: Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Table 4: Percentage deviation in weight variation

Sr. No.	Average Weight of A Tablet	Percentage Deviation
1.	130 mg or less	10
2.	More than 130 mg and less than 324 mg	7.5
3.	324 mg or more	5

In all the formulations the tablets weight is more than 130 mg and less than 324 mg, hence 7.5% maximum difference allowed.

Hardness Test: The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2**.**

Friability Test: For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%Friability = (Loss\ in\ weight/Initial\ weight) \times 100$$

The test complies if tablets not loose more than 1% of their weight

Floating Property: The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in 100-mL beaker containing 0.1M HCL. The time required for the tablet to rise to the surface for floating was determined as the BLT and further floating duration of all tablets was determined by visual observation.

Drug Content

I Stock Solution: Twenty tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 100 mg of metformin and transferred to a 100 ml volumetric flask containing few ml of 0.1M HCL and shake for some time and make up the volume up to 100 ml with 0.1M HCL.

II Stock Solution: Pipette out 10 ml from the I stock solution into another 100 ml volumetric flask and make up the volume with 0.1M (i.e. 100 µg/ml).

Aliquots: From the above solution withdraw 1ml quantity (as per Beer's range 5-30 µg/ml) and the volume was made up to 10 ml with 0.1M HCl. The absorbance was measured spectrophotometrically at 318 nm using 0.1 M HCL as blank.[20,21,22]

In Vitro Release Studies: The release rate of metformin from floating tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1M HCL, at 37 ± 0.5°C and 50 r/min. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 318 nm. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot.[25,26,27]

Curve Fitting Analysis: The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows: Cumulative % drug released versus time (Zero –order kinetic model); Log cumulative percent drug remaining versus time (First-order kinetic model) ; Cumulative % drug released versus square route of time (Higuchi model); Log percentage cumulative release versus log time. (Korsemeyer-Peppas model). For Fickian release n=0.45 while for anomalous (non-Fickian) transport, n ranges between 0.45 and 0.89.

RESULTS AND DISCCUSION

Preformulation Studies

Organoleptic Properties

The drug source is identified and found complying with the specifications.

Table 5: Organoleptic property of Metformin

Description	Specification	Result
Colour	White crystalline powder	White crystalline powder
Odour	Odourless	Odourless
Taste	Tasteless	Tasteless

Physical Characteristics

Solubility Studies

Table 6: Solubility of Metformin

Solvent	Solubility
Water	Freely Soluble
0.1N HCl	Freely soluble
Phosphate buffer pH 6.8	Freely soluble
Ethanol	Slightly soluble
Acetone	Practically insoluble
Chloroform	Practically insoluble
Dichloromethane	Practically insoluble
Diethylether	Practically insoluble

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.

Table 7: Melting point of Metformin

Reported Melting point	Observed melting point
222-226°C	223 – 225°C

Partition Coefficient: The partition coefficient of metformin conducted by shake-flask method was found to be 0.066. Metformin is highly soluble in water and having poor lipid solubility coming under the category of class 3 of biopharmaceutical classification (BCS) system.

Loss on Drying: The drug source is identified and found complying with the specifications.

Table 8: Loss on drying of Metformin

Test	Specification	Result
Loss on drying	Not more than 0.5% W/W	0.25% W/W

Compatibility Studies: The results of UV spectroscopic analysis indicated that there was no chemical interaction between the drug and the additives as the respective formulation (Drug and Polymer combination) exhibited absorption nearly similar to those of the pure drug sample.

Table 9: Interference of Additives/Compatibility Testing

Formul-ation	Absorbance of solutions			Interference Yes / No
	Polymer blend with drug	Placebo	Pure drug	
Metformin-HPMC K15M	0.214	0.003	0.211	No
Metformin-Xanthin Gum	0.213	0.002	0.211	No
Metformin-Xanthin Gum - HPMC K15M	0.213	0.002	0.211	No

Analytical Methods

The λmax was found to be 233 nm and considered as analytical wavelength

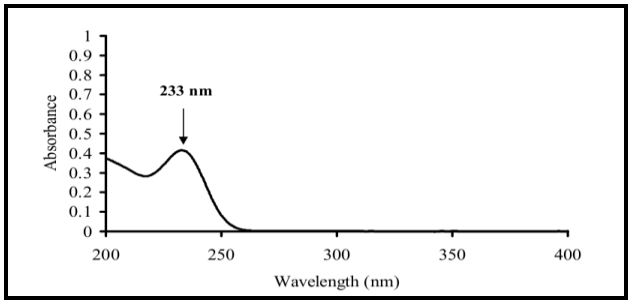

Figure 1: λmax of Metformin

Calibration Curve of Metformin Hydrochloride in 0.1 N HCl Solution

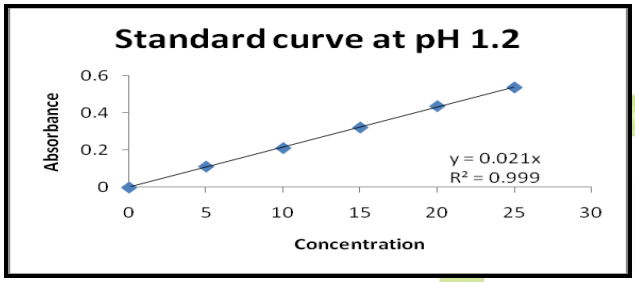

Figure 2: Calibration curve of Metformin

Pre-Compression Evaluation of Metformin Floating Tablets: Flow properties play an important role in pharmaceuticals especially in tablet formulation. The bulk density of the granules for formulations was in the range of 0.412 to 0.455 gm/cc; the tapped density was in the range of 0.511 to 0.551 gm/cc, which indicate powder was not bulky. The angle of repose of the drug powder was in the range of 20.1^0 to 23.1^0, which indicate good flow of the granules, the Carr's index was found to be in the range of 12.42 to 16.38 indicating compressibility of the tablet granules is good as reported in table.

Post Compression Parameters

Thickness Test: reveals that all the formulations showed uniform thickness. The thickness of the tablet indicates that die fill was uniform.

Weight Variation: It was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per Pharmacopoeial standard the deviation should not be more than 5%). All formulations showed values within ranges.

Table 10: Pre-compression evaluation parameters

Formulation code	Bulk density (g/cc) ± SD	Tapped density (g/cc) ± SD	Angle of repose (Ɵ) ± SD	Carr's index ± SD
F1	0.446 ± 0.011	0.514 ± 0.041	20.1^0 ± 0.7	12.42 ± 0.74
F2	0.453 ± 0.005	0.528 ± 0.096	21.2^0 ± 0.4	14.61 ± 0.52
F3	0.428 ± 0.113	0.518 ± 0.013	22.4^0 ± 0.3	16.40 ± 0.79
F4	0.412 ± 0.035	0.511 ± 0.038	21.5^0 ± 0.4	15.26 ± 0.32
F5	0.433 ± 0.147	0.551 ± 0.052	23.1^0 ± 0.5	16.17 ± 0.27
F6	0.455 ± 0.012	0.527 ± 0.016	22.1^0 ± 0.4	16.38 ± 0.13

SD=Standard deviation (n=3)

Hardness: Hardness test states that all the formulations were found in the range 5 to 6 kg/cm^2.

Friability: Another measure of tablet hardness was the friability. Compressed tablets that lose less than 1 %of their weight are generally considered acceptable. For all formulation tried here the weight loss was <1 %hence acceptable.

In Vitro Buoyancy Studies: Buoyancy Studies were performed using 0.1M HCL solution pH at 37 ^{o} C; the tablets floated and remained buoyant without disintegration. Table showed the results of Buoyancy study and buoyancy character of prepared tablet. Duration of floating for prepared tablet of each batch remained buoyant up to 12 hrs.

Table 11: Post Compression Parameters

Formulation Code	Thickness ± SD (mm)	Hardness ± SD (kg/cm^2)	Friability (%) ± SD	Average weight variation ± SD
F1	4.30 ± 0.021	5.14 ± 0.041	0.513 ±0.090	2.655 ±0.124
F2	4.42 ± 0.034	5.28 ± 0.096	0.380 ±0.044	4.516 ±0.214
F3	4.51 ± 0.012	5.18 ± 0.013	0.485 ±0.086	3.311 ±0.154
F4	4.55 ± 0.001	5.11 ± 0.038	0.266 ±0.027	2.963 ±0.413
F5	4.23 ± 0.005	5.51 ± 0.052	0.385 ±0.020	1.051 ±0.622
F6	4.10 ± 0.011	5.27 ± 0.016	0.578 ±0.04	2.922 ±0.266

SD=Standard deviation (n=3)

Drug Content Uniformity of Metformin Floating Tablets: The drug content estimation data for all the formulations were shown in table and found to be within the limit.

Table 12: % Drug content

Formulation Code	%Drug Content ± SD
F1	96.18 ± 0.005
F2	95.25 ± 0.003
F3	96.71 ± 0.004
F4	95.36 ± 0.005
F5	95.27 ± 0.004
F6	96.33 ± 0.005

* SD=Standard deviation (n=3)

Table 13: Floating lag time and total floating time

Formulation Code	Floating lag time (S)	Total Floating Time (h)
F1	24.13 ±1.12	>12
F2	45.0 ± 1.03	>12
F3	63.46 ± 0.27	>12
F4	72.76 ± 2.18	>12
F5	51.04± 2.05	>12
F6	74.09 ± 1.1	>12

* SD=Standard deviation (n=3)

In vitro Drug Release Data of Metformin Floating Tablets: *In- vitro* dissolution studies were performed for all the formulations using USP type II tablet dissolution tester employing basket type at 50 rpm using 900 ml of 0.1M HCL as dissolution medium. The formulation F1 containing Drug: HPMC shown cumulative percentage release of 98.55 % at 8th hr. But the objective of the formulation is to develop metformin tablet which sustain the release upto 12 hrs. Formulation F2 containing Drug: HPMC was increased showed 98.6% cumulative release at the end of 10th hr. In the formulation F3 and F4 attempt was made to achieve the objective by incorporating Xanthan gum instead of HPMC. The formulation F3 containing Drug:Xanthan gum shown cumulative percentage release of 98.33% at 9th hr. F4 formulation containing Drug: Xanthan gum, showed 98.3% cumulative release at the end of 11th hrs. An attempt was made to optimize the release by using mixture of HPMC and Xanthan gum in different ratio. Formulation F5 containing combination of HPMC: Xanthan gum (2:1) showed cumulative percentage release of 98.47 % at 10th hrs. Formulation F6 containing HPMC: Xanthan gum (1:2) showed 98.38% cumulative release at the end of 12th hrs. Formulation F9 was found to achieve the objective.

Zero Order Release Kinetics Data

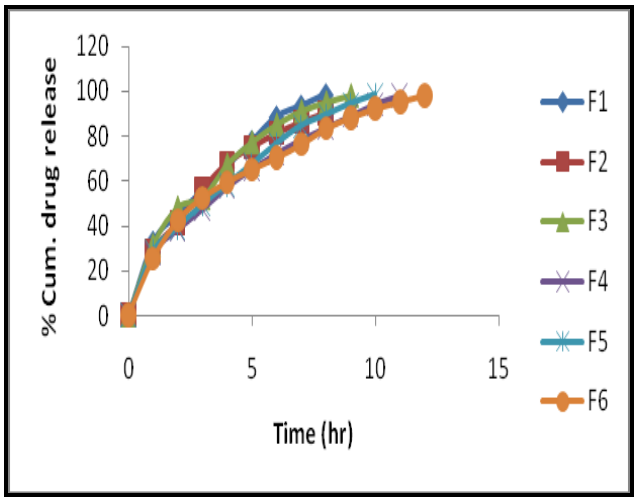

Figure 3: Zero Order Release Kinetics Graph

First Order Release Kinetics Data

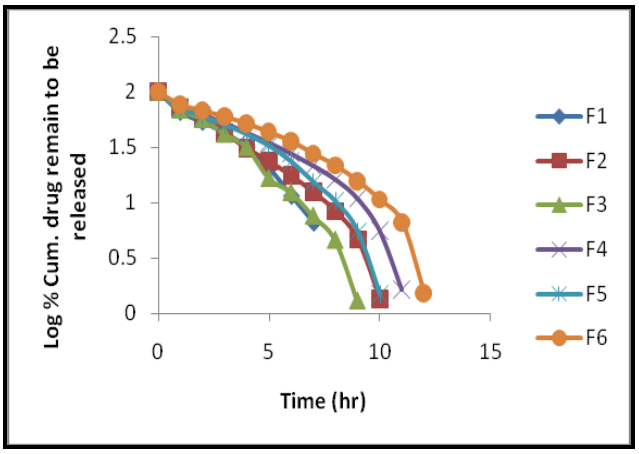

Figure 4: First Order Release Kinetics Graph

Higuchi Matrix Release Kinetics Data

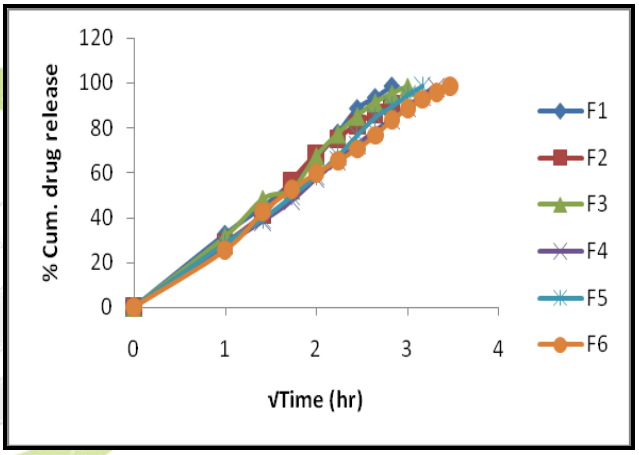

Figure 5: Higuchi matrix release kinetics data graph

Peppas Release Kinetics Data

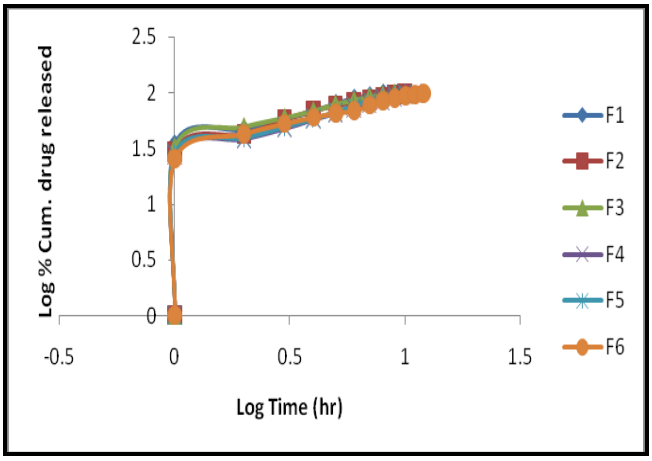

Figure 6: Peppas Release Kinetics Data Graph

Curve Fitting Analysis: Calculated regression co-efficient for different formulations are shown in Table. These values of in-vitro release were attempted to fit into various mathematical models, plot of zero order, first order, higuchi matrix and peppas. These values were compared with each other for model fitting equation. Observed that formulation F1, F2 and F3 follows first order release kinetics, remaining all formulations F4, F5, F6 follows zero order kinetics, korsemeyer- Peppas model indicates drug release from the tablets were non fickian diffusion and controlled by both diffusion and erosion.

CONCLUSIONS

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 and xanthin gum 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.

Table 14: Curve Fitting Analysis

Formulation code	Correlation coefficient of Model fitting (R^2)				'n' values for -Peppas	Best fit model
	Zero order	First order	Higuchi matrix	Peppas kinetics		
F1	0.964 ±0.147	0.984±0.001	0.975±0.001	0.972±0.0002	0.482±0.003	First Order
F2	0.891±0.025	0.994±0.003	0.984±0.001	0.974±0.0004	0.524±0.006	First Order
F3	0.936±0.021	0.989±0.004	0.982±0.001	0.980.001	0.534±0.005	First Order
F4	0.985±0.001	0.904±0.024	0.960±0.001	0.975±0.001	0.484±0.004	Zero Model
F5	0.995±0.003	0.937±0.021	0.981±0.001	0.984±0.001	0.508±0.006	Zero Model
F6	0.997±0.000	0.881±0.018	0.978±0.001	0.988±0.001	0.543±0.002	Zero Model

Compounding drugs having narrow absorption window in a unique pharmaceutical dosage form with gastroretentive properties would enable an extended absorption phase of these drugs. 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. Floating tablets of Metformin were formulated using sodium bicarbonate as gas generating agent and HPMC K4M and xanthin gum as water swellable polymer by wet granulation method. These formulations were subjected to preformulation studies and various evaluation parameters like hardness, friability, tablet density, floating test, drug content and in vitro release studies. The results of all these parameters are tabulated and depicted graphically in the result and discussion section. UV spectroscopy studies revealed that the drug and polymer used were compatible. Evaluation parameters viz. tablet dimensions, hardness, weight variation, friability and drug content were within acceptable limits for all formulations. Results of in vitro release using USP dissolution apparatus 2 method indicated that the drug release was more sustained in formulation F6 containing xanthin gum and HPMC in the ratio 2:1. The formulations subjected to curve fitting analysis showed first order release kinetics for formulations F1, F2 & F3 and zero order for formulations F4, F5 & F6. All synthesized 1,3,4 oxadiazole compounds

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