Development and Evaluation of Floating Tablet of Metformin Hydrochloride Using Different Polymers

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Abstract- **In terms of delivering the medication to the stomach for an extended period of time, the creationof a gastro-retentive dosage form for Metformin employing Xanthan gum and carbopol has shown encouraging results. The optimized formulation (F5) demonstrated the optimum drug release profile, suggesting that employing Xanthan gum and carbopol in floating tablets can be a workable strategy for obtaining the intended outcomes of gastro-retentive floating tablets. The formulation of floating tablets with various polymers can also affect how effective and bioavailable they are.This study demonstrates the potential of floating tablets as a drug delivery system, which can provide various benefits over traditional tablets, including enhanced bioavailability and therapeutic efficacy, decreased dose frequency, and improved patient compliance. Additional research can be done to assess the formulation's safety and effectiveness in living organisms and to determine the ideal concentration of Xanthan gum and carbopol for use in additional medications with comparable pharmacokinetic profiles.**

Keywords: **Metformin Hydrochloride, Floating Tablets, Xanthan gum Carbopol.**

INTRODUCTION:

Oral drug delivery systems are methods for administering drugs via the mouth and digestive system. They are the most common and convenient route of drug administration, as they do not require injections and can be easily self-administered by patients [1]. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Floating systems, Bioadhesive systems, swelling and expanding systems, High-density systems, and Modified systems Buoyant/ Floating Systems: Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate [2-4]. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and better control of fluctuations in the plasma drug concentrations [5-8].

Metformin Hydrochloride (**Figure 1**, Metformin) chemically metformin -1, 1-dimethyl biguanide hydrochloride from the division of biguanide of antidiabetic and antihyperglycemic drugs. It is used in patients with type 2 diabetes [9-14]. The molecular formula is $C_4H_{12}ClN_5$and the molecular weight is 165.62 gm/moL. Metformin is a white crystalline powder with a melting point between 218-221°C. It is soluble in water. It has a pKa value of 12.4 [15-18].

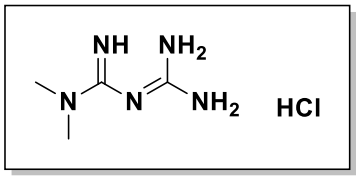

Figure 1: Structure of Metformin Hydrochloride

According to the literature review, different dosages of Metformin were available [19-22]. Also, some floating systems were reported for Metformin [23]. The present research intends to formulate and evaluate floating tablets using varied polymers to improve therapeutic action as well as the bioavailability of Metformin.

MATERIAL AND METHODS:

Materials

Preformulation Studies

Pre-formulation testing is an investigation of the physical and chemical properties of a drug substance alone and when combined with excipients. Pre-formulation studies yield the necessary knowledge to develop a suitable formulation for toxicological use. It gives information needed to define the nature of the drug substance and provide a dosage form. Hence, the following pre-formulation studies were performed for the obtained sample of the drug.

Description and Solubility

Metformin is a white crystalline powder. It was found to be highly soluble in water.

Standard graph of Metformin
Standard Stock solution:
500 mg of Metformin was dissolved in 100 ml of 0.1N HCL (1000 µg/ml).Calibration curve of Metformin in 0.1N HCL From the above stock solution, 1 ml was transferred into a 10 ml volumetric flask, and the volumewasadjustedto10mlwhichcorrespondedto100µg/ml Metformin in solution. From that solution different aliquots of 1.6, 1.8, 2, 2.2, and 2.4 ml were transferred to 10ml volumetric flask; volume was adjusted with 0.1N HCL, which gave a concentration of 16,18,20,22 and 24µg/ml of the final standard. A standard curve was plotted by taking the absorbance of secondary stock solutions in a UV double-beam spectrophotometer at 216nm.
Drug-Excipients Compatibility Study:
Metformin was mixed with all excipients, used in the formulation in different ratios, and subjected to Physical observation/FTIR.

Drug-Excipient Compatibility Study (FTIR):
The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-400 cm-1 using the KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400mg, specified quantity, of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press.

EXPERIMENTALMETHODS:
FORMULATIONANDPREPARATIONOFMETFORMIN FLOATINGTABLETS:
All the formulations were prepared by direct compression method using different Polymers.

PROCEDURE:

- Metformin and all other ingredients were individually passed through sieve□60.
- All the ingredients were mixed thoroughly by triturating for up to 15min.
- The powder mixture was lubricated with Magnesium stearate the tablets were prepared by using the direct compression method according to the formulation (**Table 1)**.

Table1: Composition of different formulations.

Ingredients (mg)	FI	F2	F3	F4	F5	F6	F7
Metformin	500	500	500	500	500	500	500
Carbapol	100	—	—	50	50	—	75
HPMCk100 M	—	100	—	50	—	100	50
Xanthan gum	—	—	50	—	50	50	25
Sodium Bi carbonate	50	50	50	50	50	50	50
Citric acid	15	15	15	15	15	15	15
PVPK30	20	20	20	20	20	20	20
Magnesium	7.5	7.5	7.5	7.5	7.5	7.5	7.5
stearate Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight	750mg	700mg	650mg	700mg	700 mg	750mg	750 mg

EVALUATIONOFPRE-COMPRESSIONPARAMETERS
Bulk density
The bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre-sieved granules into a graduated cylinder via a large funnel and measuring the volume and weight.

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

Carr's Index (CI)

Carr's index is measured using the bulk density and tapped density values. The following equation is used to find Carr's index **(Table 2).**

Table2: Flow properties and corresponding Carr's Index values

Excellent	<10
Good	11-15
Fair	16-20
Possible	21-25
Poor	26-31
Very poor	32-37
Very very poor	>38

Hausner's Ratio: It indicates the flow properties of the powder and the ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio =Tapped density/ Bulk density

Table3: Flow Properties and Corresponding Hausner's ratio

Excellent	1,001.11
Good	11-118
Fair	1.19 -1.25
Possible	1.26-1.34
Very poor	1.35-1.45
Very very poor	>1.60

Angle of repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress is reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal **(Table 4).**

Table4: Flow Properties and Corresponding Angle of Repose

ANGLEOFREPOSE	**POWDERFLOW**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

EVALUATION OF TABLETS:

The formulated tablets were evaluated for the following physicochemical characteristics:

General Appearance

The formulated tablets were assessed for their general appearance and observations were made for shape, color, texture, and odor.

Hardness:

The hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer ridden along a gauge in the barrel to indicate the force.

Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, the average weight was calculated. Each tablet's weight was then compared with the average weight to ascertain whether it was within the permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Friability test:

20 previously weighed tablets were placed in the friability apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,

Percentage friability = initial weight-final weight/initialweight×100.

Drug content:
20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Metformin was transferred into a 100 ml volumetric flask and the volume adjusted to 100 ml with 0.1N HCl. Further, 1ml of the above solution was diluted to100 ml with 0.1N HCl, and check the absorbance of the resulting solution was observed at 216 nm.

In-vitro Buoyancy studies:
The in-vitro buoyancy was determined by floating lag time and total floating time. The tablets were placed in a100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).

Swelling Index Studies:
The swelling behaviour of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of the dissolution apparatus using a dissolution medium of 0.1N HCl at 37±0.5°C. After1,4,and 6h each dissolution basket containing the tablet was withdrawn, blotted with tissue paper to remove the excess water, and weighed on the analytical balance(Schimdzu, AX 120). The experiment was performed in triplicate for each time point. The swelling index was calculated by using the following formula.

In-Vitro Dissolution Studies of Tablets:

Dissolution parameters:
Apparatus -- USP-II,
Paddle Method
Dissolution Medium -- 0.1 N HCl RPM–50
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,8 and 10
Temperature--37+0.5°C

Dissolution Study:
900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to a temp of 37 + 0.5°C. The tablet was placed in the vessel and the vessel was covered; the apparatus was operated for 10 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered, and again 5 ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 216 nm.

Release Kinetics:
The analysis of the drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data were fitted to four popular release models such as zero-order, first-order, diffusion, and Peppa's Korsemeyer equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero-order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using the Higuchi equation and Peppa's- Korsemeyer equation.

Zero Order Release Kinetics:
It defines a linear relationship between the fractions of drugs released versus time.
Q =kot
Where is the fraction of drug released at time t and ko is the zero-order release rate constant.
A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics:
Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during the dissolution process suggested that drug release from most of the slow-release tablets could be described adequately by apparent first-order kinetics. The equation that describes first-order kinetics is
In (1-Q) = -K1t

Where, Q is the fraction of drug released at time t and k1 is the first order release rate constant.
Thus, a plot of the logarithm of the fraction of drug remaining against time will be linear if the release obeys first-order release kinetics.

Higuchi equation: It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time. A plot of the fraction of the drug released against the square root of time will be linear if the release obeys the Higuchi equation. This equation describes drug release as a diffusion process based on Fick's law, square root time dependent.

Koresmeyer Peppas
In order to define a model, which would represent a better fit for the formulation, dissolution data were further analyzed by Peppa's and Korsemeyer's equation (Power Law).
Where Mt is the amount of drug released at time t and M□□is the amount released at the time □, thus the Mt/M□is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in **Table 5**. A plot between the log of Mt/M□ against the log of time will be linear if the release obeys Peppa's and Korsemeyer's equation and the slope of this plot represents—n‖ value.

Table5: Diffusion exponent and solute release mechanism for cylindrical shape.

Diffusion Exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous(non-fiction) diffusion
0.89	Case II transport
20.89	Super Case II transport

Stability studies

Stability studies were carried out according to ICH guidelines by exposing the. FormulationsF5 in their final packing mode to the temperature 40±2°C and relative humidity 75±5 % in a programmable environmental test chamber(CHM-10S,Remi Instruments Ltd. Mumbai, India). Aliquots were withdrawn at 30 and 60 days and analyzed for change in drug content and in vitro dissolution profile.

The selected Formulation was subjected to stability studies as per ICH guidelines. The following conditions were used for Stability Testing:

- 21˚C/45%RH analyzed every month for a period of three months.
- 25˚C/60%RH analyzed every month for a period of three months.
- 30˚C/70%RH analyzed every month for a period of three months.

Result and Discussion

Standard Graph of Metformin.

Table 6: Standard calibration curve of Metformin

Conc(ug/ml)	Absorbance
16	0.321
18	0.372
20	0.420
22	0.362
24	0.512

FT-IRSTUDIES:

The FTIR spectra of the drug (alone), polymer (alone), and drug-polymer (mixture) were recorded by the potassium bromide pellet method. From the infrared spectra, it is clearly evident that there were no drug-polymer interactions with the drug (**Figure3 and 4)**.

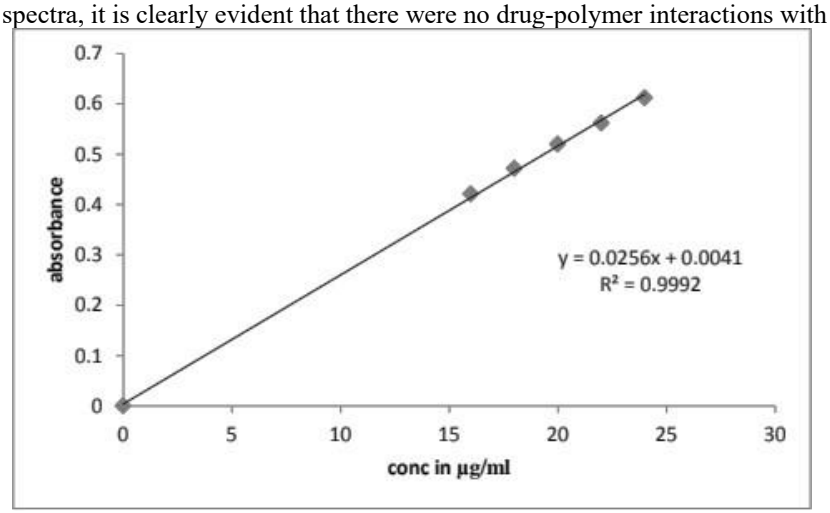

Figure2: Standard calibration curve of Metformin.

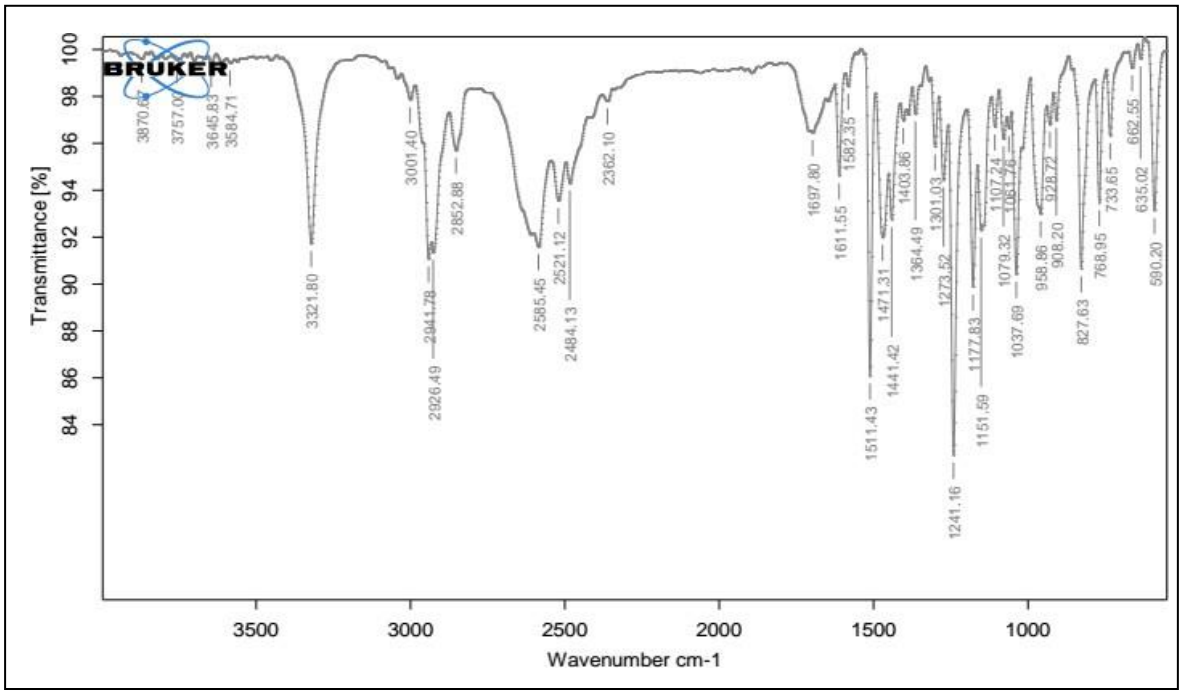

Figure3: FTIR Spectra of Metformin

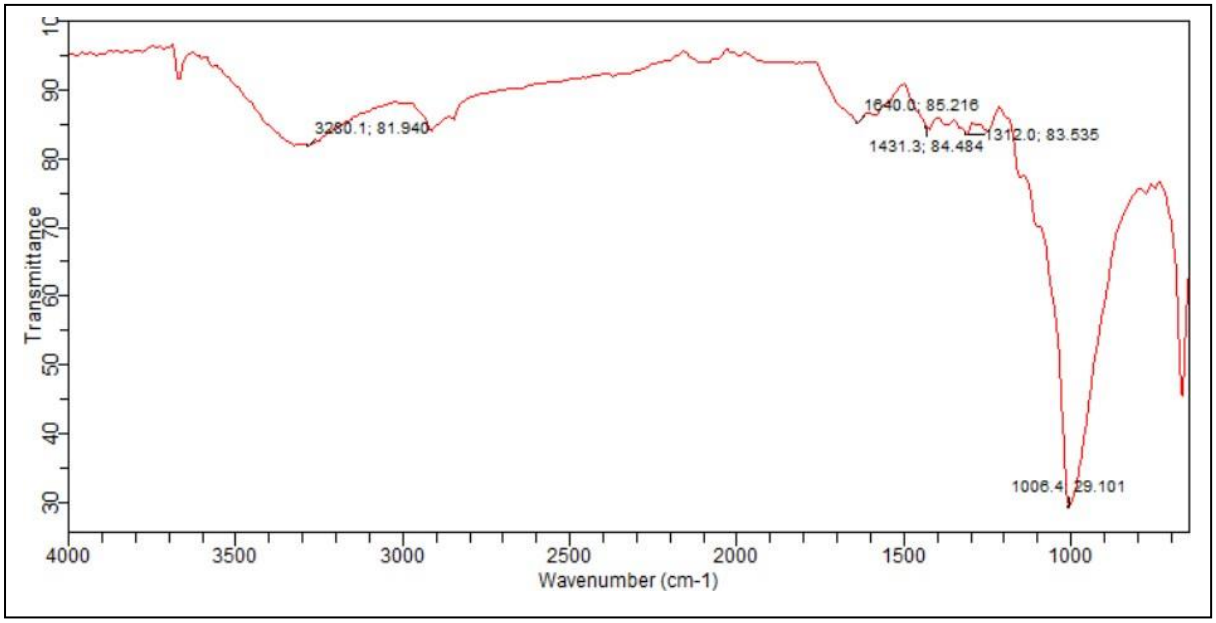

Figure 4: FTIR Spectra of Metformin final formulation.

PREFORMULATION STUDIES OF POWDERED BLEND:

Preformulation studies of powdered blend parameters like bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose as shown in the **Table 7**.

Table7: Pre-compression parameters for formulation batches

Formulations code	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility Index (%)	Hausner'sratio	Angle of repose(0)
F1	0.671 +0.045	0.57+ 0.01	16.236 +0.6	1.146 + 0.06	23.62 + 0.21
F2	0.340 + 0.043	0.533 + 0.04	14.224 +0.7	1.211 + 0.04	28.64 ± 0.11

F3	0.41 ± 0.045	0.485 + 0.5	17.313 ± 0.8	1.48 ± 0.08	29.34 + 0.31
F4	0.52 + 0.045	0.55 ± 0.09	16.10 +0.2	1.45 + 0.02	31.46 ± 0.31
F5	0.75 + 0.045	0.60 +0.07	11.23 +0.6	1.51 ± 0.04	25.28 ± 0.15
F6	0.56 + 0.044	0.50 +0.09	13.18 +0.8	1.33 ± 0.08	27.24 ± 0.11
F7	0.54+ 0.045	0.57+ 0.01	15.313 ± 0.8	1.38 ± 0.08	32.46 ± 0.31

POST COMPRESSION PARAMETERS

The results of the weight variation, hardness, friability, drug content, Buoyancy lag time, and Total floating time of the Tablets are given in the table.

In-vitro Buoyancy studies:

In-vitro buoyancy of the tablets from each formulation (F1 to F7) was evaluated and the results are mentioned in **Table8**.Where the highest and lowest floating lag time (FLT) was observed with the formulation F1 and F7 respectively. The concentration of the natural polymers increases the floating lag time also increases and the total floating time observed for all the formulations was >10hours.

Table 8: Post-compression evaluation parameters of METFORMIN floatingTablets

Formulation No.	**Avg. Weight(Mean t S.D) (n =20)**	**Hardness(kg/ cm²) (n =3)**	**Friability(Mean± S.D) (n =6)**	**content (mg) %Drug**	**(min)Buoyancy Lag time**	**Total floating Time (hrs)**
F1	343 ± 0.6	7.2 +0.4	0.636	98.11 + 0.7	24	4
F2	340 +0.9	6.5 +0.4	0.532	98.23+ 0.5	17	7
F3	347+0.3	6.4 +0.6	0.627	98 .43+ 0.6	22	11
F4	341 +0.4	6.6 ± 0.1	0.541	99.44 + 0.6	31	6
F5	336 +0.8	5.6 +0.6	0.695	98.22 + 0.6	58	8
F6	334 ± 0.8	5.3 +0.4	0.585	98.52 + 0.5	37	9
F7	367+0.3	5.4 +0.6	0.327	98 .53+ 0.6	24	12

Table 9: Swelling index studies of METFORMIN floating Tablets.

Time(hr)	**Swelling index ratio (%)**						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
2	31	33	44	42	52	53	51
4	48	42	55	54	58	65	63
6	54	55	56	64	68	73	75
8	49	50	57	56	58	63	64

Dissolution Studies:

Table10: Dissolution Data of METFORMIN Floating Tablets

	% of Drug Release						
TIME (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
1	17.8	15.3	13.3	12.5	13.4	9.5	9.2
2	38.9	25.2	24.4	28.8	34.8	18.3	12.3
3	51.3	33.6	35.8	43.9	44.3	25.7	33.6
4	75.9	43.8	47.1	54.2	46.4	35.2	47.1
5	91.8	73.8	57.4	66.1	66.3	47.8	57.4
6	92.8	92.3	68.5	76.7	76.4	59.3	76.7
8	92.8	94.3	78.9	93.3	97.2	70.4	93.3
10	92.8	95.3	91.4	96.4	98.4	87.9	96.4

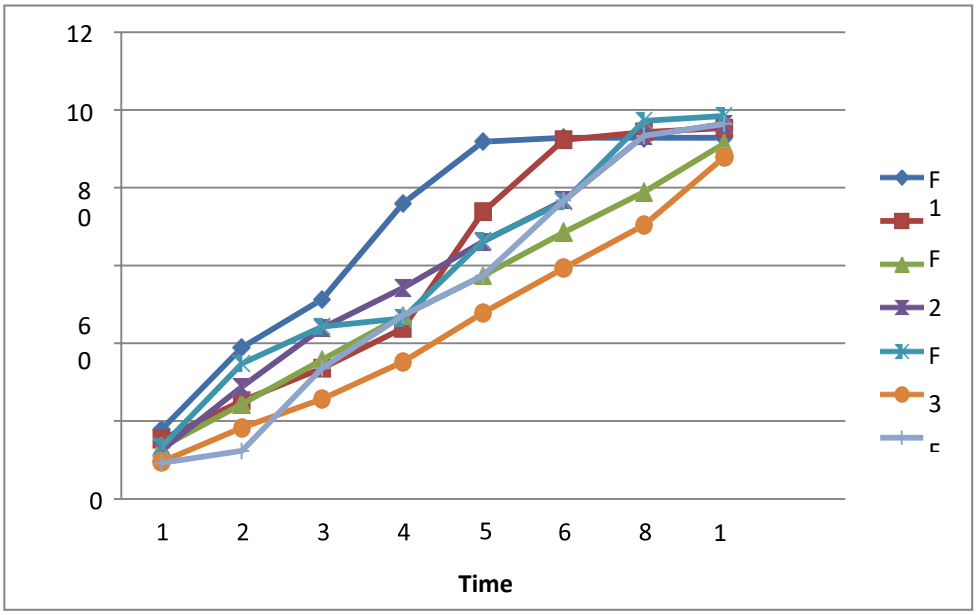

Figure 5: Dissolution profile of Metformin Floating Tablets

The % Cumulative drug release of all the formulations F1, F2, F4, F7 was not able to sustain the drug release for10 hrs.F3 andF6 formulations showed good integrity for10hrs. F4 formulation was optimised based on the floating behaviour. The optimized formulation F5showed % drug release of 98.4% for 10 hrs which shows greater release compare to all other formulation

KINETIC MODELLING AND MECHANISM OF DRUG RELEASE

The results of kinetic equations applied to dissolution profiles of optimized batch F5 were determined as follows **(Table 11).**

Table 11: Kinetic values obtained from different plots of F5formulation

	ZEROORDER	**FIRSTORDER**	**HIGUCHIORDER**	**PEPPASORDER**
	%CDRVs T	**Log % Remain Vs T**	**%CDRVs VT**	**LogC Vs Log T**
Slope	11.0480	-0.1212	33.6231	1.4567
Intercept	8.4806	2.1325	-12.1430	0.5304
Correlation	1.2823	-0.9309	0.9652	0.5513
R2	1.3649	0.9235	0.9449	0.6247

The release kinetics of all the dosage forms were calculated using zero-order, first-order, Higuchi, and krosemeyer -peppas. Optimized formulation was found to follow Higuchi release kinetics. The optimized formulation F5 was found to exhibit zero–order which shows the diffusion along with the dissolution of the drug from the tablet.

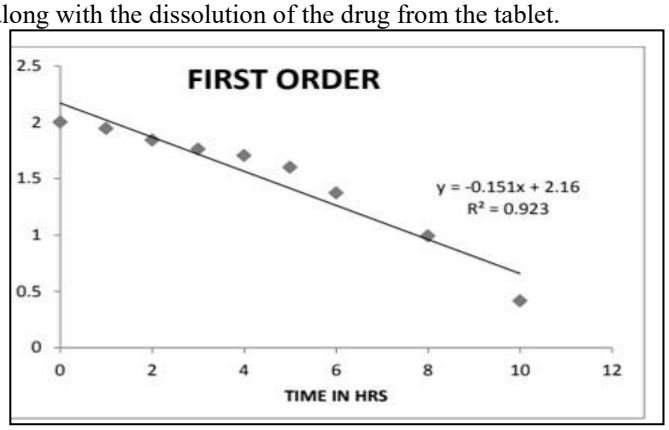

Figure 6: first order release model for F5 formulation

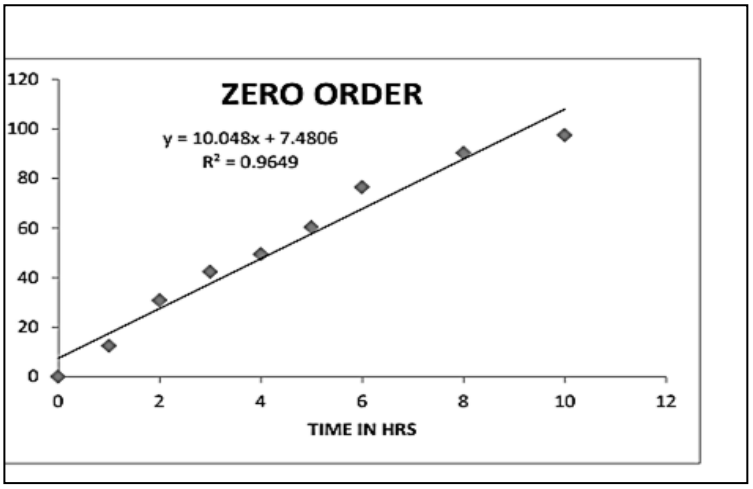

Figure 7: Zero order release model for F5 formulation

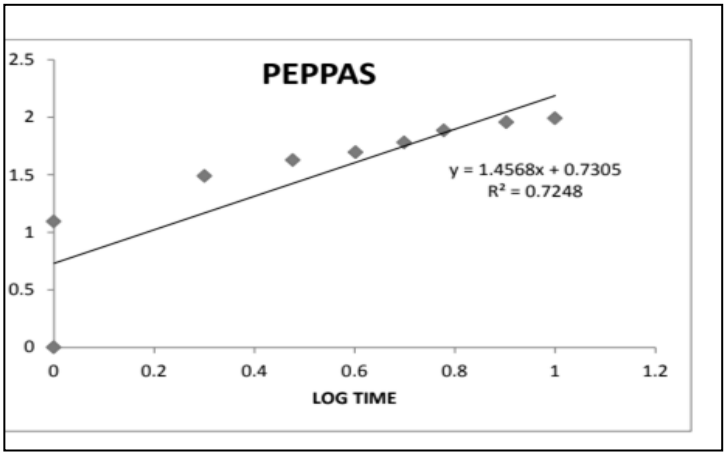

Figure 8: Peppas release modelforF5formulation

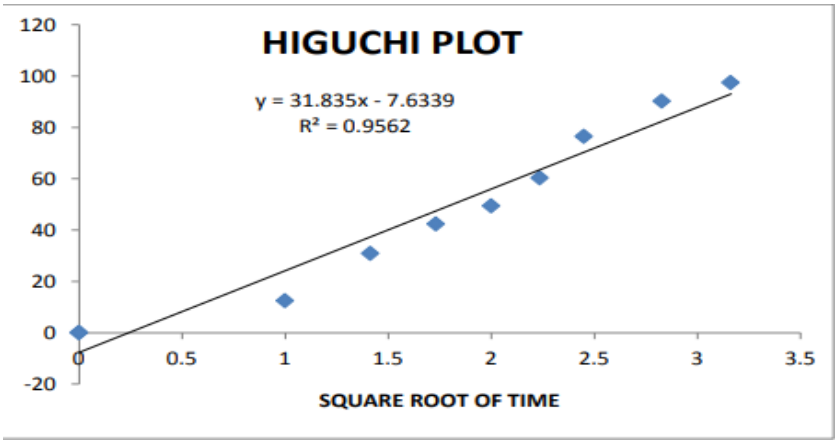

Figure 9: Higuchi release model for F5 formulation

STABILITY OF METFORMIN FLOATING TABLETS

Table12: Stability data of optimized formulation F5

S. No	Time points	Initial	Cumulative %Drug Release			
			25 °C / 60 %RH		40 °C / 75 %RH	
	(hr)		1st Month	3rd Month	1st Month	3rd Month
1	1	13.4	12.2	11.7	11.2	10.7
2	2	31.8	30.4	30.1	29.4	29.1
3	3	43.3	42.1	44.8	39.6	39.2
4	4	48.4	49.0	43.6	47.8	47.4
5	5	62.3	58.3	59.4	59.1	58.6
6	6	74.4	76.1	75.5	75.1	73.9
7	8	95.2	89.8	89.2	88.7	88.1
8	10	97.4	97.1	96.5	96.1	95.8
9	**Assay**	95.5	99.4	99.3	98.6	98.4

The optimized formula was kept for stability studies. The cumulative % Drug release kinetics was used to predict the stability of the preparation. The mean values of these parameters were compared with that obtained in 1st month as described in the table. The results are shown in**Table12.**There was a less significant change in % entrapment efficiency at storage temperatures after 3 months of production which indicates the stability of the preparation.

CONCLUSION

In conclusion, the development of a gastro retentive dosage form using Xanthan gum and carbopol for Metformin has shown promising results in terms of delivering the drug to the stomach for a prolonged period of time. The optimized formulation (F5) showed the best drug release profile, indicating that floating tablets using Xanthan gum and carbopol can be a practical approach to achieving the desired objectives of gastro retentive floating tablets .The use of different polymers in the formulation of floating tablets can further impact their effectiveness and bioavailability. This study highlights the potential of floating tablets as a drug delivery system, which can offer several advantages over conventional tablets, including improved bioavailability and therapeutic effectiveness, reduced dosing frequency, and better patient compliance. Further studies can be conducted to evaluate the safety and efficacy of this formulation in vivo and to optimize the concentration of Xanthan gum and carbopol for other drugs with similar pharmacokinetic profiles.

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Conflict of interest

Authors do not have any conflict of interest

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