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Formulation and Evaluation of Gastroretentive Floating Tablets of Glipizide

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Abstract: ***The present study outlines a systematic approach for designing and development of Glipizide floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Floating tablets of Glipizide have shown controlled release thereby proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by wet granulation technique using HPMC K100M (floating agent) and Xanthan gum as polymers along with sodium bicarbonate as gas generating agent. The formulations were evaluated for their physicochemical properties, buoyancy lag time, total floating time, swelling index and in-vitro drug release. It was found that the hardness of the tablets affects the Buoyancy characteristic of the dosage form. All nine formulations possessed good floating properties with total floating time between 8 – 12 hrs.***

Keywords: Floating drug delivery systems, Classification and application, Advantages and disadvantages, Factors affecting, Gastric Residence Time, Precompression and post compression evaluation of glipizide drug.

I. INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patient.

Glipizide is an anti-diabetic drug4 which cures the type II diabetes and with narrow therapeutic index. The recommended adult dose is 5 mg twice daily (or) 10mg once daily, due to the low bioavailability and short biological half-life (4 hours) of Glipizide following oral administration favors development of a controlled release formulation. It also leads to reduction in frequency of dosing & drug toxicity which in turn improve patient compliance. The gastro retentive drug delivery systems 5 can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Glipizide is taken because the absorption of drug is in the stomach. In the present investigation floating tablets of Glipizide were prepared by effervescent approach using two different grades of hydroxyl propyl methyl cellulose polymers . The aim of the work was to evaluate the effect of polymers on floating properties and release characteristics of Glipizide tablets.

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II. MATERIALS AND EQUIPMENTS

A. List of Materials and Supplier

Glipizide (Supra Chemicals,Thane). HPMC K100M (Yarrow Chem Products, Mumba). Xanthan gum(Loba chemicals, Mumbai, India). Sodium bicarbonate (Research Lab Fine Chem Industries, Mumbai). PVP k3 (Research Lab Fine Chem Industries, Mumbai). Microcrystalline cellulose (Research Lab Fine Chem Industries, Mumbai). Talc (Research Lab Fine Chem Industries, Mumbai). Magnesium stearate (Research Lab Fine Chem Industries, Mumbai).

B. List of Equipment and Manufacturer

Electronic Weighing Balance (Shimadzu, Mumbai)(Model: AU220) Rotary tablet compression machine(Karnavati Engineers Pvt. Ltd, Mumbai) (Model: MINI PRESS- II MT). UV Spectrophotometer (Jasco, Japan) (Model: V-530 &V-630). FTIR Spectrophotometer (Shimadzu, Japan) (Model: FTIR- 8400$). Differential Scanning calorimeter (Mettler Tolendo, Mumbai) (Model: Stare SW 920). USP Tablet Dissolution Apparatus (Electro lab, Mumbai) (Model: TDT-06P). Tap density tester(Labinda, Mumbai) (Model: TD1025). Roche friability tester(Labinda, Mumbai) (Model: FT1020). Hardness tester (Labinda, Mumbai) (Model: TH 1050 M). pH Meter(Labinda, Mumbai) (Model: GMPH).

C. Diabetes Mellitus

Diabetes mellitus is an endocrinological and/or metabolic disorder with an increasing global prevalence and incidence. High blood glucose levels are symptomatic of diabetes mellitus as a consequence of inadequate pancreatic insulin secretion or poor insulin-directed mobilization of glucose by target cells. Diabetes mellitus is aggravated by and associated with metabolic complications that can subsequently lead to premature death.

D. Glipizide

An oral hypoglycemic agent, is one the most commonly prescribed drugs for the treatment of patients with type II Diabetes mellitus . It is practically insoluble in water. Glipizide has relatively short elimination half-life (2-4 hrs), there by requiring twice daily dosing in large number of patients, which often leads to non compliance. Thus there is strong clinical need and market potential for a dosage form that will deliver glipizide in a sustained manner to a patient needing this therapy, thereby resulting in a better patient compliance. Glipizide belongs to a class II of Biopharmaceutical Classification System (BCS) having low water solubility which is rate limiting step in absorption of drug in GI tract. Very few researchers have tried to resolve the poor solubility of drug, which could hamper its release from compressed hydrophilic matrices. Hence there is strong need to explore new technique to enhance its solubility. To avoid the problem of solubility previous researchers use trimethylamine as a solubility modifier.

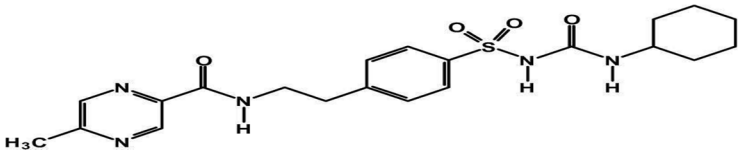


Fig. 1: Structure of Glipizide (N-[2-[4(cyclohexylcarbamoylsulfamoyl)phenyl]ethyl]-5-methylpyrazine-2-carboxamide)

E. Method Of Preparation

1) Wet granulation
2) Direct compression
3) Dry granulation

III.PREFORMULATION STUDY OF GLIPIZIDE

1) *Organoleptic Properties:* The obtained sample was examined for its appearance, color and odor and observations are reported.
2) *Solubility:* The solubility of compound was determined methanol, water.
3) *Melting Point:* Melting point of the glipizide was determined by open capillary tube method using Thiele's tube. One sided closed capillary filled with drug attached to graduated thermometer and put into the Thiele's tube contains paraffin oil and constant heat was supplied to the assembly. Temperature was noted at which solid drug changed into liquid. The melting point is reported.
4) *UV-Visible Spectroscopy:* The Glipizide was dissolved in methanol, was scanned between 200-400 nm to determine its absorption maxima. The UV spectrum of glipizide.

5) *Fourier Transform Infrared (FTIR) spectral Analysis:* The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by preparing KBr pellets with the help of KBr press taking 1 mg sample in 100 mg KBr. The scanning range was 400 to 4000 cm-1 and there solution was 1cm-1.

6) *Calibration curve:* Preparation of Acid buffer pH 1.2

a) *Preparation of 0.2 M Potassium Chloride:* 0.2 M potassium chloride was prepared according to IP 1996. A quantity of 14.9 grams of potassium chloride was dissolved in water and make up the volume to 1000 ml using water.

b) *Preparation of 0.2 M HCL:* 0.2 M HCL prepared by diluting 17 ml of conc. Hcl in to water and make up the volume to 1000 ml using water.

c) *Preparation of Acid buffer pH 1.2:* The acid buffer pH 1.2 prepared according to IP 1996 by mixing 50 ml of 0.2 M potassium chloride and 85 ml of 0.2 M HCL and make up the volume to 200 ml using water.

7) *Preparation of phosphate buffer pH 7.4*

a) *Preparation of 0.2 M Potassium Dihydrogen Phosphate:* 0.2 M potassium dihydrogen phosphate was prepared according to IP 1996. A quantity of 27.2 grams of potassium dihydrogen phosphate was dissolved in water and make up the volume to 1000ml using water.

b) *Preparation of 0.2 M NaOH:* 0.2 M NaOH prepared by dissolving 8 grams of NaOH in to water and make up the volume to 1000 ml using water.

8) *Preparation of Stock Solution:* Weighed accurately 10 mg of glipizide , transfer it to 100 ml volumetric flask, add Acid buffer pH 1.2 or Phosphate buffer pH 7.4 sonicated to dissolve Glipizide. Filtered this solution through 0.45 micron membrane filter (Whatmann filter paper) to get clear solution. Concentration of stock solution is 100 microgram per ml.

9) *Preparation of Working Solution:* From prepared stock solution pipette out 1, 2, 3, 4, 5 and 6 ml transfer to 10 ml volumetric flask and make the volume up to 10 ml with acid buffer pH 1.2 or Phosphate buffer pH 7.4 to get 10, 20, 30, 40 50 and 60 microgram per ml concentration of Glipizide. Measured the absorbance at 274 nm by using UV spectrophotometer. Plotted curve of concentration vs absorbance.

10) *Differential Scanning Calorimetry:* The DSC thermo gram of glipizide was carried out to confirm its purity. The DSC thermo gram was recorded on Differential Scanning Calorimetry. Glipizide was heated in crimped aluminum pan with a pierced lid at a scanning rate of 100C/min in an atmosphere of nitrogen flow (40mL/min) in the range of 30 to 250oC. DSC thermo gram of Glipizide are depicted.

11) *Drug-Excipient Compatibility Study:* The drug and excipient compatibility study of selected tablet of formulations performed by FTIR and DSC

IV. FORMULATION OF GLIPIZIDE FLOATING TABLETS

A. *Design of Factorial Batches*

A 3^2 factorial design was implemented for optimization of gastro retentive floatingtablet formulation of Glipizide. According to the model it contained 2 independent variables at 3 levels- +1, 0 and -1. According to model, total nine formulations are possible, the composition of different formulation are shown in Table 3. The different independent variables were- concentration of HPMC K100M(X1) and concentration of Xanthan gum (X2). Dependent factors included floating lag time (Y1), swelling index (Y2) and in-vitro drug release(Y3).

Table 1: Factorial design for preparation of batches F1-F9.

Batches code	Variable level in coded form	
	X1 (HPMC K100M)	X2 (Xanthan gum)
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table 2: Translation of coded value in actual unit.

Variable level	Coded Level		
	-1	0	+1
X1= Concentration of HPMC K100M(mg)	40	50	60
X2=Concentration of Xanthan gum (mg)	50	60	70

Table 3: Composition of Factorial Batches.

Formulation code / INGREDIENTS (mg)/tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide	15	15	15	15	15	15	15	15	15
HPMC K100 M	20	20	20	25	25	25	30	30	30
Xanthan gum	25	30	35	25	30	35	25	30	35
Sodium Bicarbonate	80	80	80	80	80	80	80	80	80
PVPK30	10	10	10	10	10	10	10	10	10
Mg. Stearate	10	10	10	10	10	10	10	10	10
Talc	7	7	7	7	7	7	7	7	7
MCC	20	20	20	20	20	20	20	20	20
Total weight (mg)	200	200	200	200	200	200	200	200	200

B. Preparation of Factorial Batches

Floating tablets are formulated as per Table 3. Floating tablets containing Glipizide are prepared by Wet granulation technique using varying concentrations of different grades of polymers. All the ingredients are accurately weighed and passed through different mesh sieves accordingly. Then, exceptmagnesium stearate and talc all other ingredients are blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, magnesium stearate and talc is added, as post lubricant, and further mixed for additional 2-3 minutes. The prepared powder blend was evaluate for pre- compression properties. 200 mg of powder blend is weighed and compression into 12mm size punches by using a rotary punch tablet compression machine (Kamavati MINI PRESS-IIMT). The weight of tablets is kept constant for all formulation. After compression, the tablets were evaluated for post compression parameters.

V. EVALUATION OF FACTORIAL DESIGN FORMULATIONS

A. Evaluation of Pre-compression Parameters of Powder Blend-

1) Bulk Density
2) Tapped Density
3) Hausner's Ratio
4) Compressibility Index
5) Angle of Repose

B. Evaluation of Post-compression Parameters of Formulated Batches-

1) Floating Duration
2) Weight Variation Test
3) Hardness Test
4) Tablet Thickness
5) Friability Test
6) Drug Content Determination
7) In-vitro Dissolution Study

VI. RESULTS AND DISCUSSIONS

A. Pre-Formulation Studies Of Drug

1) Organoleptic Properties: The obtained sample of Glipizide was studied for organoleptic properties such appearance, color and odor. Results of organoleptic properties of Glipizide were found to be complies with Indian pharmacopoeia as shown in Table 5

Table no 4: Organoleptic properties of Glipizide

Identification	Observation	Inference
Appearance	Crystalline Powder	Complies with IP
Color	White	Complies with IP
Odor	Unpleasant	Complies with IP

2) Melting Point: The melting point of Glipizide was determined and temperature was noted at which solid drug changes into liquid and observed melting point of Glipizide was in the range of reported melting point range as per Indian Pharmacopoeia as shownin Table no 6. Therefore itas confirmed that the given sample was in pure form.

Table 5: Melting point of Glipizide.

Srno	Method	Reported Melting Point as per IP	Observed MeltingPoint	Inference
1	Open capillary tube method	204°C-206°C	205°C-208°C	Complies with IP

3) Solubility

Table 6: Solubility of Glipizide

Sr no	Medium	Observation	Inference
1	Distilled water	Insoluble	Complies with IP
2	Ethanol	Insoluble	Complies with IP
3	Methanol	Soluble	Complies with IP

4) U.V-Visible Spectroscopy: The λ max of the Glipizide was found to be 274 nm in methanol.

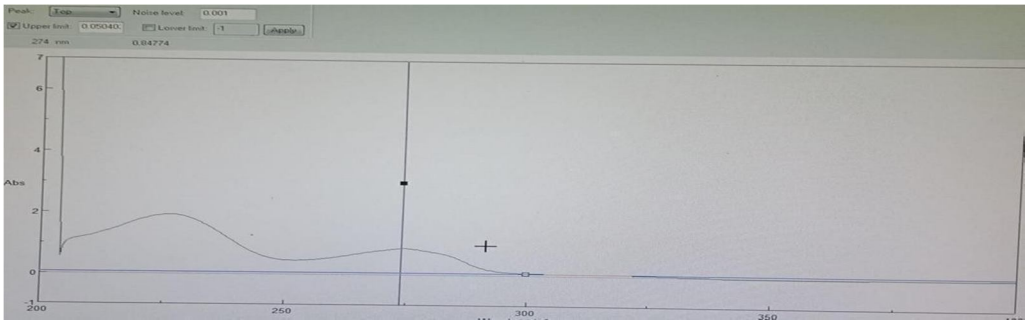


Fig 2: Glipizide having λ max at 274 nm.

5) *Calibration Curve:* The calibration curve of Glipizide was prepared in acid buffer pH 1.2. Following table shows the absorbance at λ max 274 nm.

Table no 7: Data for Calibration curve of Glipizide in Acid buffer pH 1.2

Sr .no	Concentration (µg/ml)	Absorbance at 274 nm
0	0	0
1	10	0.133
2	20	0.214
3	30	0.283
4	40	0.392
5	50	0.465
6	60	0.565

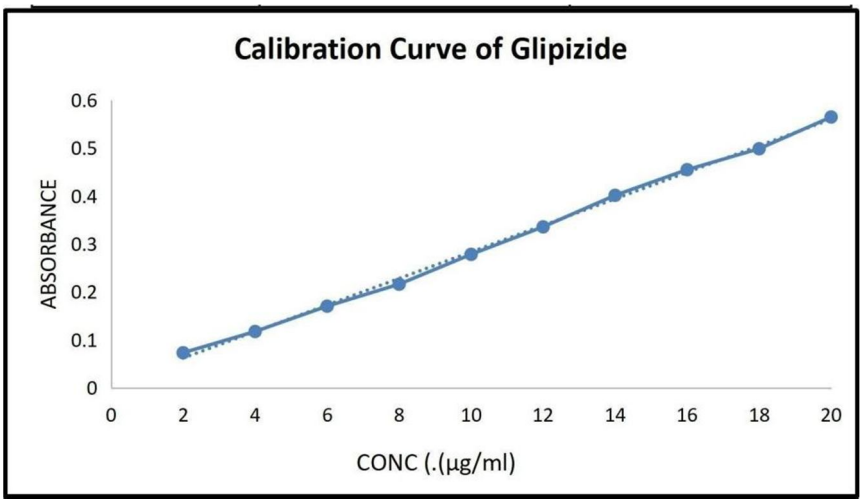


Fig. 3: Calibration curve Graph in pH 1.2 phosphate buffer.

The observed IR peaks of Glipizide matches with the reported peaks which are shown in the Table 7.

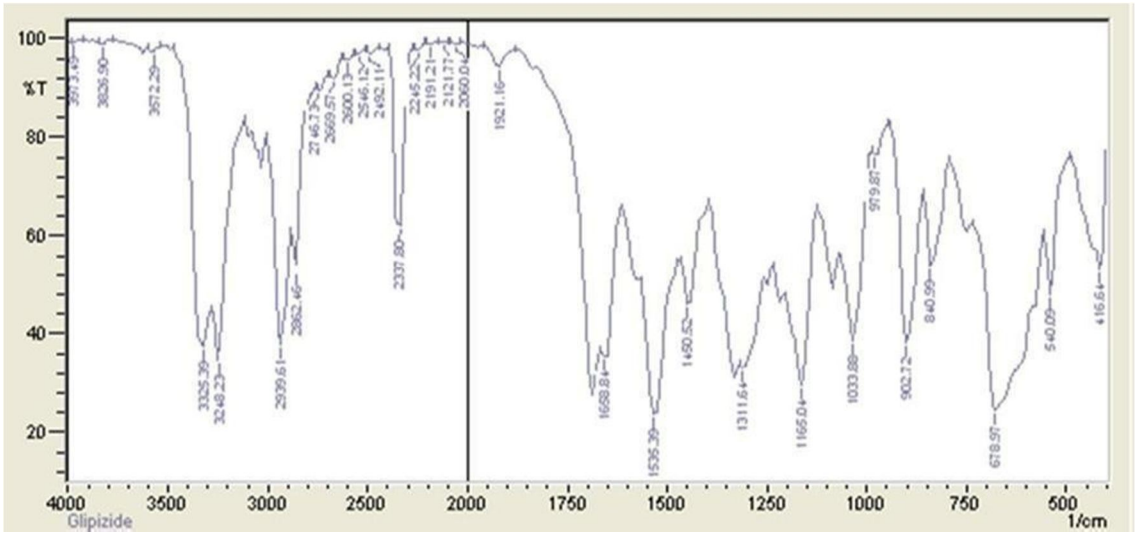


Figure 4: FT-IR spectra of Glipizide

Table 8: Reported & Observed IR peaks of Glipizide

Functional groups	Reported frequency (cm^{-1})	Observed frequence (cm^{-1})
Aromatic C-H Stretching	3000-3100	3248.23
C=C Stretching	1450-1600	1473.66
Aliphatic C-H	2700-3300	2839.31
C=O Stretching	1670-1820	1604.83
O-H Stretching	2500-3100	2962.76

Resemblance of observed IR peaks and reported peaks indicated purity of Glipizide.

B. Compatibility Study Of Drug With Polymers

The drug- excipients compatibility studies were performed in order to confirm the compatibility of drug with the used excipients in the formulation. These studies mainly include FTIR.

1) FT-IR Spectroscopy Study

FT-IR studies were carried out to confirm the compatibility between pure drug and polymers. The spectra obtained from the FT-IR studies from 4000-400 cm-1. The FT-IR spectrum of the drug & polymers were shown in the Figure 6 & 7. The comparison of IR spectrum of pure drug with IR spectra of polymers showed no appreciable change in the positions of characteristic absorption band.

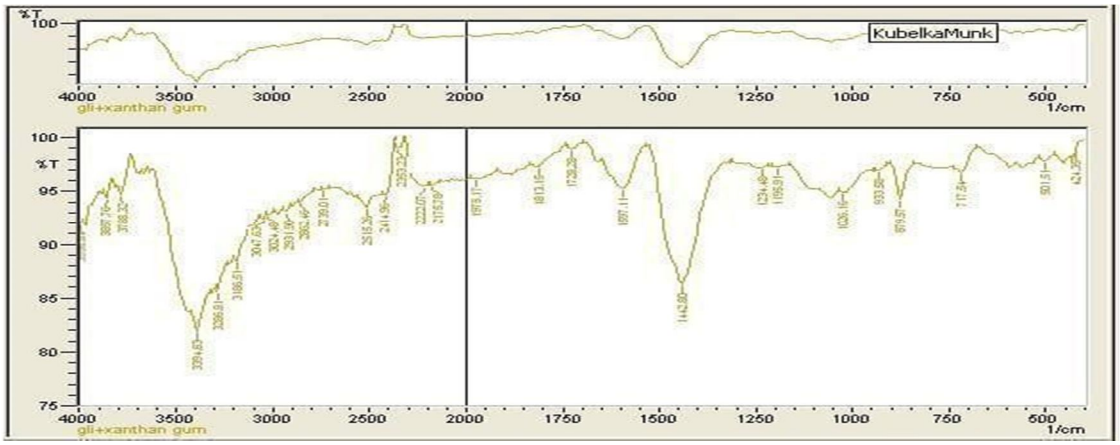


Figure 5: FTIR spectra of mixture of Glipizide and Xanthan gum

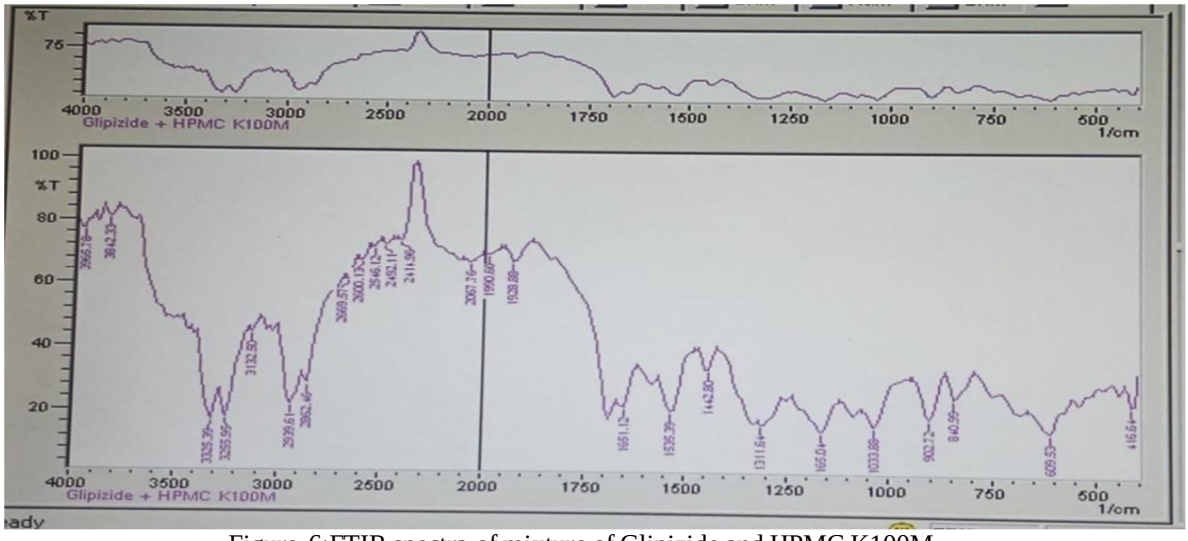


Figure 6:FTIR spectra of mixture of Glipizide and HPMC K100M

All the major bands present in the spectrum of the pure drug are clearly observed in the spectrum of polymers with negligible changes in their position. This study clearly suggests that the pure drug remains in its normal form and hence there was no interaction between the drug and polymer.

Table 9. :Results of Pre-Compressional Evaluation of Powder Blend

Batch	Bulk Density (gm/ml)	Tapped Density(gm/ml)	Angle of Repose(θ)	Hausner'sRatio	Carr's Index (%)
F1	0.566 ±0.166	0.627±0.17	24 ± 0.534	1.13 ±0.026	11.8 ±0.20
F2	0.589 ± 0.876	0.676±0.3	28 ±0.333	1.12 ±0.034	11.06 ±0.13
F3	0.612 ±0.242	0.685±0.11	25 ± 0.768	1.10 ±0.089	11.75 ±0.27
F4	0.559 ±0.495	0.695±0.7	26 ± 0.373	1.09 ±0.096	8.69 ±0.56
F5	0.591 ± 0.293	0.689±0.9	26 ± 0.635	1.10 ±0.034	11.47±0.47
F6	0.627 ±0.174	0.695±0.11	25 ± 0.635	1.10 ±0.089	9.64 ±0.18
F7	0.614 ± 0.151	0.694±0.5	25 ± 0.534	1.10 ±0.034	11.56 ±0.32
F8	0.549 ±0.583	0.662±0.3	27 ±0.847	1.09 ±0.089	9.86 ±0.34
F9	0.561 ±0.912	0.669±0.6	28 ±0.635	1.08 ±0.096	8.87 ±0.16

All values represents mean ± SD (n=3)

C. Post Compressional Evaluation Of Glipizide Floating Tablets

Tablets of different formulations were subjected to evaluation tests such as thickness, diameter, hardness, friability,weight variation, drug content, in-vitro buoyancy studies, swelling index and in-vitro drug release.

1) Tablet Thickness

Thickness of tablet was measured by vernier caliper and observed values were reported inTable10. All the tablets as the thickness limit of IP which is ± 5%.

The thickness of tablets was uniform; it indicates that uniform and proper filling ofpowder blend into the dies during compression of tablet.

Table 10: Thickness of F1-F9 formulation

Evaluation Parameter	Thickness(mm)*
F1	3.34±0.9
F2	3.35±0.8
F3	3.54±0.7
F4	3.44±0.8
F5	3.51±0.6
F6	3.39±0.3
F7	3.34±0.5
F8	3.46±0.9
F9	3.33±0.6

2) Hardness

The hardness of the tablets was found to be in the range from 5.1 kg/cm^2 to 5.9kg/cm^2, which indicates that tablets have good mechanical strength with an ability to withstand physical and chemical stress conditions while handling. The results were shown in Table11.

Table 11:Hardness of F1-F9 formulation

Evaluation Parameter	Hardness(kg/cm^2)*
F1	5.56±0.34
F2	5.43±0.43
F3	5.28±0.53
F4	5.23±0.44
F5	5.86±0.42
F6	5.92±0.41
F7	5.76±0.57
F8	5.42±0.37
F9	5.35±0.55

*All values was represented as mean ±SD (n=3)

3) Friability Test

The percentage friability of all the formulations was in between 0.30% to 0.45%.The percentage friability was less than 1% in all the formulations, which indicates good mechanical resistance of the tablet. The values of Hardness test and Percentage friability indicates good handling property of prepared tablets. TheresultswereshowninTable12.

Table 12:Friability of F1-F9 formulation

Evaluation Parameter	Friability (%)*
F1	0.40±0.04
F2	0.55±0.5
F3	0.49±0.5
F4	0.46±0.3
F5	0.52±0.4
F6	0.47±0.2
F7	0.49±0.7
F8	0.42±0.1
F9	0.45±0.3

*All values was represented as mean ±SD (n=20)

4) Weight Variation Test

The weight variation tests were performed according to the procedure given in the pharmacopeia. All the formulated (F1toF9) tablets passes weight variation test as the percentage weight variation was within the pharmacopoeia limits of ± 5% of the weight and hence all the formulations passes the weight variation within the acceptable limits as per I.P. The results were shown in Table13.

Table 13:Weight variation of F1-F9formulations

Evaluation Parameter	Weight variation(mg)*
F1	200.2±0.9
F2	199.3±1.3
F3	201.4±1.1
F4	199.3±2.1
F5	200.1±0.4
F6	199.5±1.7
F7	201.8±1.5
F8	200.4±0.8
F9	199.9±2.4

*All values was represented as mean ±SD (n=20)

5) Estimation of Drug Content for Tablets

The percentage drug content of all the formulations were within the range from 99.16% to 99.89%, showed that the drug was uniformly distributed in all the formulations**.** Hence, the percentage drug content of all the formulations complies with official specifications as per U.S.P (Limits: not less than 90% and not more than 110%).The results were shown in Table 14.

Table 14:Drug content of F1-F9 formulations

Evaluation Parameter	Drug Content (%)
F1	98.06±0.23
F2	97.03±1.13
F3	99.27±0.31
F4	99.36±0.71
F5	99.72±0.34
F6	99.51±1.07
F7	98.13±0.75
F8	98.37±0.83
F9	99.16±0.14

*All values was represented as mean ± SD (n=3)

6) In vitro Buoyancy Studies

The time taken for a dosage form to emerge on the surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remains buoyant is called Total Floating Time (TFT).

Floating lag time and duration of floating of various formulations were tabulated inTable 15. All formulations F1- F9 shows the floating lag time less than 5 min and the duration of floating was greater than 8 hrs. Sodium bicarbonate was used as an effervescent agent that maintains the buoyancy of the tablets.

Table 15: Data of In-vitro buoyancy study of F1-F9formulation

Formulation Code	Floating Lag Time(min)	Total FloatingTime(hrs)
F1	2 min	7.35
F2	3 min	8.29
F3	3 min	8.11
F4	3 min 35sec	8.48
F5	3 min 50sec	7.12
F6	2 min 35sec	8.55
F7	1 min 50sec	8.16
F8	2 min 15sec	8.38
F9	4 min 10sec	7.15

7) Swelling Studies

Swelling study was performed on all the batches (F1 –F9) for 8 hours. The results of swelling index were given in the Table 16. While the plot of the swelling index against time (hr) is shown in Figure 16. Swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outer most gelled layer of tablet into dissolution medium.

Table 16: Swelling index of F1-F9 formulations

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	38.89	44.71	43.08	42.08	55.80	52.08	46.94	61.40	56.84
2	47.72	52.81	55.47	56.75	66.93	68.45	56.02	77.84	88.54
3	51.17	57.18	60.71	60.86	75.67	90.37	75.25	86.24	101.28
4	54.19	63.37	70.75	75.78	95.54	115.20	90.10	94.49	118.02
5	67.48	75.86	86.24	91.08	110.72	121.59	95.75	101.84	131.08
6	78.45	98.45	99.75	98.65	124.32	136.21	103.42	119.54	146.66
7	102.58	114.58	123.14	109.56	135.41	143.87	110.48	122.42	159.24
8	90.12	122.37	132.25	114.78	141.58	154.87	119.26	125.65	167.54

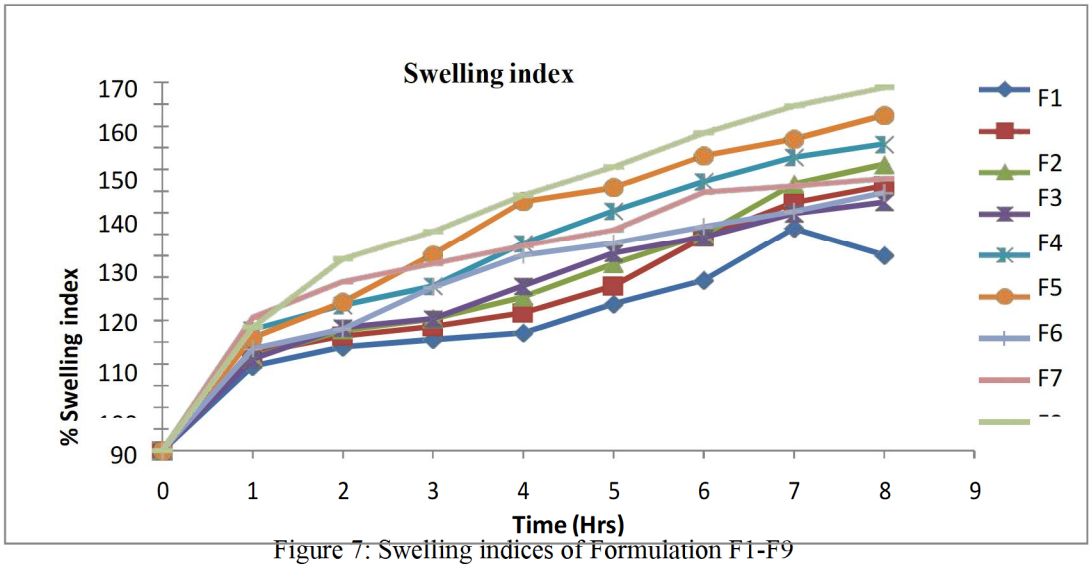


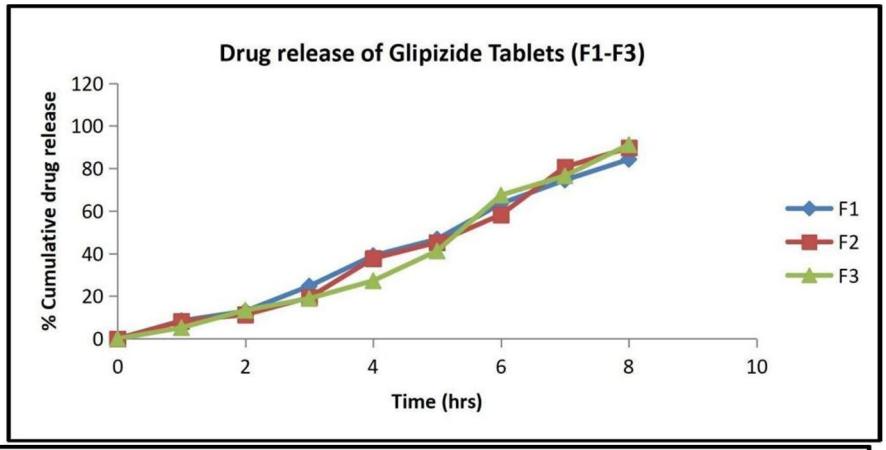
Figure 7: Swelling indices of Formulation F1-F9

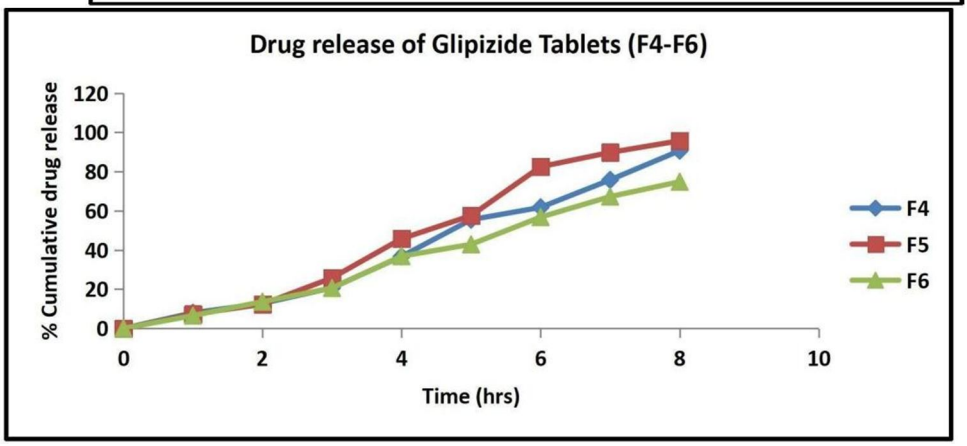
8) In vitro Drug Release Studies

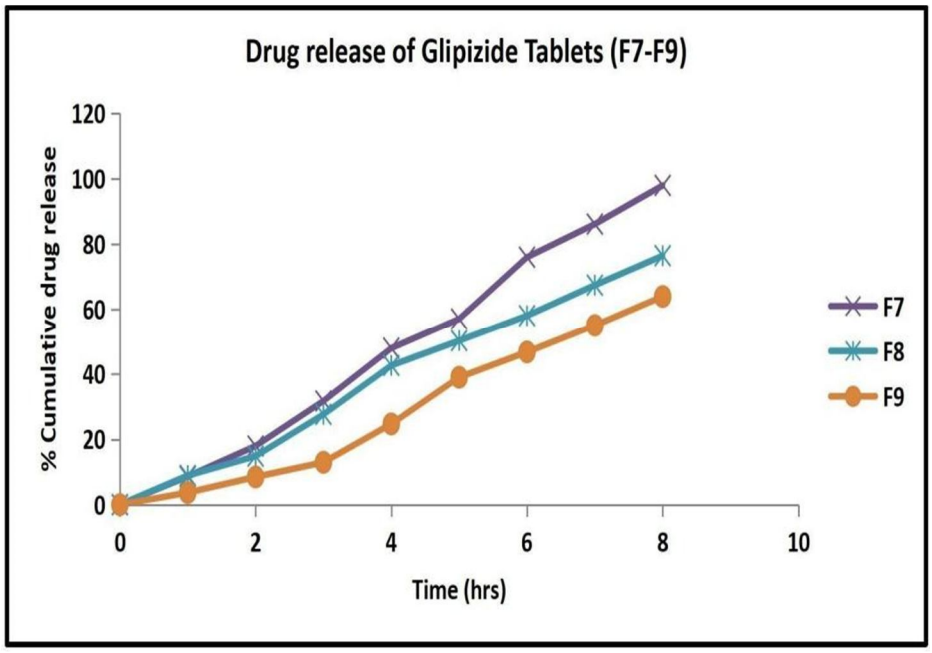
To increase the release retardation of the drug, the formulations were prepared by a combination of HPMC K100M and Xanthan gum. The high viscosity grade polymer induce the formation of strong viscous gel layer when they come in contact with the aqueous media that slowed down the rate of diffusion of medium into the tablet, which may results in the retardation or decrease the drug release. Xanthan gum in combination with HPMC K100M showed decrease in drug release with increase in concentration of Xanthan gum.Results were shown in Table 17 and figure 9(a, b, c).

Table 17: Drug release (%) of formulation F1-F9

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	8.50	8.21	5.21	7.98	7.22	6.55	8.64	8.93	3.69
2	12.97	11.34	13.39	12.74	12.34	13.62	17.97	14.87	8.50
3	24.74	19.37	18.93	20.70	25.77	20.62	31.77	27.65	12.97
4	39.04	37.71	27.26	36.70	45.76	36.86	48.00	42.67	24.73
5	46.81	45.27	41.26	55.47	57.54	42.89	57.08	50.32	39.04
6	63.49	58.29	67.48	61.75	82.50	56.79	76.00	58.08	46.81
7	74.55	80.68	76.55	75.77	89.79	67.26	86.13	67.46	55.08
8	84.2	89.68	91.19	90.67	95.72	74.83	97.94	76.46	63.99







Among all the nine formulations, F7 (Guar gum 60% & Xanthan gum 40%) wasselected as a best formulation which had the better retardant effect (98.13% in 8hours).

D. Optimization of Data Analysis

Based on the principle of design of experiments (DoE), the methodologyen compasses the use of various types of experimental designs, generation of polynomial equation and mapping of the response over the experimental domain to determine the optimum formulation. Various RSM computation for the current optimization study were performed using Design Expert software (Design Expert trail version 13). The polynomial equations can be used to draw conclusion after considering the magnitude coefficient and the mathematicalign that the coefficient carries. A positive value indicates synergistic effect that favours optimization, while negative sign represents an antagonistic effect or inverse effect of the factor on the selective response.

Generated by the Design Expert software. These plots are very useful to seeinteraction effects of the factors on responses.

1) Effect of independent variables on floating lagtime: ANOVA forSelected Factorial Model

Final Equation in Terms of Coded Factors

Floating lag time	=
+120.22	
+24.50	A
-12.33	B
+10.00	AB
+54.17	A^2
+4.67	B^2

Table18:Analysis of variance for floating lag time

Source	Sum ofSquares	df	F-value	p-value	
Model	10825.78	5	48.31	0.0046	significant
A- HPMC K100M	3601.50	1	80.36	0.0029	
B-XanthanGum	912.67	1	20.37	0.0203	
AB	400.00	1	8.93	0.0582	
A^2	5868.06	1	130.94	0.0014	
B^2	43.56	1	0.9719	0.3969	
Residual	134.44	3			
Cor Total	10960.22	8			

Std. Dev.	6.69	R^2	0.9877
Mean	159.44	AdjustedR²	0.9673
C.V. %	4.20	PredictedR²	0.8553
		AdeqPrecision	17.0754

2) Effect of Independent Variables on Swelling Index

ANOVA for selected factorial model:

Table 19: Analysis of variance for swelling index

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	3177.97	2	1588.99	18.04	0.0029	significant
A- HPMC K100M	1440.57	1	1440.57	16.36	0.0068	
B- XANTHANGUM	1737.40	1	1737.40	19.73	0.0044	
Residual	528.49	6	88.08			
CorTotal	3706.46	8				

Std.Dev.	9.39	R^2	0.8574
Mean	111.72	Adjusted R^2	0.8099
C.V. %	8.40	Predicted R^2	0.6709
		Ad eq Precision	12.0002

3) Effect of Independent Variables on Drug Release: ANOVA for Selected Factorial Model

Table 20:Analysis of variance for drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	348.18	2	174.09	5.33	0.0467	significant
A- HPMC K100M	130.85	1	130.85	4.01	0.0922	
B- XANTHANGUM	217.32	1	217.32	6.65	0.0418	
Residual	195.99	6	32.66			
CorTotal	544.16	8				

Std.Dev.	5.72	R^2	0.6398
Mean	82.18	Adjusted R^2	0.5198
C.V. %	6.95	Predicted R^2	0.4769
		Ad eq Precision	6.4783

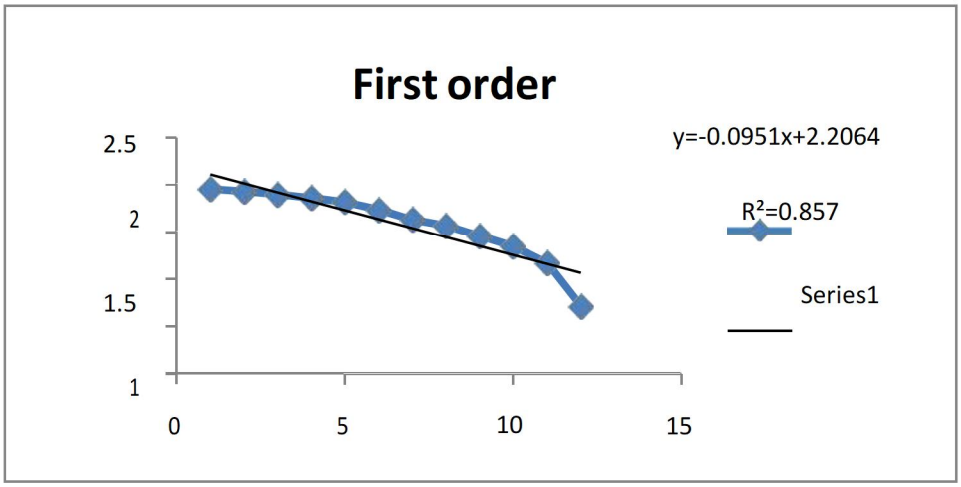
E. In-vitro Drug Release Kinetics Studies

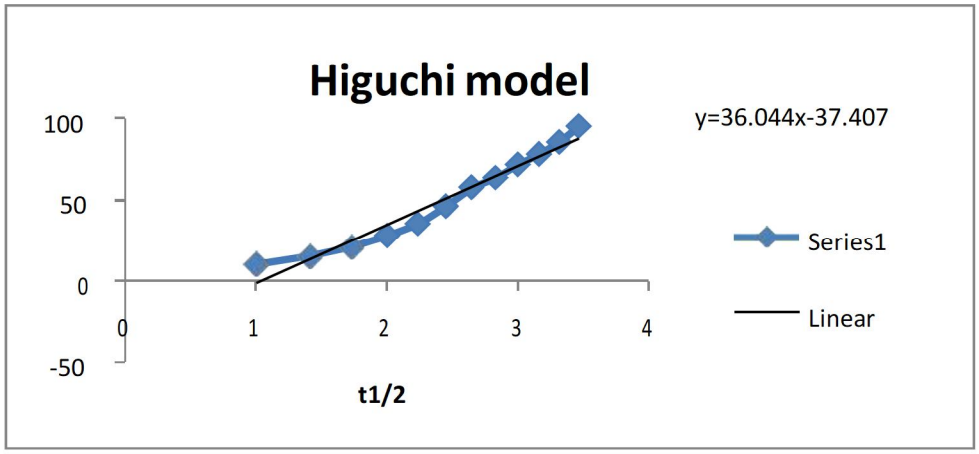
To analyze the release mechanism the *in-vitro* release data of batches F1 to F9 wasfitted to various release equation and kinetic models (zero order, first, Higuchi,Hixson-Crowell and Korsemeyer Peppas) .The release kinetic data for all the formulations were shown in the Table 21.

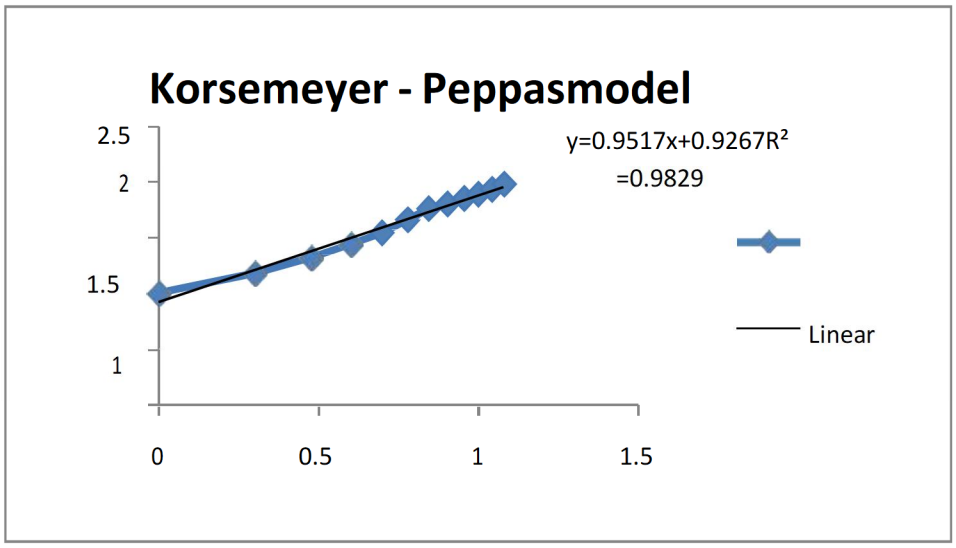
The regression coefficient (R^2) value was used as criteria to choose the best modelto describe drug release from the tablets. The value of release exponent (n) enlightens in understanding the release mechanism from dosage form. If value of n is 0.5, itindicates Fickian diffusion. If value of n is between 0.5-1, it indicates non- fickiandiffusion. If value of n is 1, it indicates case II transport or zero order release.

Table 18: Drug release kinetics of F1-F9 formulation

Formulation code	Zero order	First order	Higuchimodel	Korsemeyer-Peppasmodel	
	R^2	R^2	R^2	R^2	N
F1	0.9834	0.6921	0.9321	0.998	1.090
F2	0.9968	0.7888	0.9595	0.9979	1.041
F3	0.997	0.722	0.961	0.998	1.056
F4	0.9954	0.7215	0.9550	0.9985	1.071
F6	0.998	0.862	0.964	0.993	1.118
F7	0.994	0.931	0.965	0.996	0.973
F8	0.998	0.881	0.975	0.999	1.144
F9	0.9945	0.9001	0.9508	0.9989	1.069







igure 10: Models of the optimized formulation (F7)

VII. CONCLUSION

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time using gastrorententive dosage forms that will provide us with new and important therapeutic options. Glipizide gastroretentive effervescent floating tablets were prepared with an aim to provide the drug for prolonged period of time in the stomach. Glipizide was targeted to stomach because it has the absorption window in upper part of GIT so it has been provided for prolonged period oftime in stomach for better therapeutic activity by increasing its bioavailability. The floatation was accomplished by incorporating gas generating agent, sodium bicarbonate into a swelling polymer. All the formulations had floating lag time of less than 4 minutes and total floating time of 8 hours. Among all the formulations, F7 formulation gives best results based on floating time (1 min 50 sec) and drug release profile (97.94% in 8 hours). From the study, it has been concluded that HPMC K100M and Xanthan gum can be a promising polymers for gastroretentive drug delivery system. Drug authentication was done at the start of the project. According to the authentication research, the Glipizide sample that was obtained was pure and in accordance with IP limits.

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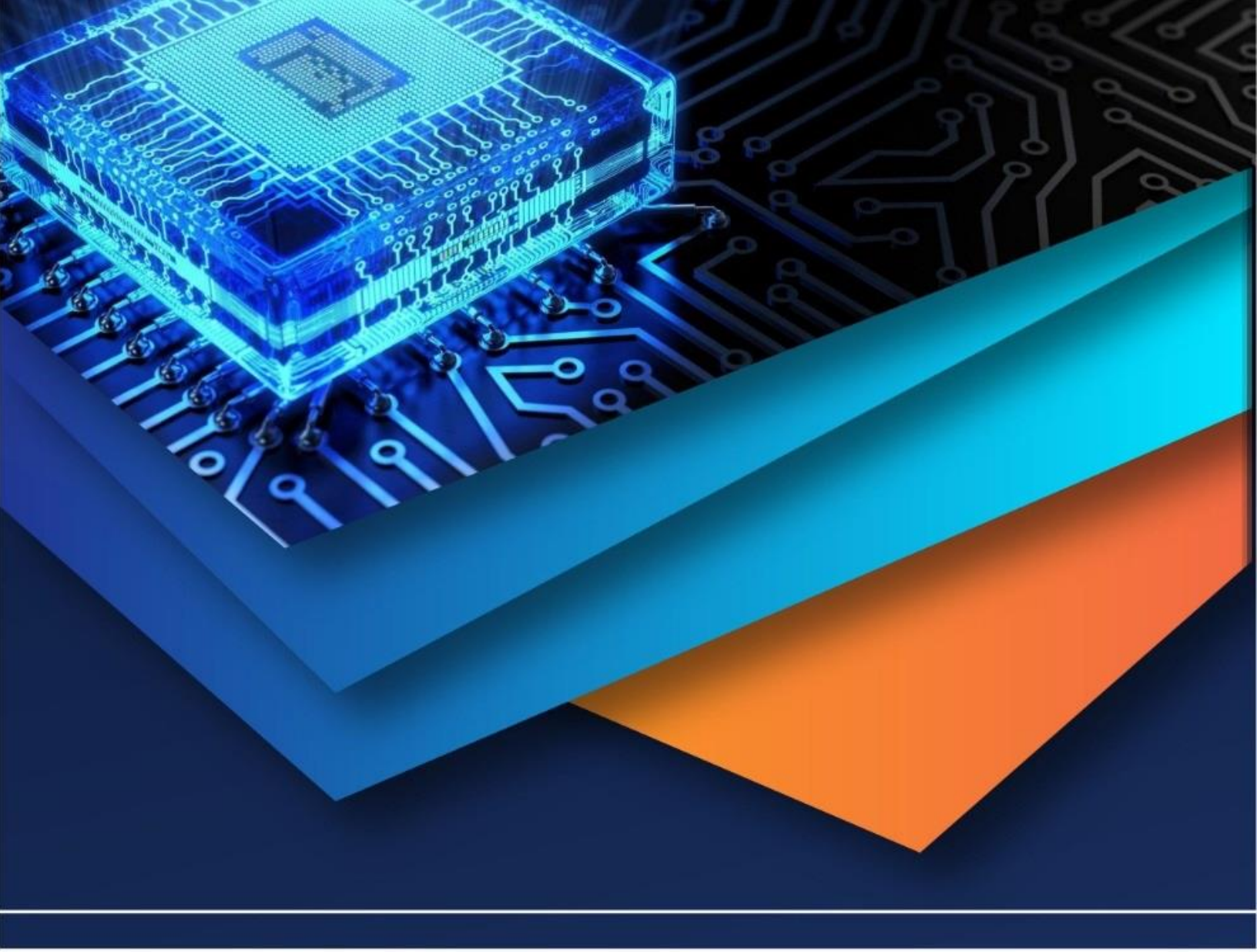

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