RESEARCH ARTICLE

Design, Development, and Evaluation of Anti-diabetic Glibenclamide Microspheres using Natural Polymers by Ionotropic Gelation Method

Sanghavi S J[1*], Sarankar S[2]

[1]*Research Scholar, Faculty of Pharmacy, Mansarovar Global University, Sehore (Madhya Pradesh)*
[2]*Professor, Faculty of Pharmacy, Mansarovar Global University, Sehore (Madhya Pradesh)*

Received: 13th Sep, 2024; Revised: 19th Nov, 2024; Accepted: 21st Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT
Anti-diabetic drugs like glibenclamide (or glyburide) are used to manage the symptoms of type 2 diabetes. This action supports the pancreas in producing more insulin, thereby reducing high blood sugar. It is best when combined with a healthy diet and regular exercise. The drug can be combined with other diabetes treatments. When dealing with type 1 diabetes, it should not be used alone. It must be ingested orally.
Using an ionic gelation process, a new SR system comprising Glibenclamidemicrospheres of alginate-chitosan was created. Its morphology and features of release were examined. The microspheres were simple to make, and as the amount of polymers increased, so did the microspheres' mean diameter. The concentration of chitosan and alginate had an impact on the microspheres' pore size. Microspheres are destroyed while stirring at high speeds above 200 rpm. When compared to traditional oral dosage forms, the microspheres demonstrated superior *in-vivo* activity and SR properties. Even when dealing with medications that don't dissolve well in water, using a drug entrapment method can be a valuable technique for creating complex, multi-particle drug delivery systems.
Keywords: glibenclamide, Microspheres, multiparticulate systems,Anti-diabetic.
How to cite this article: Saurabh Jawahar Sanghavi, Satish Sarankar. Design, Development, and Evaluation of Anti-diabetic Glibenclamide Microspheres using Natural Polymers by Ionotropic Gelation Method. International Journal of Pharmaceutical Quality Assurance. 2024;15(4):2473-81. doi: 10.25258/ijpqa.15.4.47
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Diabetics have been documented since the time of the Vedas. It was called a madhumeha, where madhu meant honey and meha meant to urinate oneself clean. The contemporary term, diabetes mellitus (DM), is nearly synonymous. "Diabetes" comes from the Greek for "passing through," and "mellitus" is from Latin for "honey urine." One of the adhyarogas, or diseases of the wealthy,

Major Types of Diabetes

While diabetes can arise from various biological processes, most instances are classified as either Type I and Type II.

IDDM

Type I diabetes mostly grows in kids and teenagers. With this type, the pancreas stops making insulin. So, kids with Type 1 diabetes need to get insulin shots so their bodies can use sugar for energy.

NIDDM

Non-Insulin Dependent Diabetic Mellitus (NIDDM) has only lately had its clinical course understood. Those diagnosed with diabetes before the age of 25 (or 30) who do not need insulin to maintain appropriate metabolic control are said to have NIDDY. Maturity-onset diabetes in the young (MODY) is a subtype of NIDDY, but they also inherit diabetes in an autosomal dominant pattern.

Blood Sugar Levels

There is consensus that microvascular problems are less likely when mean blood glucose levels are low. As a result, macrovascular disease, the leading cause of death and amputation in NIDDM, has been largely overlooked in favor of this one.[4]

Plasma Lipids

According to recent research, the risk of ischemic heart disease during a 5-year period in people with non-insulin-dependent diabetes mellitus (NIDDM) may be reduced by maintaining a healthy blood triglyceride level Young adults should have values that are close to normal (5.3 mmol/l cholesterol, 2.1 mmol/l triglycerides).

Gestational Diabetes

Women who are pregnant and have high blood sugar (glucose) levels are said to have gestational diabetes, even if they have never had diabetes before. A condition where diabetes is first detected during pregnancy. It involves consistently high blood sugar and can be dangerous for both the pregnant woman and her baby.[7]

Introduction to Microsphere

Microspheres are a type of drug delivery system in which drug particles are disseminated throughout the matrix on either a molecular or macroscopic scale. Microspheres, sometimes called "monolithic spheres," are tiny, spherical particles ranging from one to one thousand micrometers in size. They function as delivery systems for therapeutic agents, where the active compounds are dispersed at a molecular level throughout the sphere's structure.[10]

Types of Microsphere

Bioadhesive Microspheres

**Author for Correspondence*

Table: The following describes the coded formulation processes and parameter ranges essential for replicating the ionic gelation technique used to manufacture Glibenclamide microspheres.

Formulation	API	Sod. alginate	Chitosan	Distilled water	CaCl2 (5%)	D:P
F1	50 mg	+	+	15 ml	50 ml	1:0.5
F2	+	+	+	+	+	1:1
F3	+	+	+	+	+	1:1.2
F4	+	+	+	+	+	1:1.4
F5	+	+	+	+	+	1:1.6
F6	+	+	+	+	+	1:1.8
F7	+	+	+	+	+	1:2

Table: Conditions for stability testing of capsules containing drug-loaded microspheres

Type of Study	Storage Condition	Testing Frequency (months)
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	0, 1, 2, 3, 4, 5, 6
Intermediate	30°C ± 2°C / 65% RH ± 5% RH	0, 1, 2, 3, 4, 5, 6

RH = relative humidity.

Adhesion is like using a special glue made of water-loving materials to stick medicine to a surface. Bioadhesion is when a medicine delivery system uses this glue to stick to moist surfaces inside your body, like the cheek, eye, or nose .[12]

Magnetic Microspheres

Having a delivery method that can target the site of sickness is crucial. A smaller quantity of magnetically targeted medicine can be used to substitute for a larger quantity of free circulating drug.[13]

Floating Microspheres

These systems are formulated to have a lower density than gastric fluids. This allows them to remain buoyant in the stomach, preventing them from being quickly emptied. By suspending the medication in the stomach, the drug is released gradually and at the ideal pace. This approach also prolongs the time the drug stays in the stomach, leading to more consistent drug levels in the bloodstream and reducing drastic spikes and dips.[14]

Microspheres from Polymeric Materials

Polymeric microspheres can be broken down into two distinct groups: biodegradable and synthetic.

Biodegradable Polymeric Microspheres

Microspheres made of natural polymers like starch are employed because of their supposed biodegradability, biocompatibility, and Bioadhesion. The strong swelling property of biodegradable polymers in aqueous media results in gel formation, which leads to an extended retention time on mucosal surfaces.[15]

Synthetic Polymeric Microspheres

These have been shown to be safe and biocompatible and have numerous applications in medicine, including those of bulking agent, filler, embolic particle, drug delivery vehicle, etc. However, the biggest problem with these microspheres is that they can travel far from the injection site, which can cause embolisms and additional organ damage.

Table:Organolepticproperties of Glibenclamide

Sr. No.	Name of property	Specification
1.	Color	White
2.	Odour	Unpleasant
3.	Nature	Crystalline

Table: Melting point of Glibenclamide

Sr. No.	Obtained range (°C)	Mean value (°C)	Reference value
1.	168		
2.	170	169-170 °C	169 °C
3.	169		

Table: Various concentrations and corresponding absorbance values of Glibenclamide

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.178
3	15	0.260
4	20	0.335
5	25	0.424
6	30	0.532
7	35	0.577

MATERIAL AND METHODOLOGY

Kreative Organics, Hyderabad, provided a free sample of both Glipizide and Glibenclamide. Sodium alginate and chitosan from the Kerala State chitosan facility, Kerela, were bought from CDH, New Delhi. Analytical grade materials were employed for all other purposes.

Formulation of Microspheres

Chitosan-alginate Microspheres Containing Glibenclamide and Glipizide

In thirty milliliters distilled water, the necessary amount of sodium alginate was dissolved. The drug's calculated quantity was added, and it was homogenized. The necessary amount of chitosan added in 5% v/v acetic acid and the pH (5.5) was corrected with a 10% sodium hydroxide. To it was added a 5% solution of calcium chloride dehydrate. stirrer as the drug alginate combination was introduced drop by drop steady rate of 2 ml/min. After being filtered, the microspheres cleaned

Table: Parameters found in calibration curve

Sr. No.	Parameter	Finding
1	detection of Wavelength	249 nm
2	Regression equation	y = 0.0174x – 0.0011
3	Correlation coefficient	R^2 = 0.9979

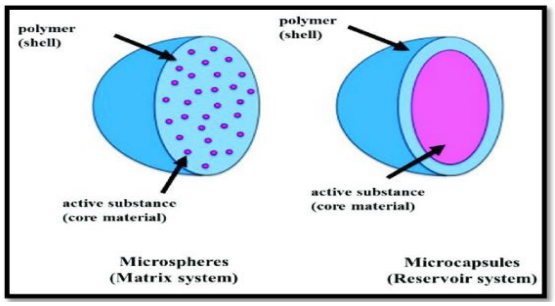

Figure 1: Microsphere

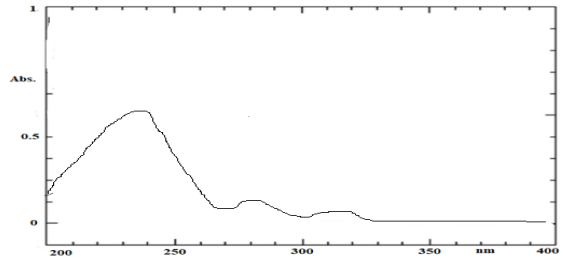

Figure : UV Spectrum of Glibenclamide

with acetone and dried at 35°C in an oven dried formulations in a bottle with an amber tint (Table).

Particle Size Distribution and Analysis

The distribution of particle sizes was determined. To calculate the mean particle size of the gel beads, refer the formula presented visually in the figure.

$$\text{Mean particle size} = \frac{\Sigma\left(\text{Mean particle size of the fraction} \times \text{weight fraction}\right)}{\Sigma\left(\text{Weight fraction}\right)}$$

Differential Scanning Calorimetry (DSC)

API, polymer, and microsphere thermograms were acquired with a Mettler Toledo DSC 822e calorimeter. DSC calculates the thermal energy that a sample absorbs or releases during heating, cooling, or maintaining a steady temperature.

SEM

For the preparation of samples for Scanning Electron Microscopy (SEM), microspheres were scattered onto one sticky side of a double-sided adhesive stub. Fine gold dust was then applied to the stub. After that, the microspheres were examined at 15 kV using a SEM (JEOL Model JSM-6390LV).

Entrapment Efficiency

The created microspheres were dissolved following a process of filtration and controlled dilution. Spectrophotometric analysis was then employed at wavelengths of 270 and 249 nm to quantify the drug content within weighed samples of the dissolved microspheres. [34]. "The procedure followed Beer's Law when concentrations were between 0 and 35 micrograms per milliliter

(%) Drug entrapment efficiency = Calculated drug content / theoretical drug content × 100

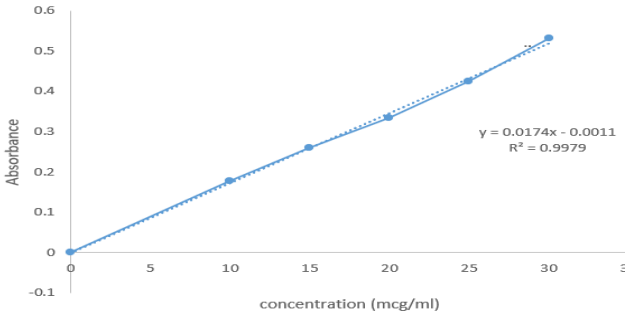

Figure : Methanolic calibration curve of Glibenclamide

Table: Investigation of Glibenclamide solubility

Sr.no.	Different buffers	% Solubility
1	Water	12.00%
2	0.1 N HCl (pH 1.2)	15.00%
3	Acetate buffer (pH 4)	18.00%
4	Phosphate buffer solution (pH 6.8)	20.00%
5	Phosphate buffer solution (pH 7.4)	24.00%

Swelling Index

A specific buffer solution's microspheres' degree of swelling was measured to calculate the swelling index. In order to guarantee total equilibrium weight, microspheres were immersed in a buffer solution to allow expansion. Blotting was used to remove any extra liquid that had adhered to the droplets, and a microbalance was used to weigh the enlarged microspheres. [35]

Mass of swollen microspheres - Mass of dry microspheres / Mass of dried microspheres × 100

Mucoadhesive Studies

To test how well tiny spheres stuck to surfaces, A wet glass slide was initially adhered to the inside of the beaker. We then spread about fifty of these microspheres evenly across the slide's surface. Next, we placed this whole setup into a standard disintegration testing machine. We regularly checked how many microspheres were still clinging to the glass slide to judge their stickiness. We repeated this measurement three times for accuracy. The results, showing the average stickiness and how much the measurements varied, are summarized in the table.

***In-vitro* Release Studies**

To create a standard curve, 50 mg of both Glipizide and Glibenclamide were added in 50 mL of methyl alcohol. This solution were then diluted to create a series of

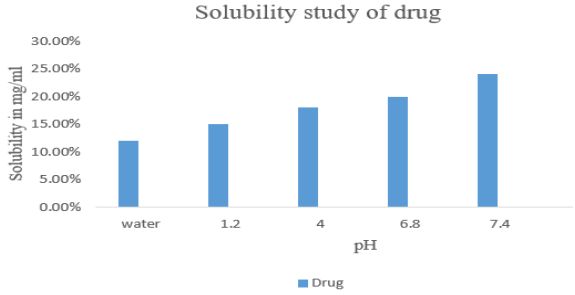

Figure: Solubility evaluation of Glibenclamide in water and various buffer solutions

Table: Interpretation data of Glibenclamide

Material	Functional group	Standard IR Ranges (cm^{-1})	Observed IR Ranges (cm^{-1})
Glibenclamide	C=O Stretching	1870-1540	1559.47, 1653.99, 1684.85
	C-C Stretching	1500-1400	1473.64
	C=C Stretching	1670-1650	1653.99
	S=O Stretching	1370-1335	1343.44

Table: Polymer Interpretation data of FTIR

Material	Functional group	Standard IR Ranges (cm^{-1})	Observed IR Ranges (cm^{-1})
Chitosan	O-H Stretching	3300-2500	2856.63
	C-O Stretching	1382-1036	1198.78
	C=O Stretching	1680-1630	1653.02

Table: The sodium alginate microspheres containing the drug Glibenclamide were measured for size, with the drug - polymer ratio ranging from 0.5:1 to 1:2.

Code	% yield	% entrapments	Shape	Color	% Swelling index	Mucoadhesive property (%) ± SD
F1	92.8	89.3 ± 0.12	Spherical	Light brown	13.7	51.3 ± 0.62
F2	87.4	86.6 ± 0.17	Spherical	Light brown	17.9	64.2 ± 1.52
F3	86.5	91.8 ± 0.12	Spherical	Light brown	19.4	67.4 ± 1.16
F4	94.2	90.6 ± 0.12	Spherical	Light brown	21.2	71.7 ± 1.54
F5	93.3	74.3 ± 0.09	Spherical	Light brown	22.7	74.7 ± 0.47
F6	87.3	91.3 ± 0.30	Spherical	Light brown	26.7	83.5 ± 0.45
F7	85.5	842 ± 0.12	Spherical	Light brown	29.2	90.4 ± 0.52

Table: In vitro release kinetics data for Glibenclamide-loaded chitosan-alginate microspheres (Drug:Polymer ratios 1:0.5 and 1:2), with values expressed as mean of n=3

Code	Zero order R_0	First order R_1	Higuchi R_H	Korsmeyer–Peppas R_K	Hixson-Crowell R_{HC}
F1	0.989	0.957	0.987	0.746	0.984
F2	0.993	0.960	0.993	0.756	0.973
F3	0.981	0.960	0.978	0.776	0.964
F4	0.982	0.970	0.983	0.816	0.980
F5	0.978	0.968	0.978	0.844	0.976
F6	0.983	0.985	0.982	0.875	0.988
F7	0.984	0.976	0.982	0.903	0.957

Table: For in-vivo grouping of animals

Group No.	Treatment	Dose	Number of animals
1	NS	10 ml/kg p.o.	06
2	STZ (STZ control)	50 mg/kg i.p.	06
3	Glibenclamide	2.5 mg/kg p.o.	06
4	F3	2.5 mg/kg p.o.	06

Table: Blood glucose level (mg/dl)

Sr.no.	Treatment	0 Day	3 Day	5 Day	7 Day
1	Normal saline (10 ml/kg)	89.92 ± 6.628	91.62 ± 6.875	92.50 ± 7.487	91.22 ± 7.431
2	STZ control	286.37 ± 13.736	291.45 ± 13.440	295.94 ± 13.022	298.75 ± 12.855
3	Glibenclamide (5 mg/kg)	284.95 ± 9.576	224.67 ± 9.027	168.92 ± 9.775	121.45 ± 10.213
4	F3 (5 mg/kg)	289.39 ± 5.625	242.74 ± 6.103	194.25 ± 6.739	147.72 ± 6.759

STZ: Streptozotocin

concentrations ranging from 0 to 35 µg/mL. A Shimadzu 1800 UV spectrophotometer was used to determine the absorbance of each solution at their respective maximum wavelengths (λmax) of 270 nm and 249 nm.

***In-vitro* Dissolution Study of Microspheres**

The rate of the drug was tested in a lab using a buffer change method. We used a diffusion cell at 37 ± 0.5°C and

Table: Rats' decreased plasma glucose levels following the administration of both the pure medication and the Glibenclamide formulation

Treatment	1 day	3 day	5 day	7 day
STZ control group	20.103	23.015	42.213	52.876
Glibenclamide				
Glibenclamide (5 mg/kg)	20.215	25.074	45.217	61.753
F3 (5 mg/kg)	12.353	18.831	36.599	52.900

75 rpm, exposing the drug to 200 ml of phosphate buffers with varying pH levels to mimic the conditions of the digestive system: first, a highly acidic environment (0.1 N HCl, 1 hour), then pH 4 (1 hour), pH 6 (3 hours), pH 6.8 (3 hours), and finally pH 7.4 (2 hours). Throughout experiment, sink conditions were maintained. The amount of Glipizide and Glibenclamide released was measured using a UV Visible Spectrophotometer.

***In-vivo* Antidiabetic Effect**

Assessment of the *In-vivo* Antidiabetic Activity of Glipizide and Glibenclamide Formulation in Healthy and Diabetic Rat Models

This study looked at how well two diabetes drugs, glibenclamide and glipizide, worked at lowering blood sugar in rats. They tested the drugs in tiny spheres, comparing them to the standard drug form in both healthy rats and rats with high blood sugar. Ethical clearance for all animal experiments was granted by the Pinnacle Biomedical Research Institute ethics committee [36].

The animals were housed in 12-hour cycles of light and dark. Eight groups of six animals each were created from the remaining animals (Table) [37].

Induction of Diabetes

1. To induce diabetes, rats were injected with dose of streptozotocin 60 mg per kilogram of body weight.
2. The STZ was added in a chilled 0.1 M citrate (buffer) solution and administered intraperitoneally.
3. To counter the initial high blood sugar caused by the STZ, the rats received a 5% glucose solution overnight.
4. On the third day post-injection, blood glucose levels were measured. Rats with levels exceeding 200 mg/dl were classified as diabetic.
5. Following STZ injection, treatment started on day four and continued until day five. Evaluations of blood glucose and body weight were carried out on days 0 (baseline), 3, 5, and 7 to monitor treatment outcomes.

Experimentation

Every animal was split up into six groups at random, each containing six animals. In this study, we divided subjects

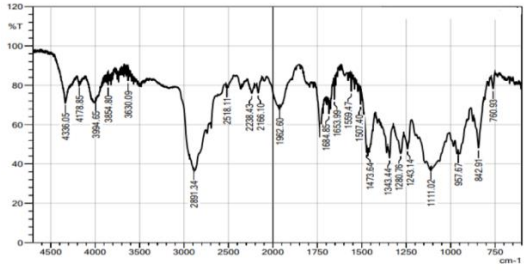

Figure: FTIR spectra of Glibenclamide

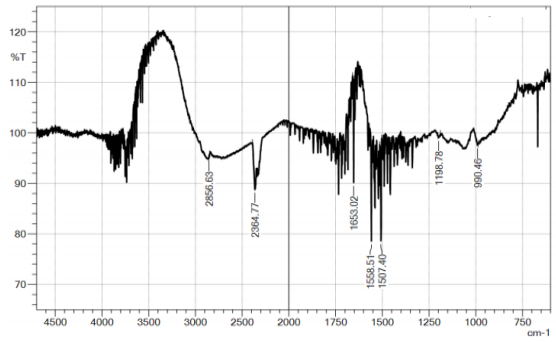

Figure: Polymer Interpretation data of FTIR

to VII groups. Group I act as the reference group and received no treatment to induce diabetes. The remaining groups (II through VII) were all made diabetic using STZ, a chemical compound that induces diabetes. Group I, the control, received only a saline solution by mouth. Groups II, VI, and VII were given an optimized medication formula dosage of 5mg/kg, orally on a daily basis. For comparison, Groups III and IV received common diabetes medications, Glipizide and Glibenclamide, respectively, also dosage of 5mg/kg and orally. Finally, Group V, also diabetic, received only saline, acting as a diabetic control group. The test samples were all dosed orally over the whole trial.

Stability Studies of Formulations

A crucial step in developing a formulation is stability testing. It produces data regarding the formulations and shelf life of medicinal compounds and suggests suitable storage guidelines [38, 39]. The stability of formulations 1 through 7 remained mostly unchanged.

Morphological Characteristics and Release Profile

During a 90-day study period, the prepared microspheres were stable at ambient temperature (32°C), 45°C in the oven, and 5°C in the freezer [40, 41].

Microspheres Loaded Capsule Preparation and Characterization

Preparation of Capsules Containing Drug-loaded Microspheres

Hard gelatin capsules of size #1 were filled with drug-loaded microspheres. Every capsule was completely filled and its weight was checked.

Evaluation of Capsule Uniformity for Formulations

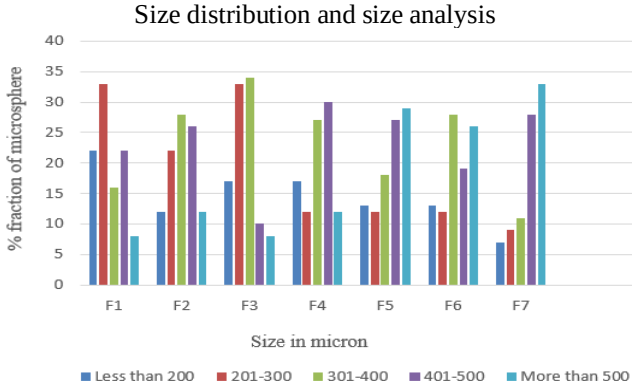

Figure: Size distribution of Glibenclamide-loaded sodium alginate microspheres (drug-to-polymer ratio: 1:0.5–1:2).

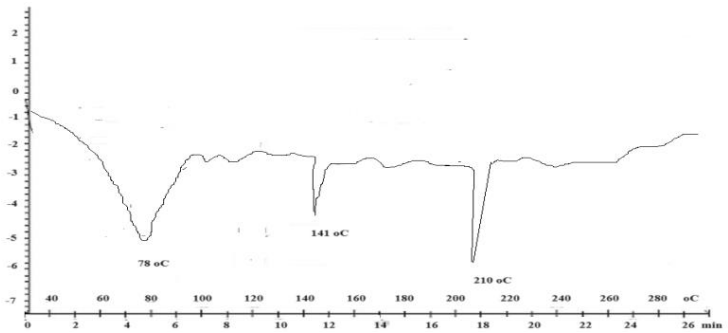

Figure: Thermal analysis of GCS-4 microspheres containing Glibenclamide using differential scanning calorimetrya

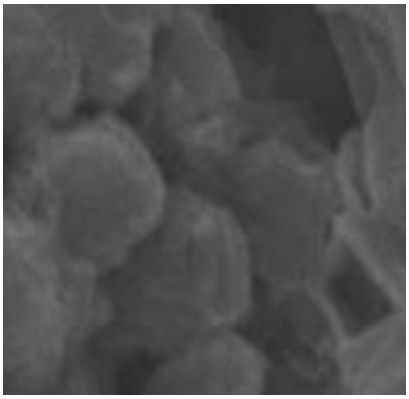

Figure: Scanning electron microscopy of F-7

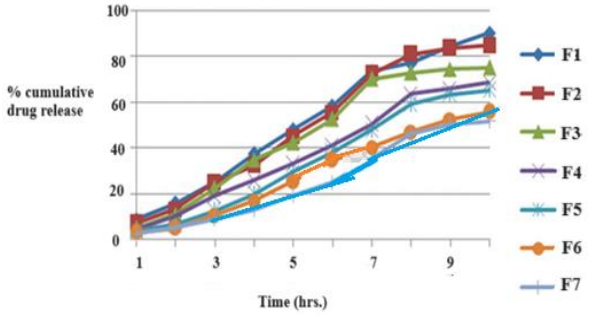

Figure: study examines how drugs are released from different formulations (F1 to F7)

Containing Drug-entrapped Microspheres

To determine the amount of medication in each capsule, we first weighed each capsule individually. We then analyzed the drug content of ten individual capsules to ensure consistency in the medication dosage. A UV-visible spectrophotometer, set to specific wavelengths (270 nm for Glipizide and 249 nm for Glibenclamide), was used to measure the concentration of each drug.

Evaluation of Disintegration Properties of Drug-loaded Microsphere Capsules

To determine how quickly capsules containing drug-loaded microspheres broke down, a Caleva DIST 20 series disintegration tester was used. This process adhered to the standards outlined in USP Chapter 701.

Drug Release Profile of Capsules Formulated with Drug-encapsulated Microspheres

To examine how the drugs were released, we employed a standard USP Type I dissolution apparatus, using a Distek water bath system (Model 2500C, North Brunswick, NJ). The experiment was performed at a consistent temperature of 37.5°C, with a stirring rate of 75 revolutions per minute, in 90 mL of pH 7.2 phosphate buffered saline (PBS). The concentration of each drug in the samples was then measured using a UV-visible spectrophotometer, which recorded the absorbance at 270 nm for Glipizide and 249 nm for Glibenclamide.

Assessing the Quality and Consistency of Drug-loaded Microsphere Capsules During Storage

Capsules containing drug-loaded microspheres underwent six-month stability testing under intermediate and accelerated conditions, compliant with FDA standards. I would recommend. The results are detailed in the table below.

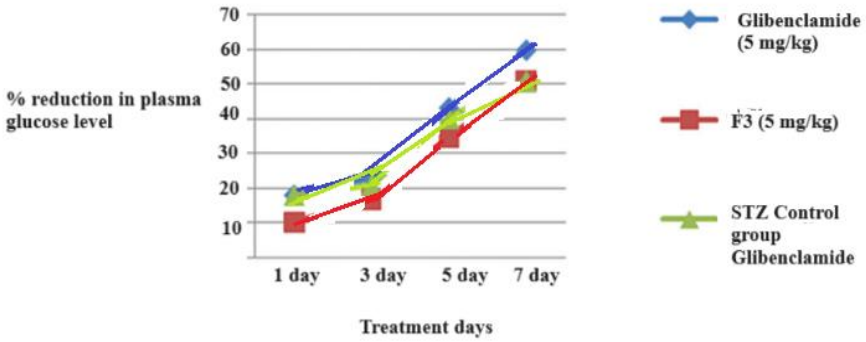

Figure: Comparative % reduction in blood glucose levels in hyperglycemic rats after treatment with formulation F3 and pure drug.

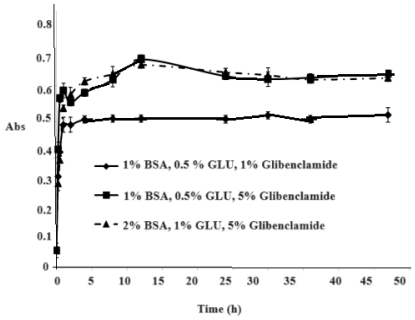

Figure (A): Various formulations of microspheres were created containing different levels of Glibenclamide. The release profiles of the drug from these microspheres were then analyzed. Glutaraldehyde (GLU) and bovine serum albumin (BSA)

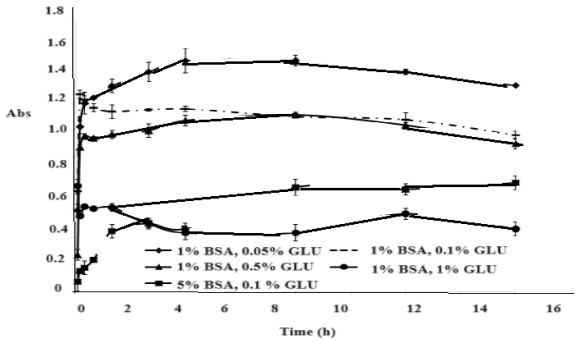

Figure (B): Glibenclamide-loaded microsphere capsules were studied for drug release over 16 hours (0.5% Glibenclamide). BSA = bovine serum albumin; GLU = glutaraldehyde. Data are mean ± SD (n=3)

RESULT AND DISCUSSION

API Characterization

Identification of Pure Druga) Melting Point

The Glibenclamide sample melted at 169°C, aligning with the published melting point range of 169-170°C. This close agreement suggests a high level of purity in the drug.

UV Spectroscopy

Determination of λ Max

A precisely measured 1 mg sample of the drug was transferred to a 100 ml volumetric flask. Methanol was used to dissolve the drug, and then more methanol was added until the solution reached the flask's 100 ml calibration mark. Finally, the resulting solution was analyzed using a UV spectrometer, scanning wavelengths from 200 to 400 nanometers.

The substance exhibited its strongest light absorption at a wavelength of 249 nanometers. Therefore, 249 nm was chosen as the λmax (lambda max) for subsequent investigations.

Calibration Curve of Glibenclamide in Methanol

To create the drug's standard stock solution, 1 mg added in 50 ml of methanol. Spectroscopic analysis showed that a 10 mcg/ml solution of the drug exhibited its peak absorbance at a wavelength of 249 nm. The drug's UV absorbance demonstrated a linear relationship with concentration in the range of 10 to 35 ug/ml

Solubility Study

Drug and Excipient Interaction Study

Fourier Transformation Infrared Spectroscopy (FTIR)

The FTIR spectrum analysis of Glibenclamide, as depicted in the figure, displayed distinct peaks that correspond to the functional groups expected based on its chemical formula. These findings suggest that the Glibenclamide sample analyzed is of high purity.

After analyzing the FT-IR spectrum of Glibenclamide, we determined that all the expected peaks, representing the functional groups within its molecular structure, were present and matched the established standards. This confirms the substance's identity as Glibenclamide.

FT-IR spectral analysis verified the identity of the chitosan polymer, revealing all characteristic peaks corresponding to its functional groups, which matched the standard reference values

Differential Scanning Calorimetric Analysis (DSC)

The thermal properties of Glibenclamide were investigated via DSC, as illustrated in the accompanying figure. The resulting thermogram shows a distinct endothermic peak near 170°C, which corresponds to the compound's melting point.

Differential Scanning Calorimetry (DSC)

The thermograph shows that the medication and polymers don't react with each other. The thermogram clearly displays distinct peaks for both the medications and the polymers, indicating no interaction (see Figure).

Scanning Electron Microscopy (SEM)

After that, the microspheres were examined at 15 kV using a SEM (JEOL Model JSM-6390LV). It displayed distinct, roughly equal, and evenly spaced microspheres (Fig.).

As the amount of polymer in the mixture increased, the microspheres became better at sticking to mucus membranes. The microspheres varied in size, ranging from 200 to 500 micrometers. Importantly, increasing the proportion of polymer used also resulted in larger microspheres. This is likely due to the insoluble medications being spread throughout the spaces within the polymer structure; therefore, more polymer results in a larger overall product.

In-vitro Release of Microspheres

In-vivo Hypoglycemic Activity

Statistical Analysis of *In-vivo* Data

To determine statistical differences between groups, data underwent a one-way ANOVA. Significant differences were identified with a Bonferroni correction for multiple comparisons ($p < 0.05$). Data are expressed as mean ± SD.

Microspheres Loaded Capsule

Evaluation of Content Uniformity and Disintegration Behavior of Capsules Containing Drug-loaded Microspheres

The capsules were tested rigorously and passed all requirements for uniformity as set by the (USP). This was demonstrated by their consistent weight (averaging 98.4% with a narrow variation of ± 0.4%) and consistent drug content (averaging 98.4% with a very small variation of ± 0.1%). Additionally, the capsules disintegrated within an average of 22 minutes ± 2 minutes, a rate similar to what's expected for oral medications to dissolve in the body.

Comparative Release Studies of Standalone Microspheres and Capsule-filled Microspheres

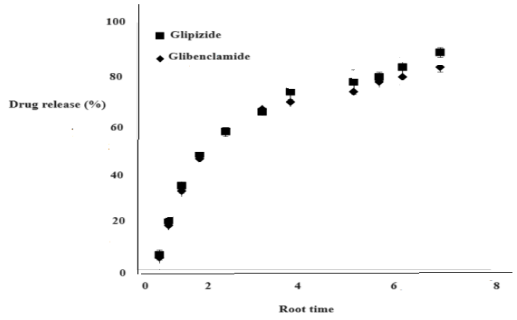

Figure: Higuchi analysis of drug release from microsphere-loaded capsules was performed by plotting √time vs. % release. Data are mean ± SD (n=3)

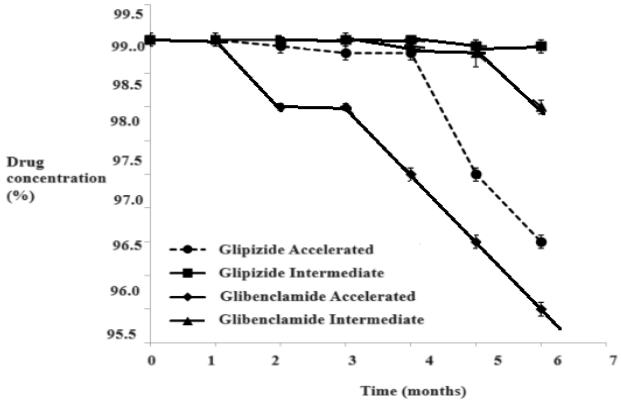

Figure: The stability of microsphere capsules containing Glipizide and Glibenclamide was evaluated under both intermediate and accelerated storage conditions. All results are expressed as the average value plus or minus the standard deviation, based on three replicate measurements (n=3)

Glibenclamide served as model medications for our investigation. The medication was released steadily from the microsphere powder over a 40-hour period, as seen in Figures A and B.

It was found to be the best. Similarly, with capsules containing Glibenclamide loaded microspheres, 1% BSA / 0.05% glutaraldehyde showed the maximum absorbance (Figure A).

Glutaraldehyde can be added at 0.05%, 0.1%, or 0.5% in cases where the concentration of polymeric BSA is 1%. Optimizing the glutaraldehyde concentration to achieve the ideal release profile is necessary if a greater BSA concentration is needed. The drug's protracted release profile following an initial burst release is depicted in the following figure.

Stability Testing of Capsules Containing Drug-loaded Microspheres

To create the most effective drug delivery system, we conducted a six-month stability study on capsules filled with drug-loaded microspheres. This testing was performed under both accelerated and standard conditions to identify the ideal formulation. Glibenclamide formulations retained at least 95% of their initial concentrations after six months (Figure).

SUMMARY AND CONCLUSION

The purpose of this effort is to create and assess Glipizide and Glibenclamide alginate-chitosan microspheres for efficient usage in the management of diabetes. The preparation of sustained release (SR) microspheres involved gently combining the medication with polymers in water and stirring the mixture.Using an ionic gelation process, a new Sustained Relearse system comprising Glipizide and Glibenclamide microspheres of alginate-chitosan was created. Its morphology and features of release were examined. The microspheres were simple to make, and as the amount of polymers increased, so did the microspheres' mean diameter. The concentration of chitosan and alginate had an impact on the microspheres' pore size. Microspheres are destroyed while stirring at high speeds above 200 rpm. When compared to traditional oral dosage forms, the microspheres demonstrated superior *in-vivo* activity and SR properties. Therefore, even for drugs that are water-insoluble, the drug incorporating approach is a helpful for the construction of multiparticulate systems.

REFERENCES

1. Yadav N., Mudgal D., Anand R., Jindal S., Mishra V. “Recent development in nanoencapsulation and delivery of natural bioactive through chitosan scaffolds for various biological applications”. Int J BiolMacromol. 2022; 220(1):537- 572.
2. Jain, Akhlesh K.; Upadhyay, Richa; Mishra, Keerti; Jain, Sunil K. “Current Drug Delivery”. Bentham Science Publishers. 2022; 9(1): 93-103.
3. B. Da.s, S.O. Sen, R. Maji, A.K. Nayak, K.K. Sen. “Transferosomal gel for transdermal delivery of risperidone”. J. Drug Deliv. Sci. Tech.2017;38 (1): 59-71.
4. Sharma M., Jain K., Dev SK., Choudhury PK. “Formulation and evaluation of sodium alginate beads by emulsion gelation method”. Asian J Pharm. 2017;11 (1):101-6.
5. Menshawe EL., Shahira F., Rasha MK., Doaa SH., Abdelkhalek H. “Effect of biodegradable co-polymers and divalent cations on the sustained release ability of propranolol hydrochloride loaded biomaterial microspheres”. Int J Pharm Sci. 2016;8 (1):311-7.
6. Ararath D., Velmurugan S. “Formulation and evaluation of nevirapine Mucoadhesive microspheres”. Int J Pharm Sci. 2015;7 (1):342-8.
7. Hong X., Wei L., Ma L., Chen Y., Liu Z., Yuan W. “Novel preparation method for sustained-release PLGA microspheres using water in-oil-in-hydrophilic-oil-in-water emulsion”. Int J Nanomedicine. 2013; 8 (1): 2433-41.
8. Mishra P., Singh DN, Purohit S. “Box Behnken design in optimization and evaluation of metformin HCl loaded guar gum microspheres”. Invent Rapid NDDS. 2012; 1(4):1-8.
9. Prisilla DH., Balamurugan R., Shah HR. “Antidiabetic activity of methanol extract of Acorus calamus in STZ induced diabetic rats”. Asian Pac J Trop Biomed. 2012;2 (2): 941-6.

10. Rajurkar BM. “Phyto-pharmacological investigations of Clerodendruminfortunatumgartns”. Int Res J Pharm. 2011;2(11):130-2.
11. Sarode SM., Mittal M., Magar RM., Shelke AD., Shrivastava B., Vidyasagar G. “Formulation and evaluation of floating microspheres of Glipizide”. J Chem Pharm Res. 2011;3(3): 775-83.
12. Goyal S., Rai JK., Narang RK., Rajesh KS. “Sulfonyl ureas for Antidiabetic therapy, an overview for Glipizide - Review article”. Int J Pharm Sci. 2010; 2(2): 1-6.
13. Phutane P., Shidhaye S., Lotlikar V., Ghule A., Sutar S., Kadam V. “In vitro evaluation of novel sustained release microspheres of Glipizide prepared by the emulsion solvent diffusion-evaporation method”. J Young Pharm. 2(1):35-41.
14. Nair R., Haritha B., Reddy CK., Kumar A., Kumar JK. “Application of chitosan microspheres as drug carriers: A review”. J Pharm Sci Res. 2009; 1(3):1-12.
15. Choudhury PK., Kar M., Chauhan CS. “Cellulose acetate microspheres as floating depot systems to increase gastric retention of Antidiabetic drug: Formulation, characterization and in vitro-in vivo evaluation”. Drug Dev Ind Pharm. 2008; 34(4):349-54.
16. Jorgensen L., Moeller EH., van de Weert M., Nielsen HM., Frokjaer S. “Preparing and evaluating delivery systems for proteins”. Eur J Pharm Sci. 2006; 29(3):174-82.
17. Choudhury PK., Kar M. “Preparation of alginate gel beads containing metformin hydrochloride using emulsion - Gelation method”. Trop J Pharm Res. 2005; 4(2): 489-93.
18. Sinha VR., Singla AK., Wadhawan S., Kaushik R., Kumria R., Bansal K. “Chitosan microspheres as a potential carrier for drugs”. Int J Pharm. 2004; 274(1):1-33.
19. Deruiter J. “Overview of the Antidiabetic Agents”, Endocrine Pharmacotherapy Module Spring. 2003; 25(1):1-33.
20. Castellanos IJ., Cruz G., Crespo R., Griebenow K. “Encapsulation induced aggregation and loss in activity of gamma-chymotrypsin and their prevention”. J Control Release. 2002; 81(3):307-19.
21. Mathiowitz E., Chickering D., Jacob JS., Santos C. “Bioadhesive drug delivery systems”. Encycl Control Drug Deliv. 1999; 1(1): 9-44.
22. Ceriello A. “The emerging role of post-prandial hyperglycemic spikes in the pathogenesis of diabetic complications”. Diabet Med. 1998; 15(3):188- 93.
23. Mesiha M., Sidhom M. “Increased oral absorption enhancement of insulin by medium viscosity hydroxyl propyl cellulose”. Int J Pharm. 1995; 115(1): 137- 40.
24. Wan LS., Heng PW., Wong LF. “Matrix swelling: Simple model describing extent of swelling of HPMC matrices”. Int J Pharm. 1995; 116(2):159-68.