How to Cite:
Anand, A., Pahwa, S., & Dhamija, K. (2022). Development and in-vitro evaluation of poloxamer alginate floating bead containing glimepiride using foam technology. *International Journal of Health Sciences*, *6*(S5), 10827–10839. https://doi.org/10.53730/ijhs.v6nS5.10910

Development and in-vitro evaluation of poloxamer alginate floating bead containing glimepiride using foam technology

Achal Anand
Research Scholar (M Pharm), Pharmacy Department, Lloyd Institute of Management and Technology (Pharma.), Greater Noida, Uttar Pradesh
Corresponding author email: anandachal97@gmail.com

Dr. Shilpa Pahwa
HoD, Pharmacy Department, Lloyd Institute of Management and Technology (Pharma.), Greater Noida, Uttar Pradesh

Koushal Dhamija
Assistant Professor, Pharmacy Department, Lloyd Institute of Management and Technology (Pharma.), Greater Noida, Uttar Pradesh

***Abstract*---**An attempt was made to prepare the floating beads of antidiabetic drug sulphonyl-urea derivatives like glimepiride. It is one such type of type 2 diabetes mellitus. The study contains two poloxamers, sodium alginate and poloxamer 188, which shows simple and reproducible nature. The poloxamer helps to provide buoyancy to glimepiride beads using different concertation of polymer. A total of nine formulations of glimepiride were analysed using techniques like organoleptic properties, swelling index, buoyancy, drug entrapment and SEM. The in vitro drug release studies show satisfactory floating beads. The in vitro studies performed 0.1 normal HCl solution containing pH 1.2, showing characteristic results for up to 10 hours. The SEM model also shows the breaking of bubbles that will result in the busting phenomena of drug release. The cross-section of the image results shows the inner porous nature of the bead and the thin wall of bubbles stacked to each other. The study will help formulate the floating beads' new dosage form for further development.

***Keywords*---**Floating Beads, Diabetes, FDDS, Glimepiride, Poloxamer.

Introduction

Diabetes mellitus (T2DM) is a degenerative illness with long-term consequences for the micro and macrovascular systems. As a result, T2DM is a significant

cause of mortality and disability globally. (Shelesh & Swarnlata, 2010). T2DM can be treated with glimepiride, a newer sulfonylurea. Glimepiride has the conventional SU backbone and demonstrates the extensive array of effects typical of ordinary SUs. Numerous preclinical and clinical studies have shown that glimepiride enhances insulin secretion and sensitivity and exerts extra-pancreatic effects. (Kouichi et al., 2005). Nonetheless, glimepiride is a hydrophobic drug. The low dissolution velocity and restricted solubility of less water-soluble medicines, which result in inadequate and uneven bioavailability, provide the largest barrier to the oral absorption of such interventions.

Gastric resident time (GRT) is a significant factor in determining medication absorption in dose form. Due to a variable and short gastric emptying interval, insufficient drug release from the drug delivery system (DDS) above the absorption zone (stomach and upper portion of small intestine) may result in reduced efficiency of the provided dosage.[1.] Gastro retentive drug delivery systems favour prolonged drug release in the stomach.[2] Unlike traditionally controlled release formulations, they bypass the gastric emptying process, which interferes with drug delivery to the upper GIT. Floating drug delivery systems (FDDS) may increase medicine bioavailability by extending GRT. Hydrodynamically balanced system or HBS is another floating medication delivery system.[3]. Floating medication delivery methods are either non-effervescent or effervescent. The gel must form in a cellulose-like environment that contains polyacrylate, polystyrene, and polycarbonate. After being taken by mouth, the gel-forming hydrocolloid becomes bulky when it comes in contact with stomach fluid. The FDDS system helps in enhancing the bioavailability and is also used as a sustained drug delivery system.[4.]

This study aimed to develop a particulate gastro-retentive drug delivery technique to boost the bioavailability of glimepiride.[5] As a result, it was considered that the body would absorb more of the drug if it had a long time to do so. As part of this study, alginate-based gastro-retentive beads containing glimepiride were designed and tested.

1. Material and Methods

Materials: Glimepiride was a kind gift from Navi Mumbai, Maharashtra. Sodium Alginate, Poloxamer 188 and Calcium Chloride were procured from Loba Chemie, India. The remaining materials were all of the analytical standards.

2. Methodology

2.1. Preformulation Investigation

Preformulation studies are needed to design optimal dosage forms for medication delivery. Preformulation testing helps formulators design stable, bioavailable dosage forms.

Characterization of Glimepiride

The drug sample was identified using several analytical techniques, including IR spectroscopy, UV spectroscopy, melting point, partition coefficient, and solubility.

Drug absorption maxima were determined using a UV-Vis spectrophotometer. The partition coefficient measures a drug's lipophilicity and capacity to cross cell membranes. Using a separating funnel and 5 ml of octanol diluted with 5 ml of water, the partition coefficient of glimepiride was measured at 37.5 °C. After shaking, the system was unaffected for thirty minutes. After adding 100 mg of the drug, this mixture was shaken twice. The amount of glimepiride solubilised was determined by measuring the absorbance at 317 nm against a reagent blank using a double beam UV/Vis spectrophotometer after two layers had been separated and filtered through a Whatman grade filter after 24 hours.

Solvents like 0.1 N HCl, Phosphate buffer (pH= 6.8 and 7.4), ethanol, methanol, and acetone were used in a water bath shaker at 37°C for a 24-hour solubility test. Took 2 ml of each solvent and put it in a culture tube. Add surfeit of drug to 2 ml of 0.1N HCl, phosphate buffer pH6.8, pH7.4, and 2 ml of water. Using a vortex shaker, make a methanol, ethanol, DCM, and acetone solution. At 37°C, shake the solution in a water bath for 48 hours. After 48 hours, spin the sample at 10,000 pm, then take the liquid on top and, if needed, dilute it with buffer. Diluted and analysed for drug substance using a UV spectrophotometer at 228 nm. Fourier Transform Infrared Spectrophotometric was used for structural analysis of the glimepiride with KBr (IR grade) in the ratio of 100: 1 and then scanned over a wave number range of 4000- 500 cm-1. Measurements were carried out using IR Spectrometer, IR-435 U-04 Shimadzu (Japan).

2.2. Drug and excipient compatibility study

The Fourier transform infrared spectroscopy method was utilised, and potassium bromide (KBr) pellets were used to analyse pure pharmaceuticals and polymers. The structure of the pure drug and the drug's mixture was broken down into parts by analysing the FTIR spectrum and interpreting the various peaks. FT-IR spectroscopy makes it possible to look into and predict the physical and chemical interactions between different parts. [8]

2.3 Creating a foam solution using various foaming agents

Foams were made using a magnetic stirrer with Sodium Alginate and Poloxamer 188. Foaming agents have added to water, and at 2600 rpm, it was agitated for 20 minutes, and foams were, without delay, transferred to a marked cylinder for further examination.

2.4 Foaming study of polymers

The capacity of a method to generate foam is referred to as foamability. Magnetic stirring was used to make the foams. Sodium Alginate and Poloxamer 188 were added to water, and at 2600 rpm, it was agitated for 20 minutes. Then foams were, without delay, transferred to a marked cylinder for further examination. The underlying froth volume after the arrangement is utilised to assess foamability. Foamability (FD) was portrayed as the froth's thickness (proportion of the volume of froth/volume of fluid utilized).

FD = (Volume (foam))/(Volume (liquid))

Where V (Foam) is the volume of foam later than stirring, and V (liquid) is the volume of liquid before stirring. [11]

2.5 Foam Stability
Froth strength is described as the period after which 10% of the first measure of fluid has depleted from the froth. [11]

3.1 Preparation of floatable alginate and poloxamer beads of glimepiride

Following the dissolution of sodium alginate (Alg) in distilled water, Poloxamer188 was added to the solution of sodium alginate, and the mixture was vigorously stirred for twenty minutes. The foam solution was constantly supplemented with glimepiride while being vigorously stirred. With the help of a peristaltic pump and a pipe diameter of 2 millimetres, the foam solution was forced into the solution containing calcium chloride. At the same time, the mixture was stirred gently at a rate of 3 millilitres per minute. The distance of approximately 10 centimetres that separated the tip of the needle and the surface of the $CaCl_2$ medium was present. The beads were allowed to sit in the solution at room temperature for ten minutes while gently stirring to cure them. After collecting the beads, they were washed twice with distilled water and then dried in an oven at forty degrees celsius.

3.2. In vitro assessment of alginate/poloxamer floating beads of glimepiride

Visual Appearance Alginate/Poloxamer Floating Beads of Glimepiride
The prepared Alginate/Poloxamer Floating Beads of Glimepiride were visually analysed. The beads were noted down for their successful preparation and their shape.

Percentage yield of Alginate/Poloxamer Floating Beads of Glimepiride
The formulations' percentage yield was estimated as a % of the total amount of polymers and medication utilised to make the beads. The following formula was used to obtain the percentage yield. [9]

$$\text{Production yield (\%)} = \frac{\text{Total amount of prepared beads}}{\text{Amount of drug + total amount of polymers}} \text{ x100}$$

Percentage drug entrapment of Alginate/Poloxamer Floating Beads of Glimepiride
By dissolving a known number of beads in methanol and vigorously shaking them on a Vortex mixer at room temperature, the amount of Glimepiride entrapped in the beads could be calculated. Spectrophotometric analysis was used to assess the amount of Glimepiride loaded in the beads. The loading efficiency percentage was obtained using the equation below. [8]

$$EE\,(\%) = \frac{(W_{\text{total drug}} - W_{\text{free drug}})}{W_{\text{total drug}}} \times 100\%$$

In vitro assessment of the drifting capacity of Beads of Glimepiride
A hundred globules of each pile were immersed in 100 mL of 0.1 N HCl and stirred at 100 rpm while the temperature was kept at 37°C + 2°C. The number of plunging beads was measured peripherally. The degree of coasting dots was calculated using the formula:

Drifting/Floating Ability (%) = $\frac{NF}{NT} \times 100$
As NF: no. of drifting beads; NT: total no of the globules/beads.[11]

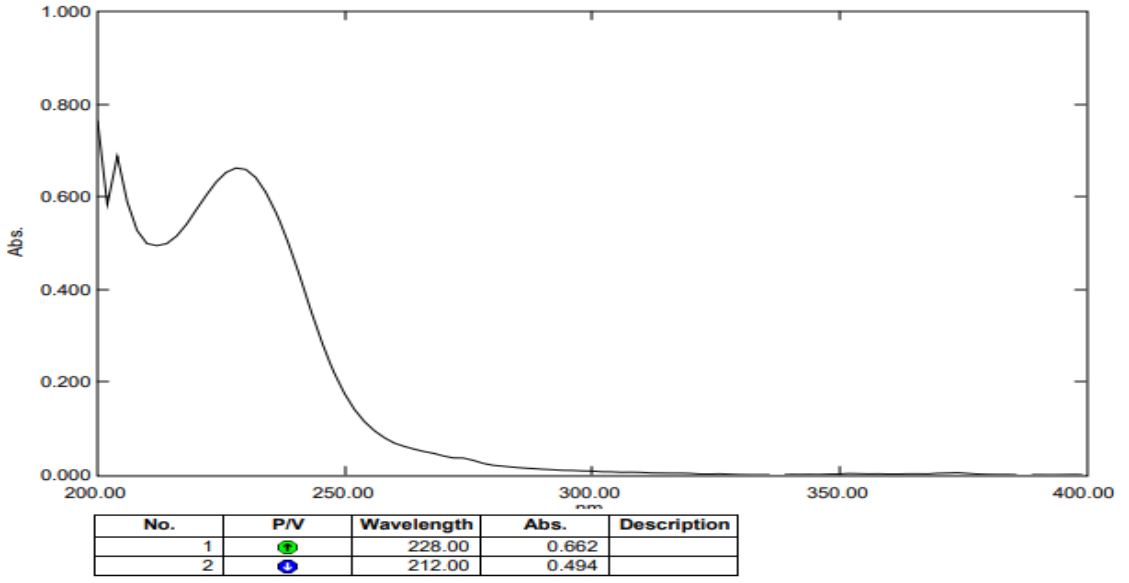
Studies of In-Vitro Drug Release
The in vitro arrival of Glimepiride from the beads was investigated using a USP paddle disintegration apparatus (USP type-II). The disintegration medium was 900 ml of recreated stomach liquid (0.1N HCl, pH: 1.2, no catalysts) at 37 0.5 °C and 100 rpm. At predetermined intervals (15 minutes, 30 minutes, 45 minutes, 60 minutes, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 12 hours, 18 hours, and 24 hours), an aliquot of 5 ml of the solution was removed and replaced with 5 ml of new dissolving media. Tests were spectrophotometrically estimated at 228 nm after filtration using a 0.45 m film channel (Millipore). The entirety of the analyses was done three-fold. [11].

4. Result and Discussion

4.1 Preformulation Studies
This information is critical for drug development. Physical and chemical properties are investigated before compounding. These researches concentrate on the drug's physicochemical properties, which may influence its performance and dosage form. These characteristics could help to justify design or molecular change. Pre- formulation studies may confirm that the compound's growth is rampant. [9] These studies contribute to developing a safe, effective, and stable dosage form. The drug sample was identified using melting point, UV, IR, solubility, and other analytical methods.

Melting Point
The melting point of Glimepiride was found to be 221.67±1.155°C; hence drug sample does not contain any foreign substances.

Determination of Absorption Maxima By UV Spectroscopy
When exposed to visible/ultraviolet light, absorbing light of specific wavelengths depending on the type of electronic transition, ultraviolet-visible spectroscopy is primarily used for quantitative analysis and as a useful auxiliary tool for structural elucidation of different drugs to find exact information on the molecular chromophore part in the solution. Absorbance vs wavelength represents the UV spectrum. [2] Glimepiride's UV spectrum is in **Figure 4.1**.
Figure 4.1: Glimepiride’s UV Spectrum.



No.	P/V	Wavelength	Abs.	Description
1		228.00	0.662	
2		212.00	0.494	

Figure 4.1: Glimepiride's UV Spectrum.

Glimepiride's maximum wavelength is 228 nm, which matches reference standards.

Calibration Curve Of Glimepiride In Methanol

A standard stock solution of Glimepiride (100 g/ml) was prepared in methanol and spectrophotometrically measured at 228 nm. Figure 4.2 depicts the results. The regression equation can be seen in the graph of Glimepiride's standard curve y=0.0449x+0.0174, and the R2 value is 0.9999, indicating good linearity.

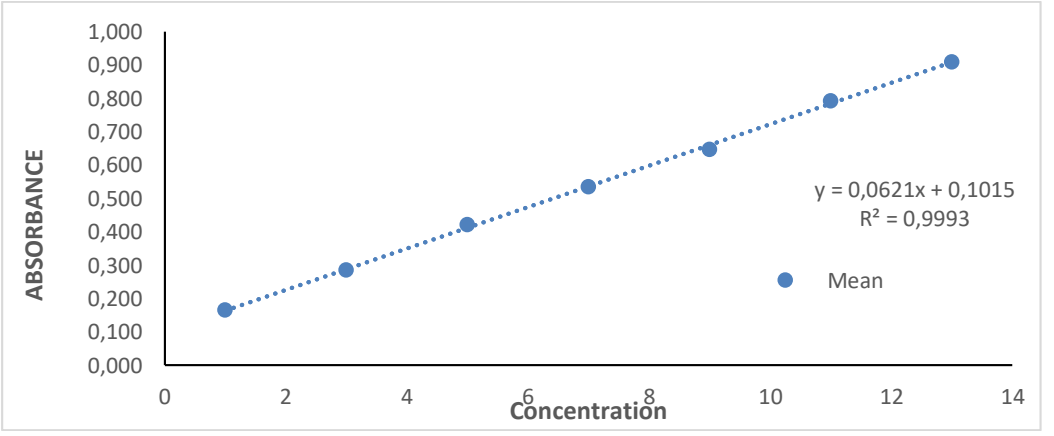


Figure 4.2: Calibration Curve Of Glimepiride In Methanol

Partition Coefficient determination

The shaking flask technique was used to calculate the partition coefficient. The partition coefficient of glimepiride in n-octanol is 3.0700.024, which is consistent with the literature, and glimepiride appears to be a lipophilic compound.

Solubility Studies

Solubility is the spontaneous interaction of two or more compounds resulting in homogenous molecular distribution. For solubility tests, excess medication was added to each solvent (5.0 ml). Test tubes were shaken in a water bath at room temperature for 24 hours. After 24 hours, samples were centrifuged, diluted, and tested for drug substance at 228 nm; the glimepiride solubility profile is shown in Table 4.1, and acetone, ethanol, methanol, and chloroform readily dissolve glimepiride.

Table 4.1: Solubility Profile Of Glimepiride In Different Solvents

S.No.	Solvent Name	Solubility mg/ml
1	Water	0.638±0.003
4	Phosphate Buffer pH 6.8	1.063±0.004
3	0.1N HCl	2.128±0.007
4	Acetone	10.706±0.017
5	Ethanol	12.797±0.084
6	Methanol	18.153±0.139
7	Chloroform	20.302±0.169

FTIR Analysis of Pure Drug And Excipient

Glimepiride's FTIR spectra are shown in Figure 4.3, and glimepiride's major IR absorption peaks at 3369.16 cm^{-1} (N-H stretching), 2928.86 cm^{-1} (C-H stretching), 1540.84 cm^{-1} (N=O stretching) and 1151.70 cm^{-1} (C-N stretching) were found to be identical to those of known compounds. [10] Such characteristic peaks confirmed the purity and efficacy of the Glimepiride.

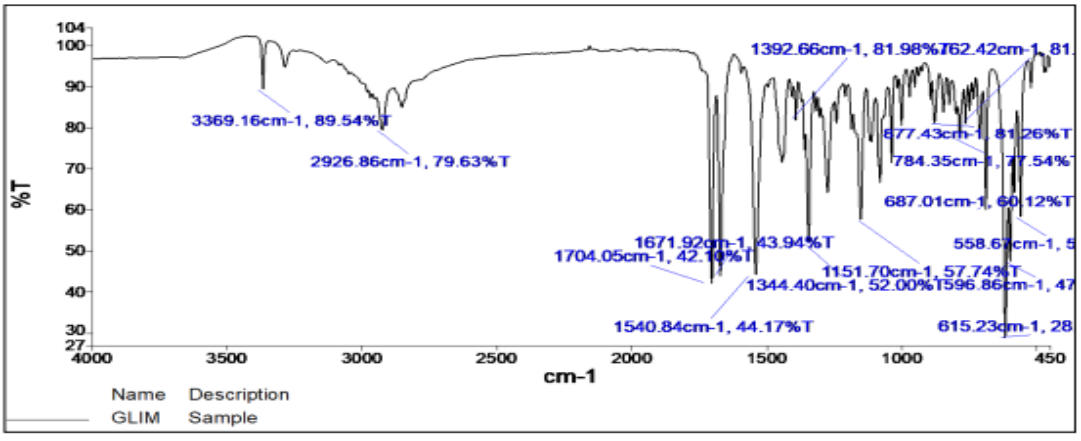


Figure 4.3: FTIR spectrum of Glimepiride

Figure 4.4 displays the FTIR spectra of sodium alginate. Principal IR absorption peaks of Sodium Alginate were observed at 2981.19 cm^{-1} (C–H stretching), 1393.22 cm^{-1} (C–OH deformation vibration), 1251.38 cm^{-1} (O–C–H deformation and C-C-H), 1071.62 cm^{-1} (C-O stretching vibrations) and 813.69 cm^{-1} (α-L-Gulopyranuronic asymmetric ring's vibration). [11] The presence of the major peaks verified the purity and efficacy of the sodium alginate.

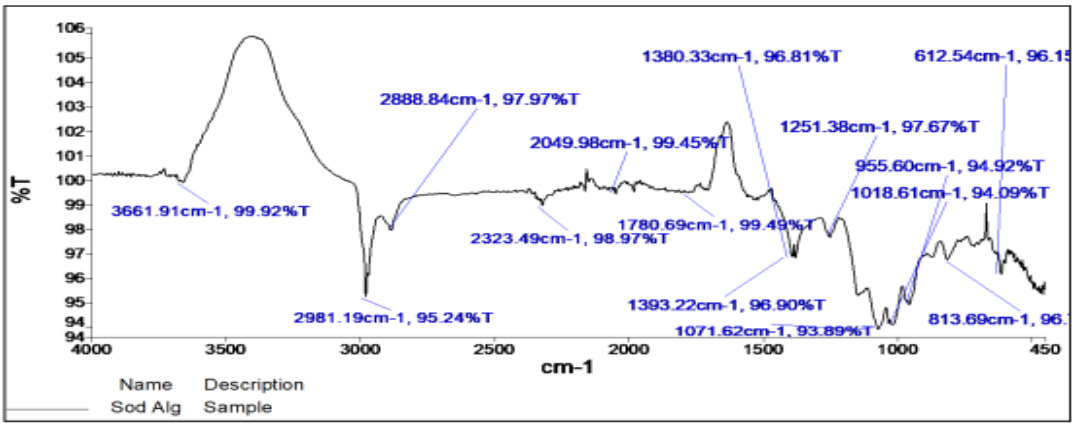


Figure 4.4: FTIR Spectrum of Sodium Alginate

Polaxer 188's FTIR spectrum is depicted in Figure 4.5. Poloxamer 188 exhibits principal IR absorption peaks at 2882.05 cm^{-1}C-H bond valence vibrations in the CH and CH2 groups), 1341.85 cm^{-1} (C-H bond vibrations of deformation in primary and secondary hydroxyl groups), 1148.28 cm^{-1} (In the ether, C-H bond's valence vibrations), 1060.03 cm^{-1} (valence vibrations of C-H bond in the hydroxyl groups) and 841.45 cm^{-1} (C-H bond deformation vibrations) The presence of these principal peaks confirmed Poloxamer 188's purity and authenticity.

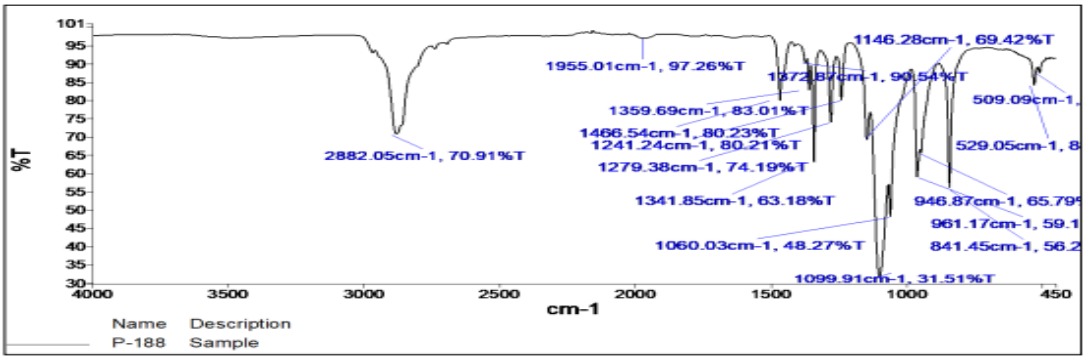


Figure 4.5: FTIR Spectrum Of Poloxamer 188

Drug excipient compatibility study by FTIR spectroscopy

The analytical method for drug estimation was used in conjunction with FTIR analysis of physical mixtures (Figure 4.6) to rule out the possibility of drug-excipient interactions. [8]There was no interaction in this mixture because all of the

peaks in the spectra showed the same amounts of drug and excipient.

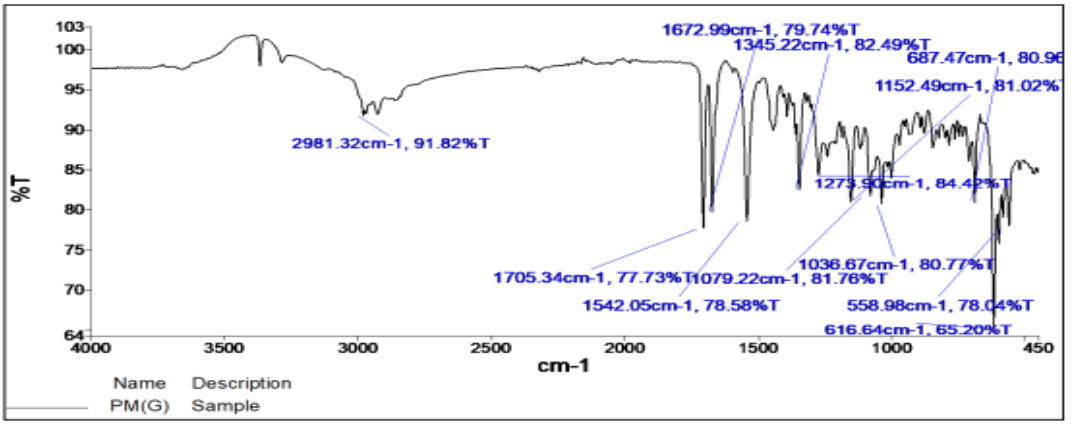


Figure 4.6: FTIR spectrum of Physical mixture

4.2 Foaming Study of polymers

The different concentration of polymer mixture was subjected to a foaming study for profligate foam generation to prepare a Glimepiride multi-particulate delivery system capable of regulated release.

Foamability Study

Table 4.2 depicts the foamability and foam stability studies of the Alginate/Poloxamer mixture. Foamability studies revealed that the concentration of poloxamer used directly influenced foam generation. It was discovered to be in the range of 2.00±0.400 to 14.27±0.611per cent. Further research into the foam stability of alginate/poloxamer mixtures revealed that foam generation is directly related to the concentration of poloxamer used. It was discovered to be between 25.00±2.00 to 85.33±1.53.

Table 4.2: Foamability and foam stability study of various Alginate/Poloxamer Combinations

S. No	Formulation Code	Foamability (%)	Foam Stability (minutes)
1	AP1	2.00±0.400	85.33±1.53
2	AP2	5.60±0.400	62.00±2.00
3	AP3	8.93±0.611	43.33±2.31
4	AP4	14.27±0.611	25.00±2.00

4.3. Preparation of Alginate/Poloxamer Floating Beads of Glimepiride

A multi-particulate Glimepiride delivery device capable of regulated release was developed in the current study. The Alginate/Poloxamer Floating Beads preparation process was easy and repeatable.

4.4. Invitro Evaluation of Alginate/Poloxamer Floating of Glimepiride

Visual Appearance

The aesthetic appearance of glimepiride alginate/poloxamer floating beads formulations (GFB1-GFB5) is determined (Figure 4.7). We got uniform beads when we used a larger amount of potassium chloride and Alginate/Poloxamer as the main salt and polymer.

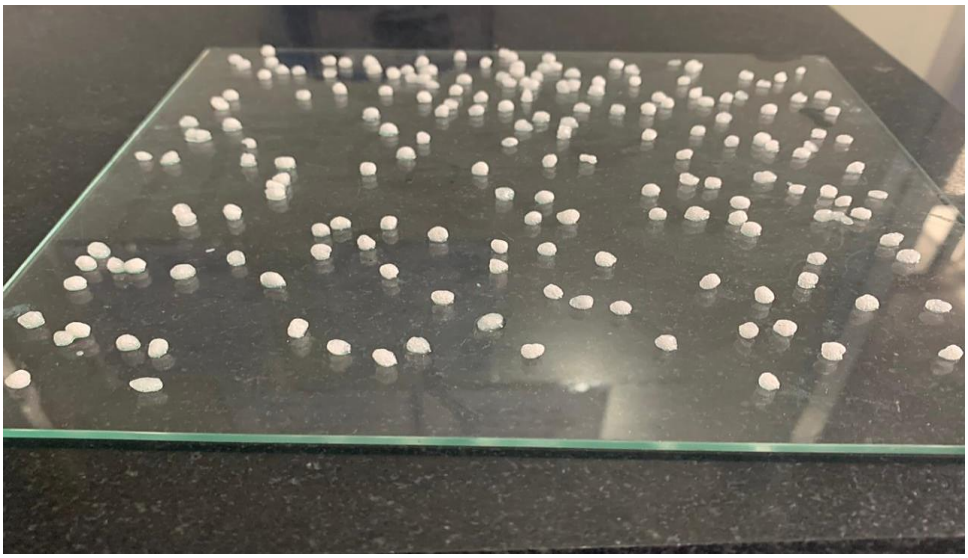


Figure 4.7: Visual Appearance of different Alginate/Poloxamer Floating Beads of Glimepiride

Percentage Yield, Drug Content, Particle Size Analysis, and Drug Entrapment Percentage of Glimepiride Alginate/Poloxamer Floating Beads

There are comprehensive explanations of each formulation provided in Table 4.3. Following the completion of the data analysis, it was found that the percentage yield for each formulation fell somewhere within the range of 69.20±0.536 to 89.85±0.350. These discoveries explain why there is a significant production of beads. The amount of the active ingredient in various formulations ranged from 80.95±0.390 to 87.30±0.237per cent, with the average being 87.300.237 per cent. According to these findings, there was a discernible impact on the amount of drug content correlated with the concentration of the polymer. It was found that the particle size of each formulation varied from 2.1±0.110 to 2.8±0.126 millimetres.

Additionally, it was discovered that the percentage of drug entrapment in each formulation fell somewhere in the range of 89.02±0.123 to 95.81±0.061. According to these findings, a discernible influence on the drug content percentage was associated with the polymer concentration. These findings explain why there was no change in the size profile of the alginate/poloxamer floating beads when the polymer concentration was altered.

Table 4.3 Percentage Yield, Drug Content, Particle Size Analysis, and Drug Entrapment Percentage of Glimepiride Alginate/Poloxamer Floating Beads

Sr. No.	Formulation Code	Yield (%)	Drug Content (%)	Particle Size (mm)	Drug Entrapment (%)
01.	GF1	69.20±0.536	89.02±0.123	2.4±0.100	89.02±0.123
02.	GF2	80.79±0.235	89.74±0.084	2.4±0.058	89.74±0.084
03.	GF3	70.34±0.255	91.77±0.081	2.5±0.050	91.77±0.081
04.	GF4	84.53±0.865	93.75±0.101	2.1±0.110	93.75±0.101

Percentage In-Vitro Drug Bead Floatation.

The percentage floating ability of all formulations is given in **Table 4.4. It** was found that all formulations' percentage floating ability was in a range of 81.3±2.082 to 88.6±1.1528. These results explain that a significant effect on per cent drug content was observed with polymer concentration.

Table 4.4 Percentage In-Vitro Drug bead Floatation

Sr. No.	Formulation Code	Drug Bead Floatation (%)
01.	GF1	87.6±0.577
02.	GF2	88.6±1.528
03.	GF3	81.3±2.082
04.	GF4	88.6±1.155

Study of drug release in vitro

Table 4.5 shows the Formulation of GF4s drug released by in-vitro revealed a considerable difference in drug release rate among formulation and pure drug suspension. The data of drug retention of 12 hours have shown maximum drug retention (82.22±0.277) with formulation GF4 compared to a plain drug (38.74±0.277). [6] Furthermore, the release profiles of Glimepiride from Alginate/Poloxamer Floating Beads showed that it yielded a controlled Glimepiride release. [5] In drug release by in-vitro research discovered that the F8 formulation released more than the pure drug. [13]

Table 4.5: In-Vitro Drug Release Study of Alginate/Poloxamer Floating Beads of Glimepiride

Time (hr)	% Drug Release of Glimepiride from Formulation GF4	% Drug Release of Pure Drug
0 mins	0.00±0.000	0.00±0.000
15 mins	12.29±0.456	4.56±0.456
30 mins	21.11±0.181	8.73±0.181
45 mins	28.29±0.553	13.92±0.553
1 hr	33.06±0.790	17.06±0.790
2 hr	39.10±0.209	21.89±0.209
3 hr	50.63±0.362	24.00±0.362
5 hr	58.79±0.314	24.37±0.314

4 hr	64.16±0.377	28.89±0.377
6 hr	70.08±0.732	33.85±0.732
8 hr	76.54±0.543	36.68±0.543
12 hr	82.22±0.277	38.74±0.277

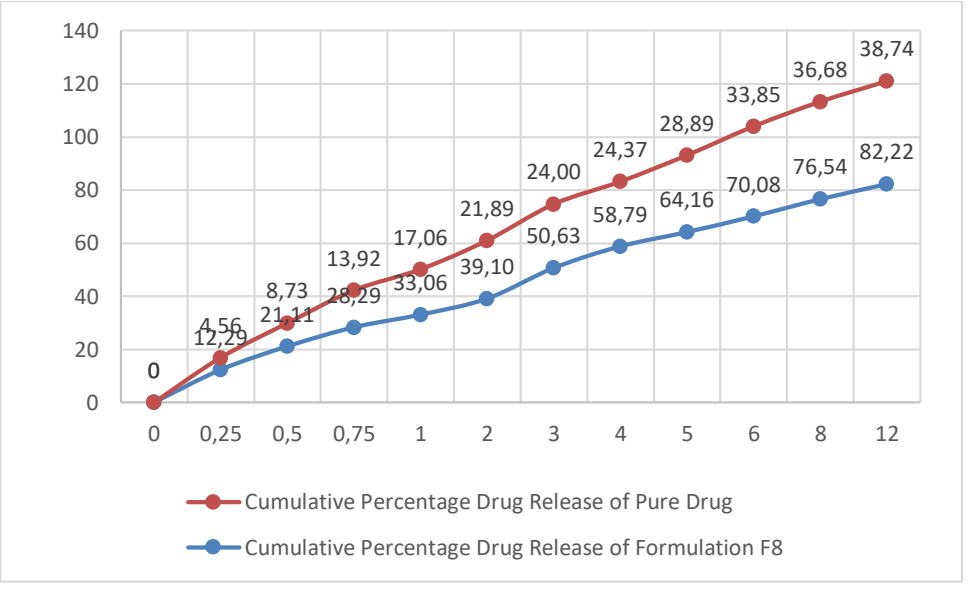


Figure 3.18: Glimepiride Alginate/Poloxamer Floating Beads Drug Release in Vitro

Summary and Conclusion

The current study aims to develop and introduce a new gastric floating formulation. Glimepiride beads were foamed with poloxamer 188, stabilising the foam with sodium alginate. By dripping, sodium alginate was dissolved in double-distilled water at concentrations of 0.5w/v, 1%w/v, and 2%w/v calcium chloride as a cross-linking agent to increase gastric retention time, provide a sustained release effect, and keep the drug from breaking down in the stomach's acidic environment. [6] The foaming agent was enhanced based on foamability and stability, with stability increasing up to 150 mg of surfactant and then decreasing. The beads' drug release lasted up to 24 hours. Glimepiride's cumulative per cent drug release was 82 per cent.

Acknowledgement
The authors are thankful to the Pharmacy Department of Lloyd college for their valuable support during the completion of the research work.

References

1. AL-Otaibi, S. N. (2021). The legal regulation of blood money in Civil Kuwaiti law. International Journal of Social Sciences and Humanities, 5(1), 16–31. https://doi.org/10.29332/ijssh.v5n1.775

2. Amos Nussinovitch (2010) Polymer Macro- and Micro-Gel Beads: Fundamentals and Applications. Springer New York DOI 10.1007/978-1-4419-6618-6.
3. Basappa VB, 2013. Formulation and evaluation of floating alginate beads of anti-ulcer drug. Int J Pharm Sci Rev Res; 21(2): 120-24.
4. Desai, S. and Bolton, S. 1993. A floating controlled-release drug delivery systems: in vitro–in vivo evaluation. Pharm. Res. 10, 1321-1325.
5. Grant, G.T., Morris, E.R., Rees, D.A., Smith, P.J.C. and Thom, D. 1973. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Lett. 2, 195-198.
6. Kaur T, 2012. Site-specific sustained drug delivery to stomach using floating systems. Int J Dru For Res 3(1): 1-12.
7. Kouichi I, Masaki W, Youhei N, et al. 2005. Efficacy of glimepiride in Japanese type 2 diabetic subjects. Diab Res Clin Prac 68:250–7.
8. Muthusamy G, Govindarajan and Ravi TK: Preparation and evaluation of lansoprazole floating micro pellets. Indian J Pharm Sci 2005; 67(1): 75-79.
9. Namaste K 2010. Preparation and evaluation of floating calcium alginate beads of Clarithromycin. Der Pharmacia Sinica; 1(1): 29-35.
10. Petra kovarikova, Jiri klimes, Jiri dohnal, Lucie Tisovska. HPLC study of Glimperide under hydrolytic stress conditions; Journal ofHyma.P / WJPBT, 2014, 1(1): 01–07 World Journal of Pharmacy and Biotechnology 7 pharmaceutical and biomedical analysis, 2004, 36: 205-209.
11. Richa Tiwari, Amit Verma, Nutan and Gaurav Saxena 2020 "A Descriptive Analysis of Phytochemical Agonists of PPAR-g Wes Jl Res, 13; 51 , 49-62
12. Saraswati, P. A. I. ., Gunawan, I. M. K., & Budiyasa, D. G. A. (2021). Overview of glomerulus filtration in type 2 of diabetes mellitus at Sanjiwani Gianyar hospital year of 2018-2019. International Journal of Health & Medical Sciences, 4(1), 50-55. https://doi.org/10.31295/ijhms.v4n1.726
13. Shelesh J, and Swarnlata S. 2010. Type 2 diabetes mellitus – its global prevalence and therapeutic strategies. Diab Metab Syndr 4:48–56.
14. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. International Journal of Health Sciences, 5(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864
15. Umar S and Onyekachi MK 2017. Development and evaluation of transdermal gel of Lornoxicam. Universal Jl of Pharm Res; 2(1): 17-20.
16. Zhang JP, Wang Q, Xie XL, Li X and Wang AQ, 2010. Preparation and swelling properties of pH-sensitive sodium alginate/layered double hydroxides hybrid beads for controlled release of diclofenac sodium. J Biomed Mater Res Part B Appl Biomater; 92: 205-14.