DESIGN, DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF GLICLAZIDE: *IN VITRO* AND *IN VIVO* STUDIES

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ABSTRACT

The current research work attempts to design and develop the stomach specific sustained floating drug delivery by Hydroxy Propyl Methyl Cellulose E15 (METHOCEL™) – Carbopol 934P (Carbopol®) based polymeric matrices as a carrier for effervescent floating tablets of gliclazide. Here gliclazide was mixed with different polymeric mixtures by addition of any other ingredients needed for direct compression and suitable effervescent floating tablets of gliclazide were prepared. *In vitro* floatation of all effervescent floating tablets (especially GT3) of gliclazide was not less than 12 h in 0.1 N HCl (pH: - 1.2) and similarly *in vivo* gastroretention was found to be excellent by X- ray images of rabbit with changing the drug by barium sulphate. FTIR and DSC studies demonstrated negligible incompatibility between the drug and polymer in this formulation. So, these results could be very useful for future drugs for gastroretentive sustained floating drug delivery over prolonged periods of time.

Keywords: Gastroretention, effervescent, buoyancy, hydroxyl propyl methyl cellulose, Carbopol

INTRODUCTION

Oral delivery of drugs is the preferred route of administration due to its numerous advantages, including ease of administration, improved patient compliance, and low cost[1, 2]. Among various dosage forms and routes of administration, oral controlled release delivery systems play a significant role in drug delivery, providing controlled and sustained release over extended periods, which enhances bioavailability and reduces drug wastage[3, 4]. In recent decades, several controlled release drug delivery systems have been developed. Among these, stomach-specific or gastroretentive drug delivery systems have gained prominence due to their ability to retain drugs in the gastric region for extended periods, ensuring better absorption and sustained release at a desired rate[5-7]. Different gastroretentive system including floating drug delivery system[8-10], high density system[11], mucoadhesive or bioadhesive system[12-14], superporous hydrogel system[15], swellable system [16], magnetic system[17], expendable and unfoldable system[18-21], among these low density or floating system have proven effective for delivering drugs with good absorption capabilities in gastric fluid, particularly in the stomach or upper intestinal tract[6, 7, 22]. The recent work aimed to design and formulate the most reliable gastroretentive effervescent floating tablets of gliclazide using Hydroxy Propyl Methyl Cellulose (HPMC E15) and Carbopol 934P as matrix and drug release polymers for sustained drug delivery.

Gliclazide, an oral anti-diabetic drug belonging to the sulfonylurea group, has moderate bioavailability and a biological half-life, and is absorbed from the stomach[23, 24]. HPMC E15 and Carbopol 934P are biocompatible and biodegradable polymers that form hydrocolloidal gels, enhancing sustained release and reducing dosing frequency and drug wastage[25-28]. Previously many work reported on this field[9, 19, 29, 30] but this study aimed to design a model for formulating gastroretentive, gas-generating, effervescent gliclazide floating tablets using a combination of these two polymers with other excipients. The study evaluated compatibility and release using FTIR and DSC methods, as well as pre-compression characterizations, weight uniformity, swelling index, post-compression characterizations, content uniformity of the drug, and drug release through in vitro studies in 0.1 N HCl. Additionally, in vitro buoyancy and in vivo gastroretention capability were assessed using an animal model to demonstrate the sustained release of gliclazide from this system.

MATERIALS AND METHODS

Materials

Different ingredients used in this research work were collected from different sources having good quality. Drug gliclazide was obtained from Ajanta Pharma Limited., Assam. Hydroxy Propyl Methyl Cellulose E15 and Carbopol 934P were purchased from Sigma Aldrich Chemicals Private Limited., Bangalore. PVP K30, lactose, sodium bicarbonate, citric acid, talc and magnesium stearate were sourced from Loba Chemie Pvt. Limited., Mumbai.

Formulation of gliclazide gas generating effervescent floating tablet

The gas-generating effervescent floating tablets of gliclazide were formulated by mixing all the ingredients (except talc and magnesium stearate) and passing them through a sieve (No. 60). The drug was then mixed with other ingredients, including HPMC E15 and Carbopol 934P as low-density matrix and release biopolymers, PVP K30 as a binding polymer, lactose as a diluent, and sodium bicarbonate and citric acid as effervescent gas-generating agents. Suitable glidant and lubricating agents, talc and magnesium stearate, were added and mixed for a few minutes. The composition was then compressed using a single-punch tablet compression machine. The composition of various formulations is presented in Table I.

Table I: Formula of different effervescent floating tablets of gliclazide

Ingredients	Formulation code				
	GT1	GT2	GT3	GT4	GT5
Gliclazide	100	100	100	100	100
HPMC E15	75	125	150	50	100
Carbopol 934P	125	75	50	150	100
PVP K30	20	20	20	20	20
Lactose	100	100	100	100	100
Sodium bicarbonate	50	0	50	50	50
Citric acid	15	15	15	15	15
Talc	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10

Evaluation of pre compression characterization

Evaluating the micromeritic properties of powder samples before formulation is crucial. These properties include morphology, density, porosity, compressibility, and flowability, which help develop the formulation. In this study, we investigated various properties, including[9].

Bulk Density

The bulk density (B.D.) of the powder samples was determined by taking a known quantity of powder from each formulation, weighing it, and transferring it to a 20 ml measuring cylinder. The powder volume was calculated without tapping. The B.D. was calculated using the following equation:

B.D. = Total weight of the powders / Powders volume without tapping

Tapped Density

The tapped density (T.D.) was determined by taking a known quantity of powder from each formulation, weighing it, and transferring it to a 20 ml measuring cylinder fitted with a tapped density apparatus. After tapping, the powder volume was measured. The T.D. was calculated using the following equation:

Tapped Density = Total weight of the powders / Powders volume after tapping

Compressibility Index

The compressibility index (C.I.) evaluates the compressibility of powder samples, which is essential for tablet formulation using a single-punch tablet compression machine. The C.I. is calculated using the bulk density (B.D.) and tapped density (T.D.) values in the following formula:

C.I. = (T.D.-B.D.)/T.D. x 100

Hausner's Ratio

Hausner's ratio (H.R.) assesses the flowability and particle size distribution of compressed samples. The H.R. is calculated using the B.D. and T.D. values in the following equation:

H.R. = T.D. / B.D.

Angle of Repose

The angle of repose (A.O.R.) determines the flowability of powder samples. It is expressed as the maximum angle formed between the horizontal layer of the plain base and the hip of the sample produced by the upper layer. To determine the A.O.R., a glass funnel is fixed above a 5 cm plain base surface using a stand. A known quantity of powder sample is introduced into the funnel, and the powder accumulates in a cone shape on the plain base surface. The height of the powder hip on the base surface (h) and the radius (r) of the circle produced by the hip of the powder sample and the plain base are measured. The values are inputted into the following formula to calculate the A.O.R.:

$\tan \theta = h/r$ or $\theta = \tan^{-1}(h/r)$ (Here θ = A.O.R.)

Evaluation of post compression characterization

Characterizing the effervescent floating tablets of gliclazide after formulation is crucial. In this study, we evaluated the appearance of the tablets, including their shape, size, strength, and friability[9, 11, 28, 29].

Microscopic Examination

Microscopic examination was performed to determine the shape of the formulated effervescent floating tablets of gliclazide, checking for any cracks, damage, holes, or lines.

Tablet Size and Dimension

The size and dimension of the tablets were evaluated by measuring their diameter and thickness using standard vernier calipers. Ten tablets from each formulation were randomly selected, and their hardness and thickness were measured in millimeters. The average or mean value with standard deviation was calculated.

Tablet Hardness

The crushing strength or hardness of the tablets was determined using a Monsanto Hardness Tester. Ten tablets from each formulation were selected, and the force required to break the tablets was measured in kilograms. The average or mean value with standard deviation was calculated.

Tablet Friability

The friability of the tablets was evaluated using a Roche Friabilator to assess their strength and stability. Twenty tablets from each batch were randomly selected, and their initial weight (Wi) was measured. The tablets were then placed in the Roche Friabilator, and the instrument was rotated at 100 rpm, causing the tablets to fall from a height of 6 inches repeatedly, resulting in dusting. Finally, the tablets were weighed again (Wf), and the percentage loss in weight due to friability was calculated using the following equation:

$$\text{Friability (\%)} = (Wi - Wf) / Wi \times 100$$

Evaluation of uniformity of weight variation

The uniformity of weight variation was analyzed by randomly selecting 20 tablets from each formulation and weighing them individually using an analytical balance. The average or mean weight of the tablets was calculated, and the percentage weight difference or weight variation was determined using the following equation[19] (according to I.P. specification):

$$\text{Weight variation/Coefficient of variation} = \text{Standard deviation} / \text{Mean weight} \times 100$$

Evaluation of Swelling Activity

The water uptake activity of the floating tablets of gliclazide was determined by weighing the tablets individually (Wi) from each formulation and then allowing them to stand in a

dissolution apparatus (USP Type-II) using 500 ml of simulated gastric fluid (pH 1.2) at a rotational speed of 100 rpm. At regular intervals, the immersed tablets were withdrawn, washed with tissue paper to remove surface liquid, and reweighed (Ws) in different swelling conditions after predetermined periods. The swelling index (S.I.) was calculated using the following equation[9]:

S.I. = (Ws - Wi) / Wi × 100

Evaluation of drug content uniformity

The drug content uniformity in the effervescent floating tablets of gliclazide was evaluated by selecting ten tablets from each batch and introducing them into a glass beaker containing simulated gastric content (pH 1.2). The beaker was stirred using a magnetic stirrer for one hour at a temperature of 37 ± 0.5°C. After this period, the final solution was filtered through Whatman filter paper and mixed to form a suitable concentration with simulated gastric content (pH 1.2) to evaluate the content uniformity of the drug using a spectrophotometer (Double Beam UV Spectrophotometer) against a blank sample at a maximum λmax of 232 nm[25].

Analysis of *in vitro* drug release

The *in vitro* release study of gliclazide effervescent tablets was conducted by introducing one tablet of each formulation into 900 ml of gastric fluid (pH 1.2) containing a paddle-type dissolution test apparatus with a rotating speed of 100 rpm at a temperature of 37 ± 0.5°C. At specific intervals, 5 ml samples were withdrawn from the medium and replaced with the same quantity of fresh content to maintain sink conditions. This process was continued for a prolonged period. After completing the sampling, the samples were filtered using Whatman filter paper, diluted with suitable dilution, and evaluated for *in vitro* release of gliclazide using a Double Beam UV-Visible Spectrophotometer against a blank sample at a maximum λmax of 232 nm[28].

Evaluation of release data by kinetics analysis

The *in vitro* release kinetics mechanism of gliclazide effervescent tablets was determined by fitting the *in vitro* release data to mathematically curve-fitted kinetics models, including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hickson-Crowell models[25]. The release exponent (n) values were observed to clarify the release mechanism of the drug. If the n value is less than or equal to 0.5, it indicates a Fickian diffusion-controlled release mechanism. If the value ranges between 0.5 and 1, it indicates a non-Fickian release mechanism. If the value is greater than or equal to 1, it refers to Case-II transport or release[29].

Evaluation of FTIR characterization:

The samples were analyzed using potassium bromide pellets (IR-grade) in a Fourier transform infrared spectroscopy instrument (Alpha II compact FTIR Spectroscope, Germany). The drug gliclazide, polymer HPMC E15, Carbopol 934P, and the drug-polymer mixture (GT3) were placed in an IR-grade potassium bromide pellet, which was then introduced into the sample holder of the instrument. Spectroscopy scanning was performed within the range of 4000-500 cm^{-1}.

Evaluation of DSC characterization

The samples, including the drug gliclazide, polymer HPMC E15, Carbopol 934P, and the drug-polymer mixture (GT3), were tested using a Differential Scanning Calorimetric instrument (DCS-3, Mettler Toledo, Switzerland). The samples were placed in an Al pan and heated at 50°C/min with indium in the reference pan, producing a nitrogenized atmosphere up to 400°C.

Evaluation of *in vitro* flotation:

The *in vitro* buoyancy of the tablets was evaluated by immersing the tablets of the best formulation in 500 ml of gastric fluid containing a glass beaker at a maintained temperature of 37 ± 0.5°C. The time required for the tablet to reach the surface of the liquid and float was recorded as the floating lag time (FLT), and the duration for which the tablets remained float on the medium was recorded as the total floating time[9] (TFT).

Evaluation of *in vivo* gastroretention by using X-ray photography

In-vivo gastroretention studies were conducted using New Zealand white rabbits through X-ray radio images[21]. The experiment was carried out (X-radio imaging) according to the IAEC (Registration no- PCP/IAEC/2023/JAN/20) and was scrutinized by the CPCSEA (Registration no- 1698/Re/S/13/CPCSEA). Male rabbits weighing 2.75 ± 0.25 Kg were used for the experiment. The rabbits were acclimated to the new environment and fed a standard laboratory diet. The acclimated rabbits were fasted overnight before the experiment, maintaining room temperature, and were provided with sufficient water. The experiment was conducted from 6 am to 6 pm to minimize animal suffering. The formulation GT3 was replaced with BaSO4 and introduced into the rabbit's mouth using a tube with flushing water. X-ray photography of the gastric region in rabbits was captured at 3, 6, and 12-hour time intervals[29, 30].

Evaluation of Statistical analysis

Microsoft Excel was used to evaluate all the data obtained from this research work. Kinet Ds software was used to curve-fit the release kinetics model for the in vitro release of gliclazide.

RESULTS AND DISCUSSION

Preparation of effervescent gas generating floating tablets of gliclazide

Gastroretentive floating tablets are a reliable, economical, and easy-to-handle dosage system, particularly for drugs that are extensively absorbed in the small intestine[3, 5, 7]. Several similar studies have reported the use of HPMC and Carbopol for preparing sustained-release dosage forms for various drugs[11, 12, 17, 19, 24, 28]. In this study, we designed gas-generating effervescent floating tablets of gliclazide by incorporating the matrix polymer HPMC E15 and the releasing polymer Carbopol 934P, along with lactose, PVP K30, sodium bicarbonate, citric acid, and magnesium stearate. The resulting tablets exhibited good floatation due to the formation of a colloidal gel by HPMC E15, which allowed the tablets to float in the upper region of the gastrointestinal tract (GIT) for an extended period.

Pre compression characterization

The pre-compression characteristics of all formulations are presented in Table II. The compressibility index (C.I.) values ranged from 12.14 to 15.75, the Hausner's ratio (H.R.) values ranged from 1.13 to 1.19, and the angle of repose (A.O.R.) values ranged from 25.76 to 31.54. These values are within the acceptable range, indicating that the powder samples had good compressibility, flowability, and stability, making them suitable for formulation development.

Table II: Pre compression Characteristics of floating gliclazide tablets

Formulation Code	B.D.(gm/cm^3)	T.D. (gm/cm^3)	C.I. (%)	H.R. (°)	A.O.R. (°)
GT1	0.476	0.565	15.75	1.18	30.34
GT2	0.445	0.512	13.08	1.15	28.54
GT3	0.454	0.522	13.02	1.14	26.45
GT4	0.416	0.488	14.75	1.17	29.67
GT5	0.434	0.494	12.14	1.13	25.76

Mean ± standard deviation, n = 3

Post compression characterization

The post-compression characteristics of all formulations are presented in Table III. The results showed that the tablets had a smooth and circular shape. The size of the tablets was within the acceptable range, with diameters ranging from 7.25 ± 0.24 to 7.34 ± 0.28 and thickness ranging from 3.83 ± 0.05 to 3.92 ± 0.09, which meets the official U.S.P. specification.

The hardness of the tablets, an important parameter for maintaining proper strength, was within the range of 4.56 ± 0.18 to 4.72 ± 0.33, which is within the standard U.S.P. specification.

Another critical parameter for maintaining the strength of the formulated tablets is friability. The results showed that the friability values were within the acceptable range, with values less than 1%, indicating stability during transportation and handling.

Table III: Post compression Characteristics of floating gliclazide tablets

Formulation Code	Tablets diameter(mm)	Tablets thickness (mm)	Hardness (kg/cm^2)	Friability (%)
GT1	7.27 ± 0.23	3.86 ± 0.07	4.56 ± 0.18	0.53 ± 0.03
GT2	7.34 ± 0.28	3.92 ± 0.09	4.67 ± 0.26	0.52 ± 0.04
GT3	7.25 ± 0.24	3.79 ± 0.06	4.72 ± 0.33	0.54 ± 0.03
GT4	7.29 ± 0.18	3.83 ± 0.05	4.61 ± 0.20	0.56 ± 0.01
GT5	7.31 ± 0.25	3.87 ± 0.08	4.69 ± 0.26	0.58 ± 0.03

Mean ± standard deviation, n = 3

Weight uniformity

The results of the weight uniformity test for the different effervescent floating tablets of gliclazide are presented in Table IV. All the values met the USP specification, and the coefficient of weight variation was not more than 2.50%, indicating proper mixing and good compression of the floating tablets of gliclazide.

Table IV: Weight uniformity of floating gliclazide tablets

Formulation Code	Weight Uniformity	
	Mean Weight ± S. D.*	Coefficient of Variation# (%)
GT1	494.6 ± 8.50	1.71
GT2	497.5 ± 10.18	2.04
GT3	499.3± 10.58	2.11
GT4	487.1 ± 8.26	1.69
GT5	490.7 ± 9.39	1.91

*S.D. = standard deviation, Mean ± standard deviation, n = 3

Swelling activity

The swelling activity, expressed as a percentage weight (gm), of the effervescent floating tablets of gliclazide is presented in Table V. The results clearly show that as the time spent by the tablets in the dissolution medium increases, the swelling index also increases due to the

hydrophilic nature of the polymers, which form a hydrocolloidal gel. This swelling property helps the tablets to float for extended periods and sustain the release of the drug over a prolonged period

Table V: Swelling activity floating gliclazide tables

Formulation Code	Swelling Index % weight (mg)			
	1h	3h	6h	12h
GT1	553	632	719	833
GT2	578	663	759	873
GT3	589	697	803	934
GT4	522	618	744	811
GT5	546	655	769	849

Mean ± standard deviation, n = 3

Content uniformity of drug

The content uniformity of the drug from the effervescent floating tablets of gliclazide is presented in Table VI. The results indicate that the drug content in each formulation falls within the range of 97.63 ± 1.42 to 101.48 ± 1.75, confirming the presence of gliclazide in the appropriate quantity in every formulation.

Table VI: Content uniformity of drug for effervescent floating gliclazide tablets

Formulation Code	Drug content uniformity
GT1	98.35 ± 1.34
GT2	101.48 ± 1.75
GT3	100.03 ± 1.57
GT4	97.63 ± 1.42
GT5	99.77 ± 1.29

Mean ± standard deviation, n = 3

***In vitro* release of drug**

The *in vitro* release of gliclazide from effervescent floating tablets in gastric fluid is represented in Fig. 1. All these formulations exhibited good release profiles, which were prepared by mixing gliclazide with suitable polymers, HPMC E15 and Carbopol 934P, using the direct compression method. The sustained release was enhanced by increasing the quantity of polymer HPMC E15, resulting in prolonged release over time. Notably, formulation GT3 (500 mg gliclazide with 150 mg HPMC E15 and 50 mg Carbopol 934P)

demonstrated excellent in vitro sustained release over a long period. However all these formulations showed similar sustained release of the drug (*in vitro*) over more than 12 hours.

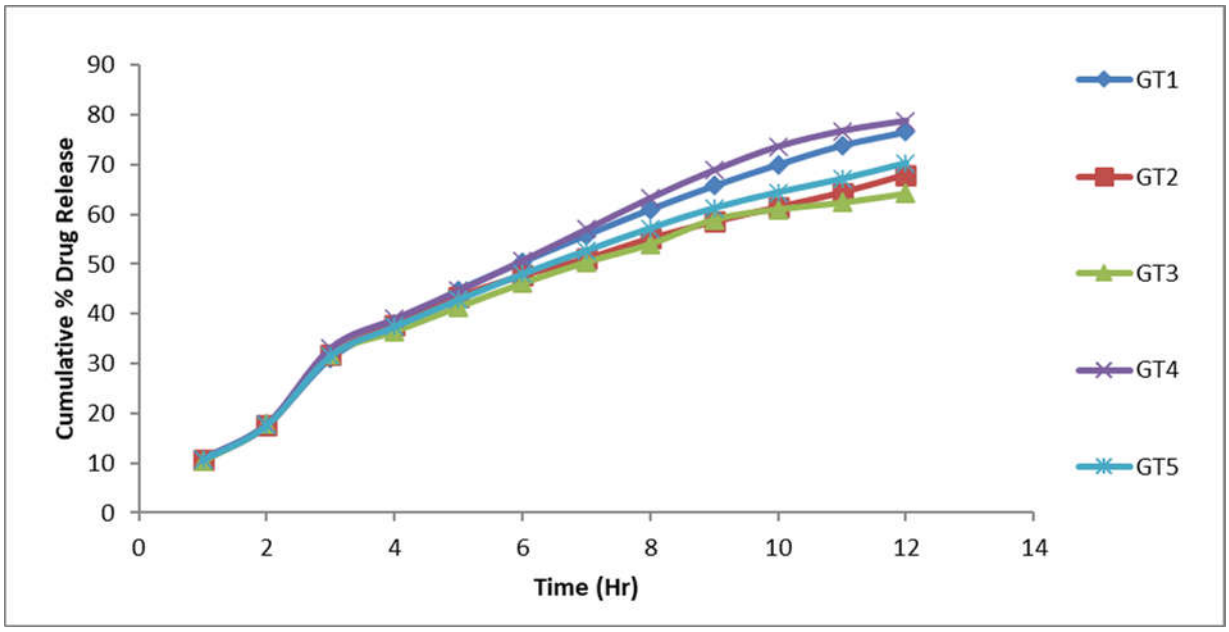

Fig. 1: Release graph of gliclazide (*in vitro*) in gastric content

The mathematically curve-fitted *in vitro* release kinetics models are represented in Table VII. All formulations of gliclazide floating tablets best fit the Korsmeyer-Peppas mathematical model (R2 = 0.968 - 0.985), and the release exponent (n) values (ranging from 0.73 to 0.82) indicate a non-Fickian mechanism.

Table VII: Release kinetics analysis data (*in vitro*) of floating gliclazide tablets

Formulation Code	R^2 Value					n value
	Zero order	First order	Higuchi	Korsmeyer-peppes	Hickson-crowell	
GT1	0.967	0.824	0.865	0.985	0.885	0.79
GT2	0.938	0.780	0.909	0.968	0.842	0.73
GT3	0.931	0.777	0.913	0.968	0.838	0.73
GT4	0.978	0.836	0.842	0.985	0.899	0.82
GT5	0.952	0.800	0.895	0.976	0.862	0.76

FTIR characterization

The FTIR spectra of HPMC E15, Carbopol 934P, Gliclazide, and the formulation GT3 (a mixture of the drug with the polymer) are presented in Fig. 2. The spectra clearly indicate the stability of the formulation, as evidenced by the characteristic peaks resulting from the presence of differential functional groups of the polymer, drug, and formulation GT3.

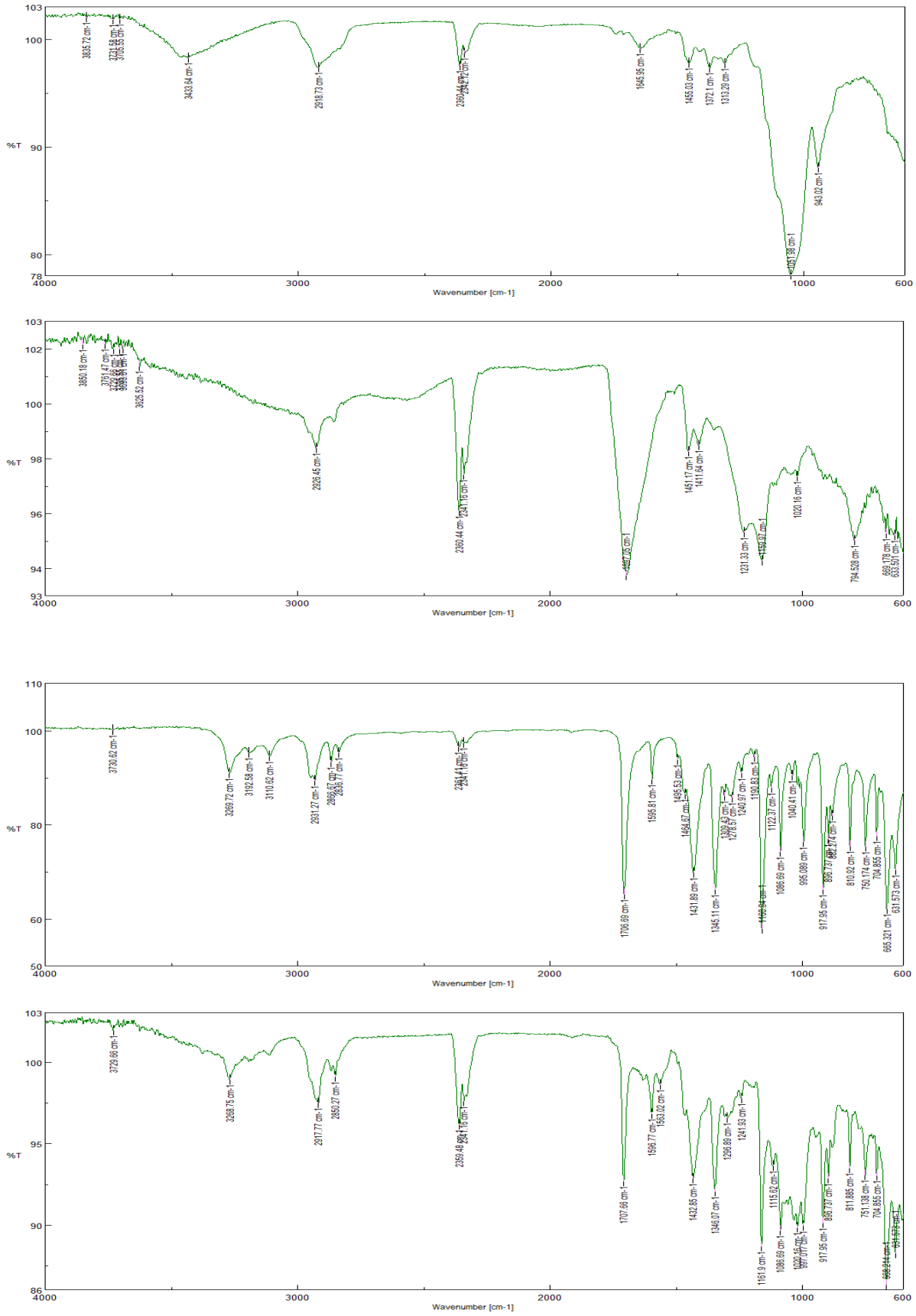

Fig. 2: FTIR spectra of HPMC E15, Carbopol 934P, Gliclazide and Formulation GT3 gliclazide floating tablet

DSC characterization

The DSC thermograms of HPMC E15, Carbopol 934P, Gliclazide, and formulation GT3 (a mixture of the drug and polymer) are shown in Fig. 3. The different endothermic peaks of the polymer, drug, and drug-polymer mixture (formulation GT3) exhibit no significant changes, indicating the stability of the formulation.

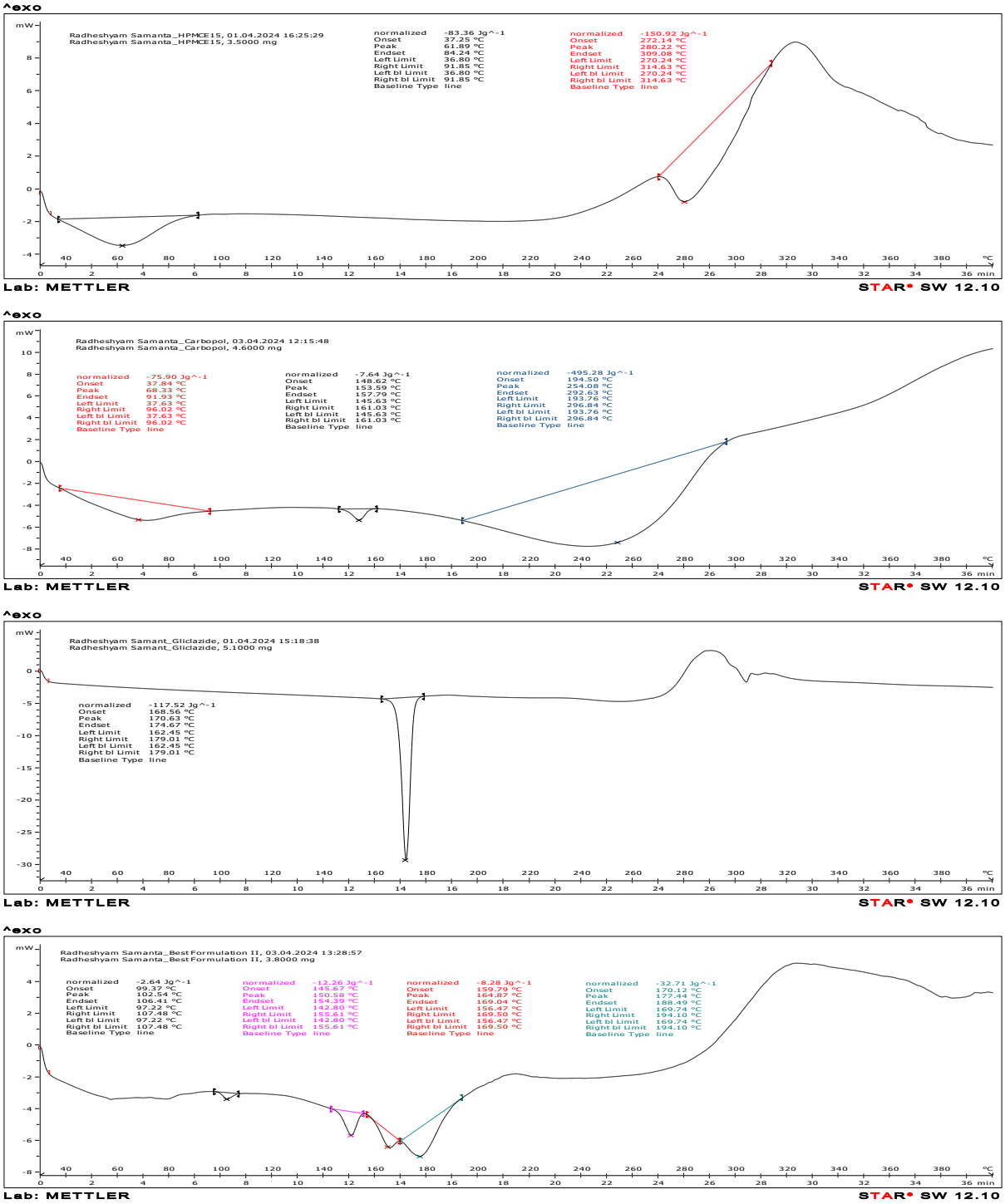

Fig. 3: DSC graph of HPMC E15, Carbopol 934P, Gliclazide and Formulation GT3 gliclazide floating tablet

Floatation (*in vitro*)

The flotation behavior (*in vitro*) of gliclazide tablets (GT3) in gastric content (pH 1.2) is depicted in Fig. 4. The formulation GT3, prepared with gliclazide, HPMC E15, and Carbopol 934P, floated for not less than 12 hours with a very small floating lag time (approximately 30 seconds). This is attributed to the presence of hydrophilic polymers, which swell quickly upon contact with the dissolution medium, hydrate, and improve viscosity. Previous studies have reported the formation of a hydrocolloidal gel that enhances the floating of tablets for prolonged periods in gastric medium.

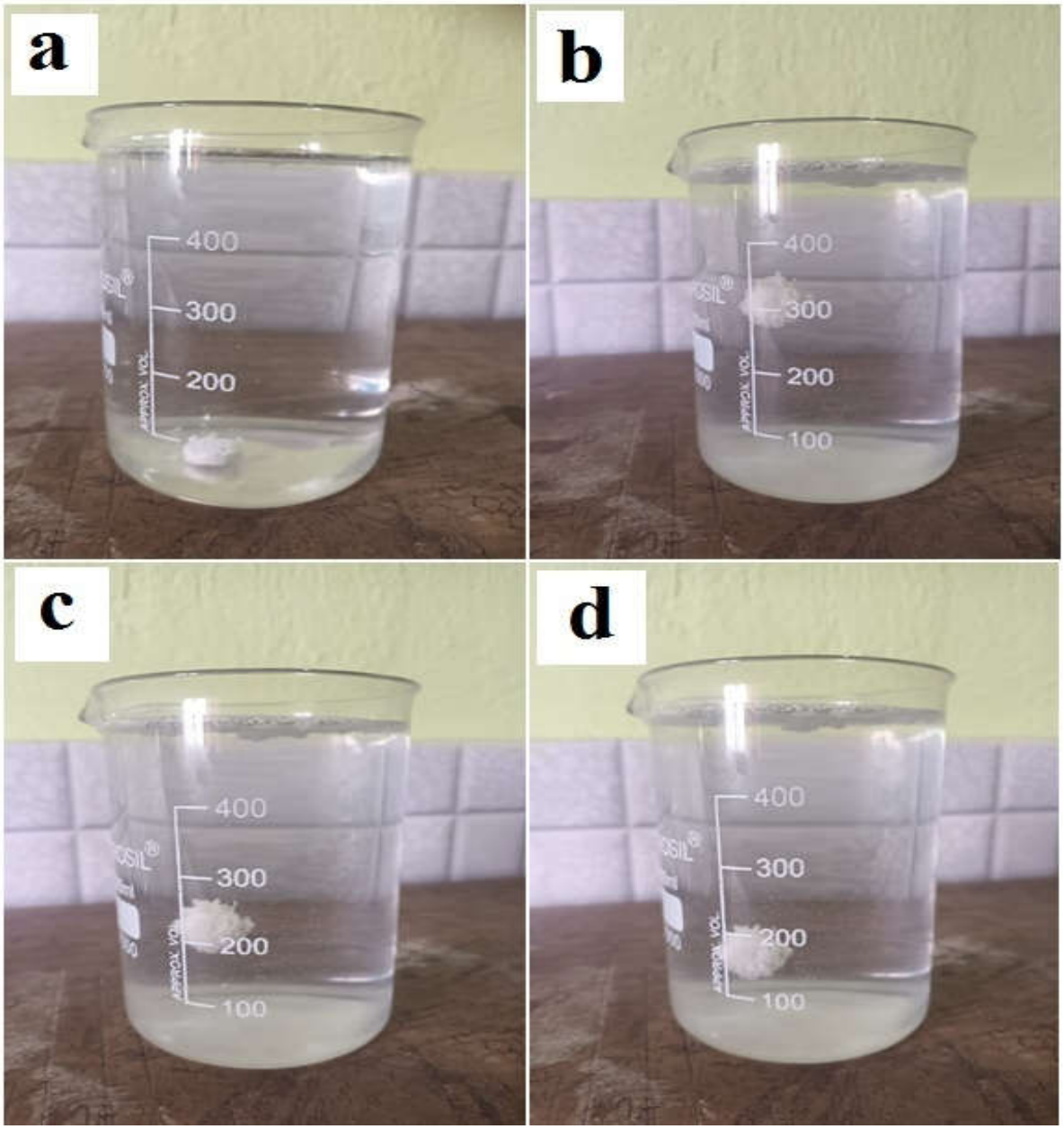

Fig. 4: Floating behavior (*in vitro*) of gliclazide tablet (GT3) in gastric fluid (pH 1.2): After 1 hours (a), 3 hours (b), 6 hours (c), and 12 hours (d)

Gastroretention (*in vivo*) by using x ray photography

The X-ray radio photography of floating tablets in a rabbit at different time intervals is shown in Fig. 5. These experiments were conducted by replacing the drug gliclazide with the radio-opaque agent barium sulfate, adding HPMC E15 and Carbopol 934P, and incorporating other necessary excipients for tablet formulation. The tablets were then administered to a New Zealand white male rabbit. After administration, X-ray photographs were taken at specific time intervals (3 hours, 6 hours, and 12 hours) and compared to those taken before tablet administration. The results clearly show that the tablet floated in the gastric region (stomach/upper part of intestine) for prolonged periods. This type of *in vivo* gastroretentive floating tablet plays a significant role in improving the floatation of the dosage form for extended periods and enhancing sustained release.

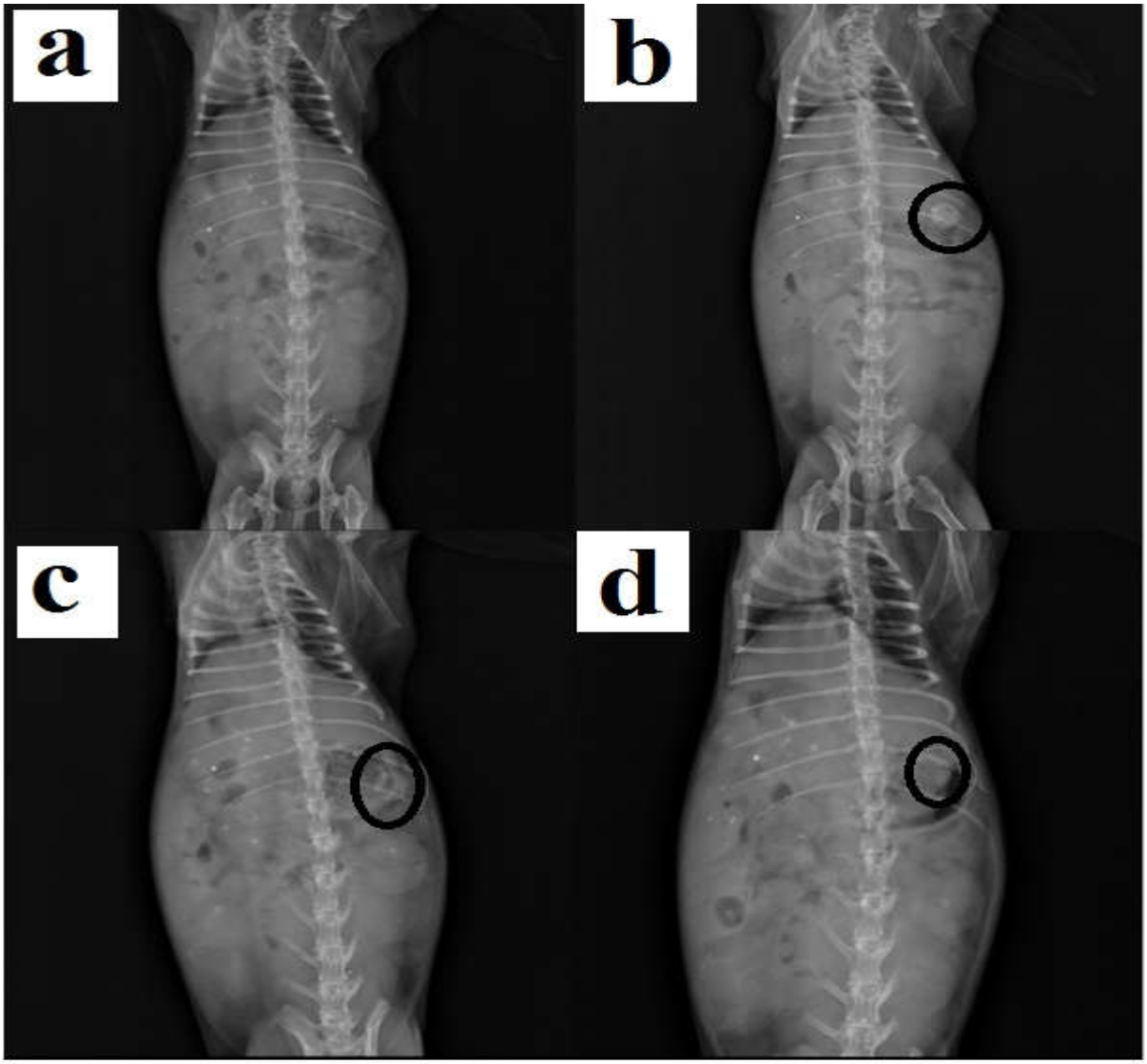

Fig. 5: X ray photography (*in vivo*) of floating tablet in stomach of rabbits: before administration (a) after 3 h (b), after 6 h (c), after 12 h (d) of administration

CONCLUSION

This research work demonstrates the successful formulation of gastroretentive effervescent gas-generating floating tablets of gliclazide. The addition of suitable polymeric matrices and releasing polymers, namely HPMC E15 and Carbopol 934P, along with other excipients, enabled the sustained release of the drug over prolonged periods. The *in vitro* release of the drug from all formulations, particularly GT3, exceeded 12 hours in gastric content (pH 1.2). Moreover, the *in vitro* floatation of all gliclazide tablets, especially GT3, lasted over 12 hours with a minimal floating lag time (approximately 30 seconds). The *in vivo* gastroretention study using X-ray radio photography in rabbits confirmed that these gastroretentive effervescent floating tablets remained in the gastric region or stomach of the animal for an extended period. These tablets, prepared with Hydroxy Propyl Methyl Cellulose E15 (METHOCEL) and Carbopol 934P (Carbopol), demonstrate potential for efficient sustained release of drugs over prolonged periods due to negligible incompatibility, excellent floatation (*in vitro*), and gastroretention (*in vivo*) properties.

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REFERENCE

1. Lou, J. Duan H. Qin, Q. Teng, Z. Gan, F and Zhou, X. Advances in oral drug delivery systems: challenges and opportunities, **Pharmaceutics** 2023, 15(2), 484.

2. Nayak, A.K. Controlled release drug delivery systems, **Sci. J. UBU**., 2011, *2*, 1-8.

3. Shivakalyani, A. and Seeram, R. Review Controlled Drug Delivery Systems: Current Status and Future Directions, **Molecules,** 2021, 26, 5905.

4. Mohapatra, S. Bindhani, Kar, S.R.K. Pani, N.R. and Nayak, A.K. Preparation and evaluation of solid self-microemulsifying drug delivery system of eprosartan mesylate using vegetable oils., **J. Drug Deliv. Sci. Tech**, 2021, 66, 102771.

5. Nayak, A.K. Malakar, J. and Sen, K.K. Gastroretentive drug delivery technologies: Current approaches and future potential. **J Pharm Educ Res**., 2010, 1(2), 1-12.

6. Dhiman, S. Philip, N. T. Singh, G. Garg, R.N. Diwan, V. and Singh, P., An insight on novel approaches & perspectives for gastro-retentive drug delivery systems. **Curr. Drug Delivery,** 2023, 20, 708–729.

7. Mathur P, Saroha K, Syan N, Verma S. and Kumar V. Floating drug delivery systems: An innovative acceptable approach in gastroretentive drug delivery. **Arch Appl Sci Res**., 2010, 2, 257-270.

8. Malakar, J. Dutta, P. Purokayastha, S.D. Dey, S. And Nayak, A.K. Floating capsules containing alginate-based beads of salbutamol sulfate: *in vitro-in vivo* evaluations, **Int. J. Biol. Macromol**. 2014, 64, 181–189.

9. Venkateswarlu, K. Preethi, J. K. and Kiran, B.S.S. Formulation Development and *In-vitro* Evaluation of Floating Tablets of Ciprofloxacin HCl, **A. J. Pharmaceutics,** 2016, 10 (4), 271.

10. Raju, D.B. Sreenivas, R. and Varma, M.M. Formulation and evaluation of floating drug delivery system of Metformin Hydrochloride, **J. Chem. Res**.*,* 2010, 2(2), 274-278.

11. Desai, N. and Purohit, R. Development of novel high density gastroretentive multiparticulate pulsatile tablet of clopidogrel bisulfate using quality by design approach, **AAPS PharmSciTech,** 2017, 18, 3208–3218.

12. Preda, M. and Leucuta, S.E. Oxprenolol-loaded bioadhesive microspheres: Preparation and *in vitro*/*in vivo* characterization. **J Microencapsul.,** 2003, 20, 777-789.

13. Nayak, A.K. and Pal, D. *Trigonella foenum-graecum* L. seed mucilage-gellan mucoadhesive beads for controlled release of metformin HCl, **Carbohydr. Polym.,** 2014, 107, 31–40.

14. Vijayabhaskar K, Venkateswarlu K. and Naik, S.B. Preparation and *in-vitro* evaluation of ranitidine mucoadhesive microspheres for prolonged gastric retention. **Br J Pharm Res.** 2016, 10, 1-12.

15. Juthi, A.Z. Wang, F.Li.B. Alam, M.M. Talukder, M.E. and Qiu, B, pH-responsive super-porous hybrid hydrogels for gastroretentive controlled-release drug delivery, **Pharmaceutics**, 2023, 15, 816.

16. Siepmann, J. Kranz, H. Bodmeier, R. and Peppas, N.A. HPMCmatrices for controlled drug delivery: A new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics. **Pharm. Res**., 1999, *16*, 1748-1756.

17. Zhou, Y. Gu, N. and Yang, F, *In situ* microbubble-assisted, ultrasound-controlled release of superparamagnetic iron oxide nanoparticles from gastro-retentive tablets, **Int. J. Pharm**., 2020, 586, 119615.

18. Nayak, A.K. Das, B. and Maji, R. Gastroretentive hydrodynamically balanced system of ofloxacin: formulation and *in vitro* evaluation, **Saudi Pharm. J**. 2013, 21, 113–117.

19. Gambhire, M.N. Ambade, K.W. Kurmi, S.D. Kadam, V.J. and Jadhav, K.R. Development and in vitro evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride., **AAPS Pharm Sci Tech**., 2007, 8 (3), 73.

20. Klausner, E.A. Lavy, E. Friedman, M. And Hoffman, A. Expandable gastroretentive dosage forms. **J Control Rel.,** 2003, 90, 143-162.

21. Veerareddy, P.R. Bajjuri,S. Sanka, K. Jukanti, R. Bandari, S. Ajmeru, R.K. and Potu, A.R, Formulation and Evaluation of Gastroretentive Dosage Form of Ofloxacin, **S. J. Pharm. Sci.** 2011, 4(1), 09-18.

22. Streubel, A. Siepmann, J. and Bodmeier, R. Drug delivery to the upper small intestine window using gastroretentive technologies. **Curr Opin Pharmacol.,** 2006, 6,501-6,508.

23. Huang, C. Kim, Y. and Caramori, M.L. Cellular basis of diabetic nephropathy: II, The transforming growth factor -beta system and diabetic nephropathy les ions in type 1 diabetes. **Diabetes**, 2002, 51, 3577-3581.

24. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Report of the expert committee on the diagnosis and classification of diabetes mellitus, **Diabetes Car,** 2003, 26, S5-S20.

25. Jagdale, S.C. Agavekar, A.J. Pandya, S.V. Kuchekar, B.S. and Chabukswar, A.R. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. **AAPSPharmSciTech.** 2009, 10(3), 10711-10719.

26. Carbopol®, U.S. FDA approves generic drug product containing Lubrizol's, **Lubrizol Corporation, Press release**, 2012.

27. METHOCEL™, World Class Leading Brand of HPMC, **Dow Chemical Company**, 2018.

28. Gao, P. Skoug, J.W. Nixon, P.R. Ju, T.R. Stemm, N.L. and Sung, K.C. Swelling of hydroxypropyl methylcellulose matrix tablets 2, Mechanistic study of the influence of formulation variables on matrix performance and drug release. **J Pharm Sci,** 1996, 85, 732-740.

29. Bhargavi, R. Duggimpudi, H. and Suria, P.K. Formulation Development and InVitro Evaluation of Gabapentin Matrix Tablets. **A. J. of Pharmtech Research**, 2012, 2(6), 234-242.

30. Biswas, M. and Gupta, R.N. Formulation and in vitro evaluation of gastro retentive floating drug delivery system of ritonavir.**Turk J Pharm Sci**., 2013, 10(1), 69-86.