Research Article

Formulation and Evaluation of Gastro Retentive Floating Microspheres of Gliclazide

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ABSTRACT

Gliclazide, an oral hypoglycemic agent employed in the management of Type 2 diabetes, poses challenges in achieving sustained release and optimal bioavailability due to its short half-life and variable absorption. This study aimed to develop and characterize Gliclazide-loaded floating microspheres as a gastro retentive drug delivery system. Ionotropic gelation methods were used with hydroxypropyl methylcellulose (HPMC K100M) and Xanthan gum as a polymer, and calcium carbonate as an agent that is gas-forming. An FTIR compatibility study lies in range of 4000-400 cm-1 revealed no significant alteration in the characteristic peaks of Gliclazide and polymer, suggesting their compatibility. The microspheres were assessed for particle size, yield, buoyancy, drug content, swelling index, morphology, and in vitro drug release. The micromeritic examination of the prepared formulations falls within the specified range, demonstrating favorable flow characteristics. Optimized formulations exhibited spherical morphology, particle sizes within the desired range (100-700 µm), and percentage yield exceeding 80%. Drug content was consistent throughout all the formulations. In vitro dissolution studies in simulated gastric fluid revealed sustained drug release of 70.05% after 6 hours, with formulations showcasing extended floating behavior. SEM analysis confirmed the spherical shape with smooth surface morphology and structural integrity of the microspheres. These findings indicate the potential of Gliclazide-loaded floating microspheres as an effective platform for prolonged drug release and enhanced gastric retention, offering a promising strategy for optimizing Gliclazide therapy in diabetes management.

Keywords: Gliclazide, floating microspheres, gastroretentive drug delivery, sustained release, SEM analysis.

INTRODUCTION

Oral route of administration is considered to be the most potential, safe and effective way to deliver drugs. Due to differential absorption from various regions of GI, the benefits of delivery method of dosage forms for long term have not been fully realized. Only recently drug delivery systems have been designed to target to differential regions of GIT, such as gastro retentive systems.[1] Floating microspheres are gastro retentive drug delivery systems based on non-effervescent approach.[2] It is new drug delivery systems developed to extend the amount of time drugs remain in the stomach and improve absorption. These microspheres are spherical, free flowing empty particles without a core, typically ranging from one to thousands of micrometers in size are engineered to float on the gastric fluid, extending drug release and absorption.[3]

An oral antihyperglycemic medication called Gliclazide is used to treat non-insulin dependent diabetic mellitus (NIDDM). It falls within the class of insulin secretagogues known as sulfonylureas, which work by inducing the pancreatic β cells to release insulin. Meal-stimulated insulin release and basal insulin secretion are both increased by sulfonylureas.[4]

The primary mechanism of action of sulphonylureas is to increase insulin secretion; as a result, they are only effective when there is some remaining pancreatic beta-cell activity. Over an extended period of time, they also have extra pancreatic effects. Gliclazide is a sulphonylurea medication having an approximately 11-hour intermediate half-life. Because of its substantial metabolism, renal clearance makes up only 4% of the drug's total clearance. The azabicyclo-octyl group in the molecule gives the basic sulphonylurea moiety unique characteristics. Gliclazide increases the release of insulin by binding to the β cell sulphonylurea receptor and potentially by directly influencing the intracellular calcium transport process. It affects both the first and second phases of insulin release in type 2 diabetes, specifically improving the aberrant first phase. Compared to some other sulphonylureas, this insulin release pattern is suggested to account for the decreased prevalence of hypoglycemic episodes and weight gain.[5]

MATERIALS AND METHODS

MATERIALS

Gliclazide was purchased from Dhamtec Pharma and Consultants. HPMC K100M, xanthan gum, sodium alginate, calcium carbonate and calcium chloride were obtained from Mr. Biologist.

METHODOLOGY

Pre-formulation Studies

Pre-formulation tests are essential initial steps in the logical progression of dosage form development. It is the examination of the physical as well as chemical characteristics of specific drugs along with the way they interact with excipients. The main goal of pre-formulation testing is to gather valuable details about the formulation process to create stable and bioavailable dosage forms suitable for large-scale production.[6]

Identification of Drug

Before the development of the formulation, the identification of the attained drug is one of the introductory tests to prove and assure the purity of the obtained drug samples. The current research was conducted by identifying the drug according to its appearance, melting point (MP), solubility and FTIR.[7]

Description of Drug

Physiochemical characteristics of the sample, like state, odour, taste, and colour were contrasted with the specifications of the sample.

Melting Point (MP)

Measuring the sample's MP was conducted as it serves as an initial indicator of the sample's purity. The drug's melting point was identified using an MP apparatus. Visually noted the temperature at which the sample melts and compared with official values of the drug.

Solubility Analysis

Solubility tests were conducted as part of the purity. The solubility of Gliclazide was determined.

Compatibility Studies

Analyses molecular interactions between Gliclazide, and polymers to confirm compatibility and chemical stability.

FTIR spectroscopy was conducted using an Alpha Bruker FTIR spectrophotometer. The drug was mixed with the correct quantity of KBr and compacted into a pellet by a KBr press at 20 psi for 10 minutes. The disc was prepared, then placed in a sample chamber and scanned in transmission mode from 4000 to 400 cm^{-1}.[8]

ANALYTICAL METHOD DEVELOPMENT

Determination of λ max:

Preparation of 0.1N HCL: 8.5 milliliters of concentrated HCl was diluted to a volume of 1000 milliliters with distilled water.

Preparation of stock solution: A 100 mg of Gliclazide was added to a 100 ml volumetric flask and then diluted with 0.1N HCl to a final volume of 100ml to acquire a stock solution of 1000 µg/ml (1 mg/ml). A 1ml volume of the stock solution had been diluted with 10 ml of 0.1N HCl to achieve a level of 100 µg/ml. The solution was analyzed within the wavelength range of 200-400 nm to identify the maximum absorption wavelength (λ max).

Preparation of standard graph: 2, 4, 6, 8, 10, & 12 ml of stock solution were diluted with 0.1N HCl to a total volume of 10 ml to obtain solutions with concentrations of 20, 40, 60, 80, 100, & 120 µg/ml. These solutions were then analyzed using a UV-visible spectrophotometer.

PREPARATION OF FLOATING MICROSPHERES

Floating microspheres were prepared by Ionotropic gelation method.

A 2% sodium alginate solution had been prepared by adding sodium alginate in 100ml of distilled water and agitating continuously until fully dissolved using a magnetic stirrer.

To the above solution weighed accurate quantity of polymers (HPMC, Xanthan gum), gas forming agent (calcium carbonate) and drug were added with continuous agitating to get a homogenous mixture.

The solution was withdrawn into the 50ml syringe (needle size of 30mm length 0.9mm width) and was drop wisely added into 100ml solution containing of 3g of calcium chloride and distilled water.

The prepared beads were washed using distilled water for 30min and then dried at room temperature for 24hrs. until fully formed.

Table 1: Composition for formulation of Gliclazide floating microspheres

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Gliclazide (mg)	160	160	160	160	160	160
Sodium alginate (g)	2	2	2	2	2	2
HPMC K100M (mg)	100	200	300	-	-	-
Xanthan gum (g)	-	-	-	100	200	300
Calcium carbonate (mg)	100	100	100	100	100	100
Calcium chloride (g)	2	2	2	2	2	2
Distilled water (ml)	100	100	100	100	100	100

EVALUATION OF PREPARED MICROSPHERES

Micromeritics Studies

The microspheres can be defined based on their micromeritic properties, including Bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio.[9]

Percentage yield

The dried prepared microspheres had been gathered and weighed. The percentage yield of the microsphere was estimated by measuring the weight of the drug and polymer utilized in the formulation. The percentage yield was calculated using the subsequent formula.[10]

$$\text{Percentage yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer}} \times 100$$

Buoyancy studies

Evaluated the buoyancy and floating capability of microspheres in simulated gastric conditions. Firstly 10 mg prepared floating microsphere was spread in 0.1 N HCl (100 ml). The mixture was agitated at 100 revolutions per minute using a magnetic stirrer. Ten hours later, the buoyant layer of microspheres was collected and isolated by filtration. Both particles were dried in desiccators until a consistent weight was achieved. The percentage buoyancy is determined by the following equation.[11]

$$\text{Percentage buoyancy} = \frac{\text{Weight of floating microspheres}}{\text{The initial weight of floating microspheres}} \times 100$$

Drug content

10 mg of crushed microspheres were precisely measured and combined with a pH 7.4 buffer solution before being transferred to a 100 ml volumetric flask. The volume was set to 100 ml by adding 0.1 N HCl. The solution was filtered employing Whatman filter paper no. 41. The drug samples had been examined employing a UV spectrophotometer having a wavelength of 235 nm.[12]

Swelling index

Immerse microspheres in simulated gastric fluid and measure changes in size or weight over time.

Firstly, 0.1 N HCl was prepared, which kept the pH at 1.2. Then they brought a Petri dish and applied a certain amount of floating microspheres, 0.1N HCl was added. The floating microspheres were separated from the hydrochloric acid, and any extra water was absorbed with paper. Weighed the items and calculated using the following formula.[13]

$$\text{Swelling Index} = \frac{\text{Mass of swollen microspheres} - \text{Mass of dried microspheres}}{\text{Mass of dried microspheres}} \times 100$$

Scanning electron microscopy

It examined the microsphere's surface properties, surface morphology, as well as shape in detail.

The microspheres are attached to the SEM sample employing double-sided tape and coated with a 200 nm thick gold film in a vacuum of 0.001 torr. Subsequently, the microspheres were observed by randomly scanning the stub and capturing photographs.[14]

In vitro drug release studies

Performed dissolution experiments using USP type II dissolution apparatus (rotating paddle) in simulated gastric fluid (900 ml) with 0.1 N HCl dissolution medium (pH 1.2) at 50 rpm at 37±0.5 °C. Five ml of samples were gathered at different time points over a 6-hour period, and an equivalent volume of newly prepared buffer was added to uphold sink conditions. The samples were examined at a wavelength of 285 nm with a UV-visible spectrophotometer.[15]

RESULTS AND DISCUSSION

Pre formulation studies

In pre formulation studies characteristics of samples were performed and results were complies with official values.

Identification of drugs

Identification of Gliclazide based on appearance, solubility, melting point, and the outcomes are mentioned in Table 2. The analysis from the table indicated that the drug sample's value was consistent with the official values, confirming that the received sample met the specified and desired requirements.

Compatibility studies

Figures 1 and 2 shows FTIR analysis of Gliclazide with polymers utilized in the formulation. The spectrum of the polymers as well as the drug exhibited all the distinctive peaks, suggesting compatibility between them.

FTIR study of Gliclazide-HPMC

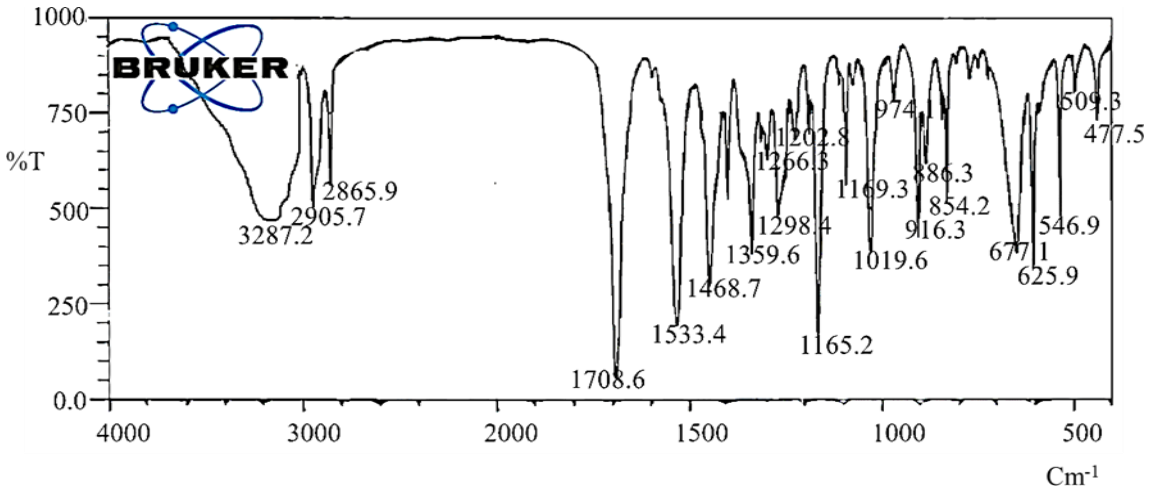


Figure 1: FTIR spectrum of Gliclazide with HPMC

FTIR Study of Gliclazide-Xanthan gum

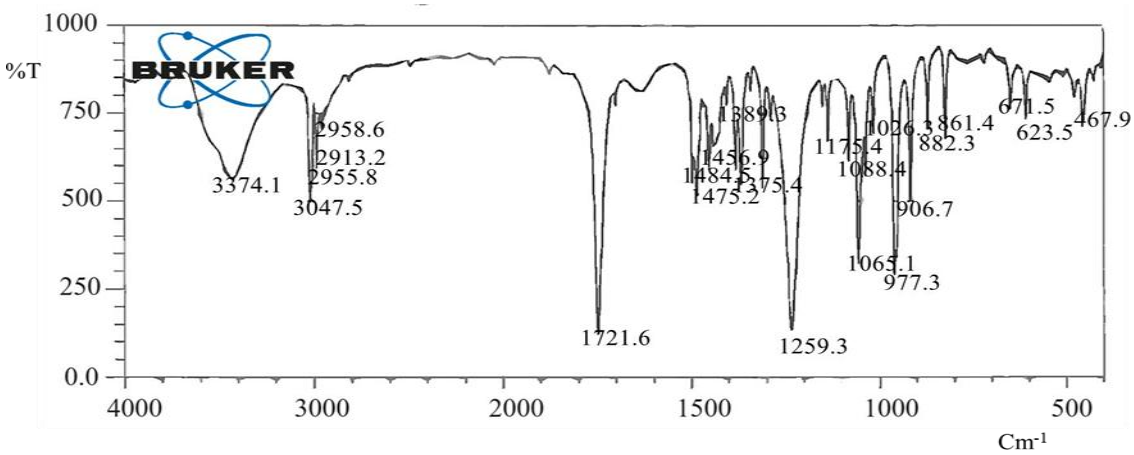


Figure 2: FTIR spectrum of Gliclazide with Xanthan Gum

Table 2: Identification of Glicazide

Sr. No.	Test	Specification	Observation	Inference
1	State	Crystalline solid	Crystalline solid	Complies
2	Color	A white or almost white powder	A white or almost white powder	Complies
3	Taste	Bitter	Not Performed	Complies
4	Melting point	180-182^{0}C	180^{0}C	Complies
5	Solubility	Insoluble in distilled water, sparingly soluble in methanol, freely soluble in 0.1N HCl, soluble in acetone	Insoluble in distilled water, sparingly soluble in methanol, freely soluble in 0.1N HCl, soluble in acetone	Complies

ANALYTICAL METHOD DEVELOPMENT

Determination of absorption maxima of Gliclazide extract in 0.1N HCl

100 µg/ml solution of Gliclazide was scanned between 200-400 nm and absorption maxima for the same was found to be at 275 nm.

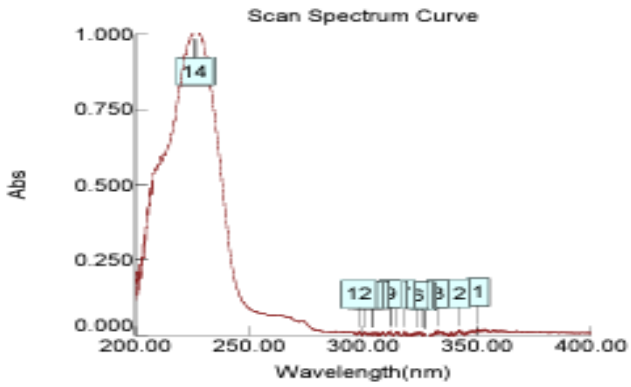


Figure 3: UV spectrum curve of pure drug

The absorbance of standard solution of Gliclazide ranging from 4 – 9 µg/ml, so the obtained standard graph is depicted in figure 3, data obtained for the standard curve is shown in table 3. The curve was found to be linear in the range of 4-9 µg/ml at 275 nm. The regression analysis for line y = 0.111x was performed and correlation coefficient of 0.975 was obtained for the standard curve.

Table 3: Absorbance value of different concentration at 275nm

Sr. No.	Conc. (µg/ml)	Absorbance
1	4	0.456
2	5	0.598
3	6	0.689
4	7	0.795
5	8	0.872
6	9	0.964

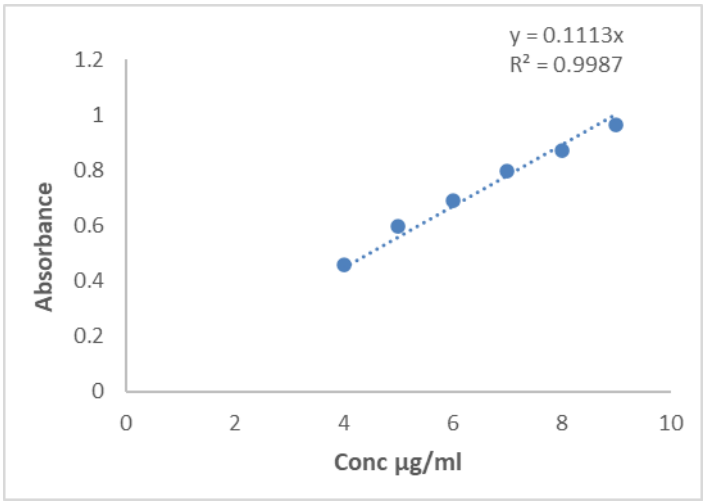


Figure 4: Standard graph of Gliclazide

EVALUATION OF PREPARED FLOATING MICROSPHERES OF GLICLAZIDE

Micromeritics properties

Table 4, shows the results of various formulations of Gliclazide floating microspheres, which were assessed for parameters including, tap density, Hausner ratio, AOR, compressibility index, and bulk density.

The table 4 shows that Carr's index for F1-F6 falls within the range of 11.1-16.7, Hausner's ratio ranges from 1.13-1.24, and the AOR ranges from 22.31-26.5°. The micromeritic analysis demonstrated that the microspheres exhibit superior flow characteristics, suggesting that they are both spherical and non-aggregated in nature.

Percentage yield

The percentage yield of different formulations F1-F6 were calculated and the yield were found to be 78.76%, 80.85%, 74.76%, 68.85%, 67.27% and 87.2% respectively as shown in Table 5.

Percentage buoyancy

According to table 5, it was found to be all the formulations have good buoyancy ability but the formulation F2 shows desirable buoyancy i.e. 98%.

Drug content

The drug content depends on the concentration of polymers, as the concentration of polymer increases the drug content also increases. According to table 5, it can be concluded that the drug content was consistent throughout all the formulations.

Swelling index

From table 5, for formulations F1-F6 percentage swelling index was increased and this is with increase in concentration of polymer.

Scanning electron microscopy

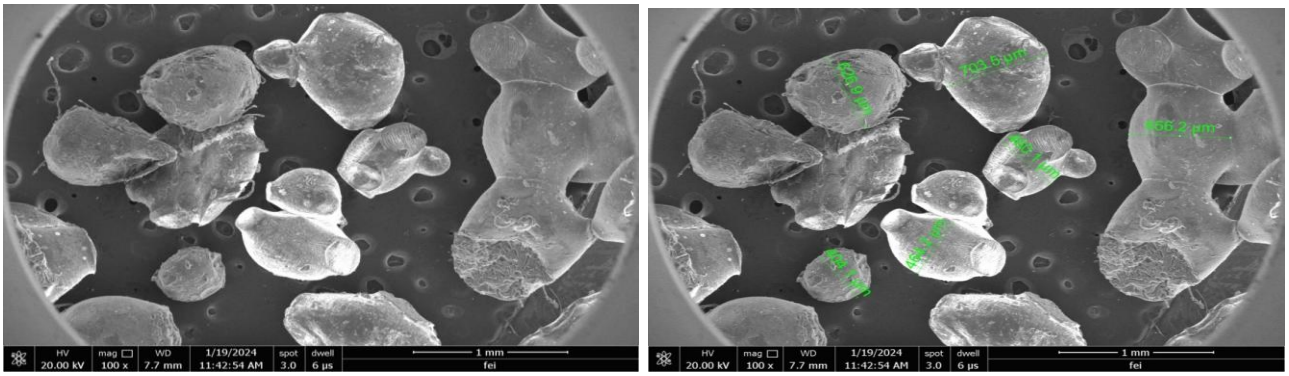
An SEM image of the prepared F2 floating microspheres of Gliclazide is displayed in figure 5, demonstrating various magnifications. The SEM images showed that the microspheres were within the specified size range, spherical in shape, and had a smooth surface morphology.

Table 4: Micromeritic properties of F1 to F6 formulations

Formulation Code	Bulk density	Tapped density	Carr's compressibility Index	Hausner's ratio	Angle of repose° (AOR)
F1	0.3241	0.3658	11.20	1.13	24.32
F2	0.3632	0.4365	12.50	1.14	26.50
F3	0.3675	0.4414	12.50	1.14	24.25
F4	0.488	0.588	16.70	1.24	25.52
F5	0.3626	0.4358	12.30	1.15	24.46
F6	0.3219	0.3834	11.13	1.13	22.31

Table 5: Percentage yield, percentage buoyancy, percentage drug content and percentage swelling of prepared formulations F1 – F6

Formulations code	Percentage yield	Percentage buoyancy	Drug content (%)	Percentage Swelling
F1	78.76%	54	93.64	65
F2	80.85%	98	96.54	72
F3	74.76%	73	96.72	76
F4	68.85%	57	94.23	81
F5	67.27%	89	94.29	89
F6	87.20%	68	96.45	79



(A) (B)

Figure 5: SEM photographs of F2 formulations at different magnifications (A and B)

***In vitro* drug release studies**

Table 6: *In-vitro* drug release studies for prepared formulations

Time	F1	F2	F3	F4	F5	F6
30 min	9.08	19.55	11.98	15.67	10.72	13.34
60 min	17.98	25.19	17.67	21.30	17.14	19.26
90 min	27.34	43.06	31.45	38.12	29.44	29.42
120 min	39.81	52.63	42.16	50.58	38.91	38.67
150 min	41.06	57.67	47.22	55.84	44.17	45.33
180 min	49.32	59.00	54.79	58.89	50.48	54.95
210 min	48.51	62.76	56.87	60.85	53.99	57.43
240 min	48.52	63.90	57.80	61.99	54.87	59.41
270 min	51.21	65.97	58.31	63.72	56.96	62.68
300 min	53.56	66.94	58.82	64.24	57.89	63.32
330 min	54.89	68.78	60.66	64.89	59.60	65.32
360 min	57.67	70.05	62.88	66.80	60.14	68.50

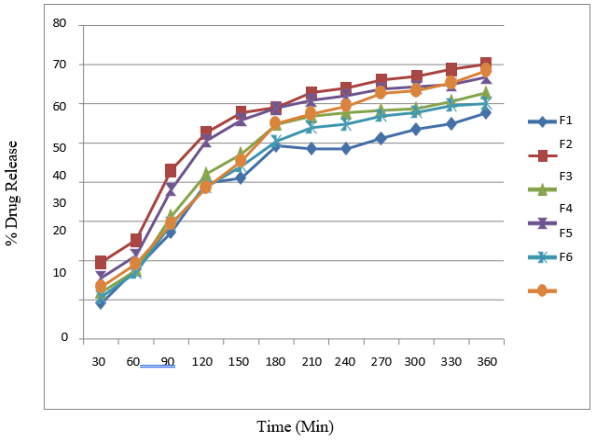


Figure 6: Drug release profiles of all the formulations

In vitro dissolution tests were conducted for formulations. The *in vitro* drug release data of different formulations are shown in table 6, and figure 6. The percentage drug release after 360 min, was found to be in the range of 57.67, 70.05, 62.88, 66.80, 60.14 and 68.50% for the formulations F1-F6 respectively.

The F2 formulation, which contains 200 mg of HPMC K100M, exhibited a drug release of 70.05% after 6 hours. It was noted that when the polymer concentration increased, the release rate of the medication decreased.

CONCLUSION

Floating drug delivery systems (DDS), including floating microspheres, extend the amount of time drugs stay in the stomach, leading to improved drug absorption. Its lower density causes it to float in the gastric fluid.

Diabetes mellitus is a long-term and intricate metabolic disorder marked by high blood sugar levels produced by a lack of insulin secretion, insulin resistance, or both.

Gliclazide was utilized as the model drug for the floating microsphere in this investigation.

Gliclazide, a second-generation sulfonylurea derivative, serves as a cornerstone in the management of Type 2 diabetes mellitus because of its potent hypoglycemic effects. The primary mechanism of action involves stimulating insulin secretion from the pancreatic β cells, resulting in decreased blood glucose levels.

The study successfully formed a gastro retentive DDS for Gliclazide in the form of floating microspheres to prolong the duration it stays in the stomach and enhance its bioavailability.

The preparation of floating microspheres of Gliclazide was involved, and the utilization of sodium alginate, HPMC, and Xanthan gum & calcium carbonate selected as the gas-forming agent by ionotropic gelation method. Six distinct formulations were prepared and assessed for their micromeritic characteristics, percentage yield swelling index, drug content, *in vitro* drug release tests and SEM.

FTIR study indicated that the drug is compatible with the polymers.

The micromeritic characteristics, including tap density, AOR, Hausner's ratio, Carr's index, and bulk density, had been measured for the formulations. The results met the specified limits for all formulations. Micromeritic studies revealed that the microspheres exhibit superior flow characteristics, suggesting that they are both spherical and non-aggregated in nature.

The percentage yield was determined for each formulation. Higher polymer concentration results in increased percentage yield. The drug content varied based on the polymer concentration, but it remained consistent across all formulations.

SEM photographs revealed that the fabricated microspheres were spherical, had a smooth surface, and were within the specified size range.

The F2 formulation, which contained 200 mg of HPMC K100M, was determined to be the superior choice due to its favorable swelling index, buoyancy, and drug release rate of 70.05% after 6 hours. Additional *in vitro* experiments should be conducted to validate the anti-diabetic activity.

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