Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL 02, ISSUE 04, 2011

Development and Evaluation of Mucoadhesive Microspheres of Glibenclamide

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Abstract

This research focuses on the development and evaluation of mucoadhesive microspheres containing Glibenclamide, an antidiabetic agent. Controlled and sustained-release drug delivery systems have emerged as an innovative approach to improve patient compliance by reducing dosing frequency and maintaining stable drug levels. Microspheres, created through microencapsulation, are micro-sized particles with a core and a coating that provide environmental protection and controlled release. The study involved formulating mucoadhesive microspheres using polymers such as sodium alginate, carbopol, sodium CMC, and HPMC through the orifice-ionic gelatin method. The developed formulations were evaluated for morphological characteristics, drug content, and *In Vitro* drug release at different pH conditions (pH 1.2 and pH 7.4). The results demonstrated that microspheres exhibited discrete, spherical, and monolithic matrix structures with excellent mucoadhesive properties, making them suitable for oral sustained-release delivery of Glibenclamide.

Keywords: *Mucoadhesive microspheres,* Glibenclamide, Sustained-release, Drug delivery, Orifice-ionic gelatin method, Polymer matrices, Controlled drug delivery systems

1. Introduction

1.1 Clinical Context: Type II Diabetes Mellitus and Current Treatment Challenges

Type II diabetes mellitus represents a significant global health burden, affecting millions of patients worldwide and requiring long-term therapeutic management. Current oral antidiabetic formulations, including conventional dosage forms of Glibenclamide (a second-generation sulfonylurea), present substantial clinical limitations. Patients typically require multiple daily administrations (2-3 times daily), leading to poor medication adherence, particularly in elderly and pediatric populations. This frequent dosing results in fluctuating plasma drug concentrations, increasing the risk of both hyperglycemic and hypoglycemic episodes. Additionally, patients often experience gastrointestinal side effects and suboptimal therapeutic control due to inconsistent dosing patterns.

1.2 Rationale for Sustained-Release Drug Delivery Systems

Conventional rapid-release dosage forms fail to address the clinical need for stable, prolonged therapeutic drug levels in chronic disease management. Controlled and sustained-release drug delivery systems offer a rational solution by providing predictable, prolonged drug release that maintains therapeutic drug concentrations over extended periods. These advanced formulations reduce dosing frequency, improve patient compliance, minimize gastrointestinal irritation through prolonged mucosal contact, and stabilize plasma drug levels—ultimately enhancing therapeutic efficacy in diabetic patients.

1.3 Microspheres: A Promising Microencapsulation Technology

Microencapsulation is a process in which tiny particles or droplets are coated to form small capsules with useful pharmaceutical properties. Microspheres—discrete solid particles with a core and outer coating—offer multiple advantages in drug delivery. Microencapsulation provides the means of converting liquids to solids, altering colloidal and surface properties, providing environmental protection, and controlling the release characteristics or availability of coated materials 1. Two major classes of microencapsulation methods have evolved: chemical methods, which involve polymerization during capsule preparation, and physical methods, which involve controlled precipitation of polymeric solutions.

1.4 Mucoadhesion: Enhancing Drug Bioavailability and Residence Time

Mucoadhesion has been a topic of significant interest in drug delivery system design 2. The primary objective is to prolong the residence time of the dosage form at the site of application or absorption and

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to facilitate intimate contact between the dosage form and the underlying absorption surface, thereby improving drug bioavailability of drugs. The development of an adhesive bond between a polymer and a biological membrane can be visualized as a two-step process: initial contact between the two surfaces, followed by the formation of secondary bonds through non-covalent interactions. Mucoadhesive polymers exhibit properties that enable them to form strong adhesive interactions with mucosal tissues, thereby extending the contact time available for drug absorption.

1.5 Glibenclamide: Properties and Mechanism of Action

Glibenclamide is a second-generation sulfonylurea antidiabetic agent suitable for incorporation into sustained-release delivery systems. The drug has the molecular formula $C_{23}H_{28}ClN_3O_5S$ with a molecular weight of 494.004 g/mol, appearing as a crystalline solid. Glibenclamide is soluble in organic solvents such as DMSO and dimethylformamide but is practically insoluble in water. The mechanism of action of Glibenclamide involves a single dose provoking a brisk release of insulin from the pancreas. The drug acts on sulfonylurea receptors on the pancreatic beta-cell membrane, depolarizing the cell by reducing ATP-sensitive K+ channel conductance, thereby enhancing calcium influx and promoting degranulation. This action increases the rate of insulin secretion at any glucose concentration. In Type II diabetes mellitus, where the kinetics of insulin release in response to glucose or meals are delayed and subdued, sulfonylureas like Glibenclamide primarily augment the second-phase insulin secretion with little effect on the first phase.

1.6 Rationale for Mucoadhesive Microspheres of Glibenclamide

The combination of mucoadhesive technology with microencapsulation represents an innovative approach to optimizing Glibenclamide delivery. By developing mucoadhesive microspheres, discrete, spherical particles with controlled-release capabilities and mucosal adhesion properties, we can simultaneously:

- Reduce dosing frequency through sustained and controlled drug release
- Maintain stable therapeutic drug plasma levels over extended periods
- Improve patient compliance and quality of life
- Enhance bioavailability through prolonged mucosal contact and residence time
- Minimise gastrointestinal side effects through controlled, extended release

This integrated delivery system addresses the critical therapeutic limitations of conventional Glibenclamide formulations and offers significant clinical advantages for diabetic patients requiring long-term antidiabetic therapy.

1.7 Study Objectives

The research aimed to develop and evaluate mucoadhesive microspheres of Glibenclamide, a second-generation antidiabetic agent. Blank and drug-loaded microspheres were formulated using biocompatible polymers, including sodium alginate, sodium CMC, carbopol, and HPMC, in various weight ratios. The study included thorough characterisation via physical evaluation, drug content determination, *In Vitro* release profiling, and mucoadhesive testing. The goal was to identify the optimal polymer combination for sustained drug release and enhanced oral bioavailability in managing Type II diabetes.

2. Materials and Methods.

2.1 Collection of Materials

All materials used in the formulation of microspheres, including Glibenclamide and polymers (sodium alginate, carbopol, sodium CMC, and HPMC), were procured as per pharmaceutical standards.

2.2 Preformulation Studies

2.2.1 Identification of Drug

Glibenclamide was identified using multiple analytical methods:

Ultraviolet Spectroscopy: The drug was dissolved in 0.1N HCl and examined using a Lambda 25 Perkin Elmer UV-spectrophotometer. The peak was observed at 229 nm.

Fourier Transform Infrared Spectrometry: FTIR spectra for drug samples were obtained on a Perkin Elmer FTIR spectrometer in transmission mode with a wave number region of 4,000-500cm^{-1}. KBr pellets were prepared by gently mixing 1 mg of sample powder with 100 mg of KBr.

2.2.2 Purity Determination of Drug

Estimation by UV Spectrophotometric Method: Glibenclamide was estimated using UV spectrophotometry. Aqueous solutions were prepared in 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4), and absorbance was measured at 229 nm. The method was validated for linearity, accuracy, and precision, and Beer's Law was obeyed over the concentration range of 1-10 µg/mL.

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2.2.3 Polymer Characterization
Sodium Alginate, Carbopol, Sodium CMC, and HPMC were characterised in accordance with pharmacopeial specifications. HPMC served multiple functional roles, including coating agent, film former, tablet binder, stabilising agent, suspending agent, and viscosity-increasing agent.

2.3 Formulation of Mucoadhesive Microspheres
Mucoadhesive microspheres of Glibenclamide were prepared using the orifice-ionic gelation method with various polymer combinations at different ratios (1:1 and 9:1) of sodium alginate with Carbopol, sodium CMC, and HPMC.

2.3.1. Methodology:
Microcapsules were prepared using the orifice-ionic gelation method. Sodium alginate and a specified mucoadhesive polymer were dissolved in purified water to form a homogenous polymer solution. Glibenclamide was added to this solution and mixed thoroughly with a stirrer to form a viscous dispersion. This dispersion was added manually, dropwise, through a size 18 needle into a 10% w/v calcium chloride solution. The droplets were retained in the solution for 15 minutes to complete the curing reaction, producing spherical, rigid microcapsules. They were then collected by decantation, washed with water, and dried at 45°C for 12 hours. Six different formulations (F1 to F6) were prepared using different polymer combinations and ratios.

2.3.2 Formulation Batches: Six different batches of microspheres (F1 to F6) were prepared by varying the combination and ratio of sodium alginate to the respective mucoadhesive polymers.

Table 1: Composition of Glibenclamide Microsphere Formulations

S.No.	Microspheres Batch	Polymer Composition	Ratio
1	F1	Sodium Alginate: Sodium CMC	1:1
2	F2	Sodium Alginate: HPMC	1:1
3	F3	Sodium Alginate: Carbopol	1:1
4	F4	Sodium Alginate: Sodium CMC	9:1
5	F5	Sodium Alginate: HPMC	9:1
6	F6	Sodium Alginate: Carbopol	9:1

2.4. Evaluation of Microspheres

- **Physical Characterization:** Scanning Electron Microscopy (SEM) was employed to assess the morphological characteristics of the microspheres
- **Drug Content Analysis:** About 500 mg of the accurately weighed microcapsules were transferred into 900 ml of pH 7.4 phosphate buffer. A 1% Sodium Lauryl Sulfate (SLS) solution was used to enhance the solubility of glibenclamide. The solution was stirred continuously at 37°C until the microcapsules completely dissolved, and the drug loading was subsequently determined spectrophotometrically at 229 nm.
- ***In Vitro* Release Profile:** The *In Vitro* release rate was determined using a dissolution test apparatus (basket method) with a rotation rate of 50 rpm. The testing was conducted in two separate dissolution mediums maintained at 37°C: 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4) supplemented with 9 gm of SLS. Samples of 5 ml were withdrawn at specific intervals, filtered, and analysed spectrophotometrically at 229 nm.
- ***In Vitro* Mucoadhesive Testing:** The mucoadhesive properties were evaluated via the wash-off method. Freshly excised goat intestinal mucosa (2x2 cm) was mounted onto glass slides. Approximately 50 microcapsules were spread over the wet tissue, and the slides were connected to the arm of a USP tablet disintegrating test apparatus. The specimens underwent a slow, regular up-and-down movement in 1-liter vessels containing either 0.1N HCl (gastric pH) or pH 7.4 phosphate buffer at 37°C. The number of adhering microcapsules was counted at definite time intervals.

3. Results and Discussion
3.1 Preformulation Studies
The FTIR (Fourier Transform Infrared) spectrometry analysis was conducted as part of the preformulation studies, which successfully identified the active drug, glibenclamide.

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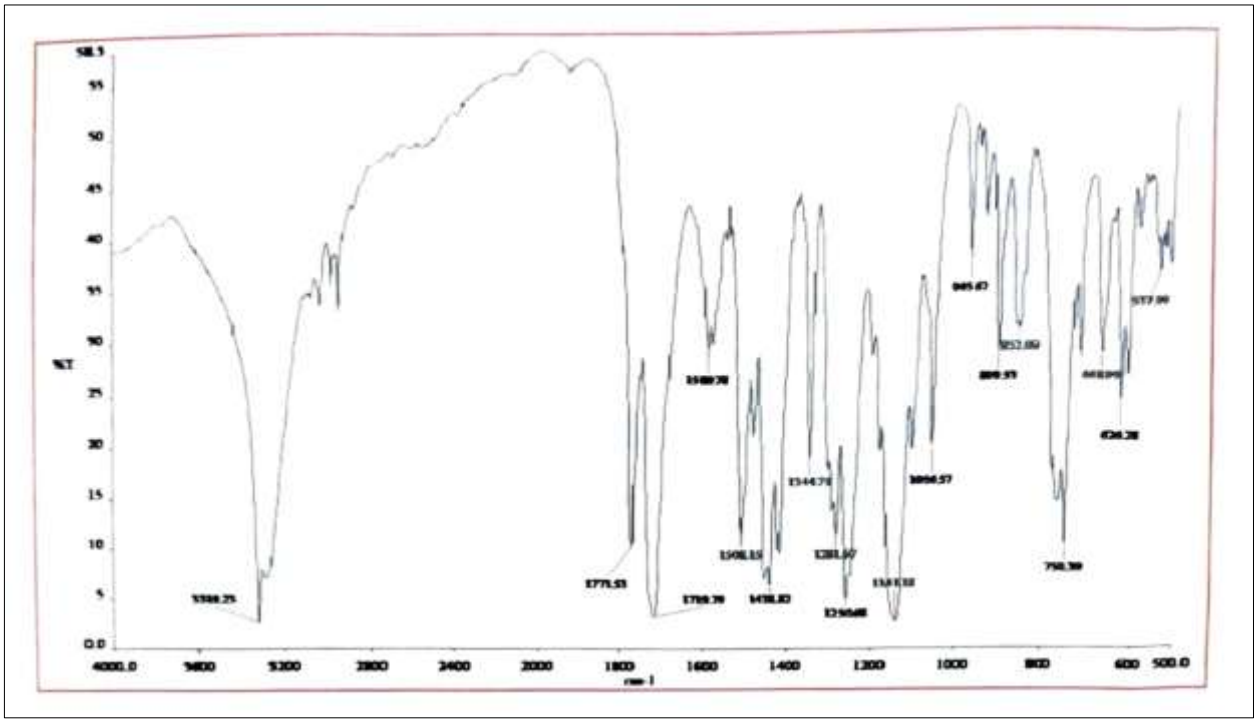

Fig 1: FTIR of Glibenclamide

The resulting FTIR spectrum produced a distinct visual "fingerprint" with prominent absorption peaks (such as 3310.23, 1771.53, 1719.79, and 1344.75 cm^{-1}) that correlate with the chemical structure of pure glibenclamide.(Fig 01)

3.2 Morphological Characteristics of the Microsphere

The mucoadhesive microspheres of Glibenclamide prepared by the orifice-ionic gelation method were found to be discrete, spherical, free-flowing, and of the monolithic matrix type. The microspheres were uniform in size with a range of approximately 300 µm. SEM photographs indicated that the microspheres were spherical and fully covered with the polymer.

The following specific morphological characteristics were observed based on the polymer ratios used:

Formulation F1 (Alginate: Sodium CMC, 1:1): Microspheres were approximately spherical, and their surfaces were rough, giving them a "sandy" appearance.

Formulation F4 (Alginate: Sodium CMC, 9:1): The surface characteristics showed an oval or slightly spherical structure with a smoother appearance. From the photographic observations, the bridging and dense nature of the formulations indicates an architecture highly capable of retarding the release of glibenclamide.(Fig 02).

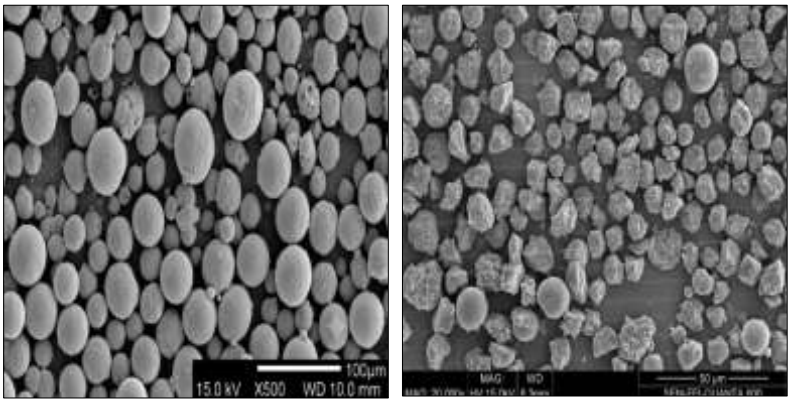

Fig 2: SEM (Formulation F1), SEM (Formulation F4)

The morphological characteristics demonstrated by SEM analysis confirmed the successful encapsulation and coating of Glibenclamide within polymer matrices.

3.3 Drug Content and Microencapsulation Efficiency The drug entrapment efficiency across all tested formulations was uniform and highly satisfactory, ranging between 80.67% and 93.12%. As shown in

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Table 2 below, Formulation F4 exhibited the highest encapsulation efficiency.

Table 2: Drug Content and Microencapsulation Efficiency of Microspheres

S.No.	Microspheres Batch	Polymer Composition	Drug Content (mg)	Microencapsulation Efficiency (%)
1	F1	Alginate: Sodium CMC (1:1)	80.67	80.67%
2	F2	Alginate: HPMC (1:1)	83.77	83.77%
3	F3	Alginate: Carbopol (1:1)	90.11	90.11%
4	F4	Alginate: Sodium CMC (9:1)	93.12	93.12%
5	F5	Alginate: HPMC (9:1)	81.27	81.27%
6	F6	Alginate: Carbopol (9:1)	86.25	86.25%

Drug entrapment efficiency values between 80-90% indicate that the microencapsulation process was highly effective, with minimal drug loss during formulation. This high entrapment efficiency is crucial for maintaining consistent drug bioavailability.

3.4 *In Vitro* Release of Glibenclamide

The *In Vitro* release of glibenclamide from the microspheres was slow, extended over a long period. The drug release was strictly diffusion-controlled and depended on the percentage of the coat material, the wall thickness, and the microsphere size.

The rate of release was highly dependent on the polymer type, with the slower increasing release rate observed in the following order: Sodium Alginate: Carbopol < Sodium Alginate: Sodium CMC < Sodium Alginate: HPMC.

Drug efficacy for sustained release increased with the concentration of the polymer. Formulations incorporating Carbopol (such as F3 and F6) demonstrated the most sustained profiles. Specifically, Formulation F6 (9:1 ratio) achieved a prolonged release of 96.89% over 14 hours in phosphate buffer (pH 7.4).

Table 3: Comparative Cumulative % Drug Release of F1 -F3 at pH 1.2. (1:1)

Time (hours)	F1: Alginate + Sodium CMC (%)	F2: Alginate + HPMC (%)	F3: Alginate + Carbopol (%)
0.5	10.37	8.41	4.99
1	43.61	44.58	42.71
2	79.42	70.93	68.76
3	86.79	87.12	80.45
4	98.06	97.99	94.31

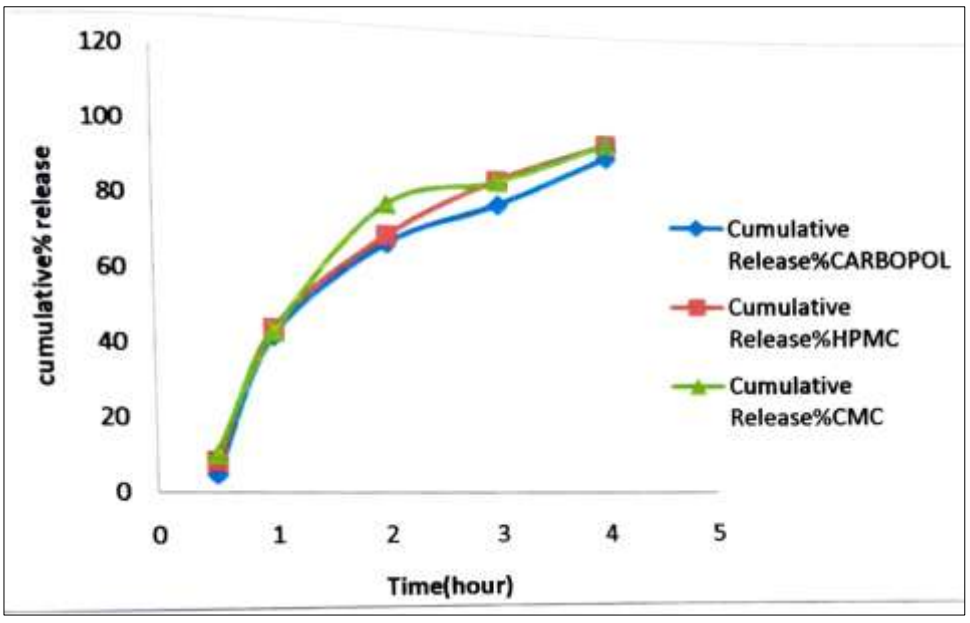

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Table 4: Comparative Cumulative % Drug Release of F1 -F3 at pH 7.4. (1:1)

Time (hours)	F1: Alginate + Sodium CMC (%)	F2: Alginate + HPMC (%)	F3: Alginate + Carbopol (%)
0.5	3.76	3.57	3.254
1	19.06	23.25	12.90
2	13.2	38.94	22.93
3	46.61	53.31	51.80
4	69.01	69.36	62.549
5	86.52	85.87	70.987
6	92.40	89.81	78.13
7	97.64	97.50	83.79
8	-	-	93.13

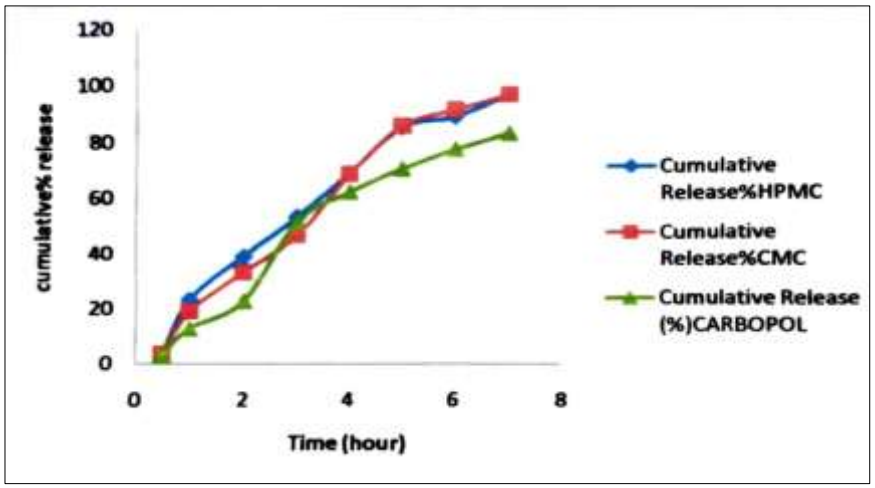

Table 5: Comparative Cumulative % Drug Release of F4 -F6 at pH 1.2 (9:1)

Time (hours)	**F4: Alginate + Sodium CMC (%)**	**F5: Alginate + HPMC (%)**	**F6: Alginate + Carbopol (%)**
0.5	9.3	7.87	4.98
1	26.19	26.10	18.49
2	44.45	49.95	30.12
3	68.97	67.14	49.61
4	75.54	85.94	66.22
5	92.86	93.46	79.69
6	96.62	98.72	83.05
7	-	-	87.59
8	-	-	93.13

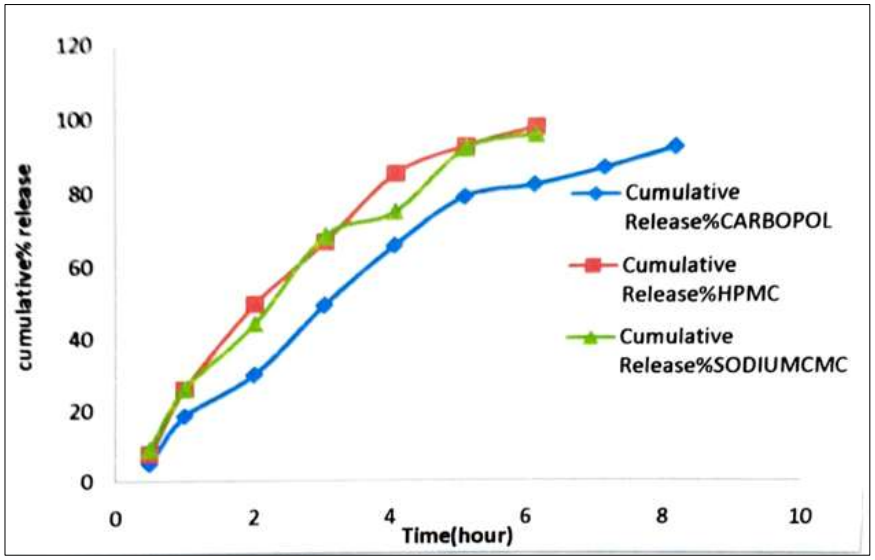

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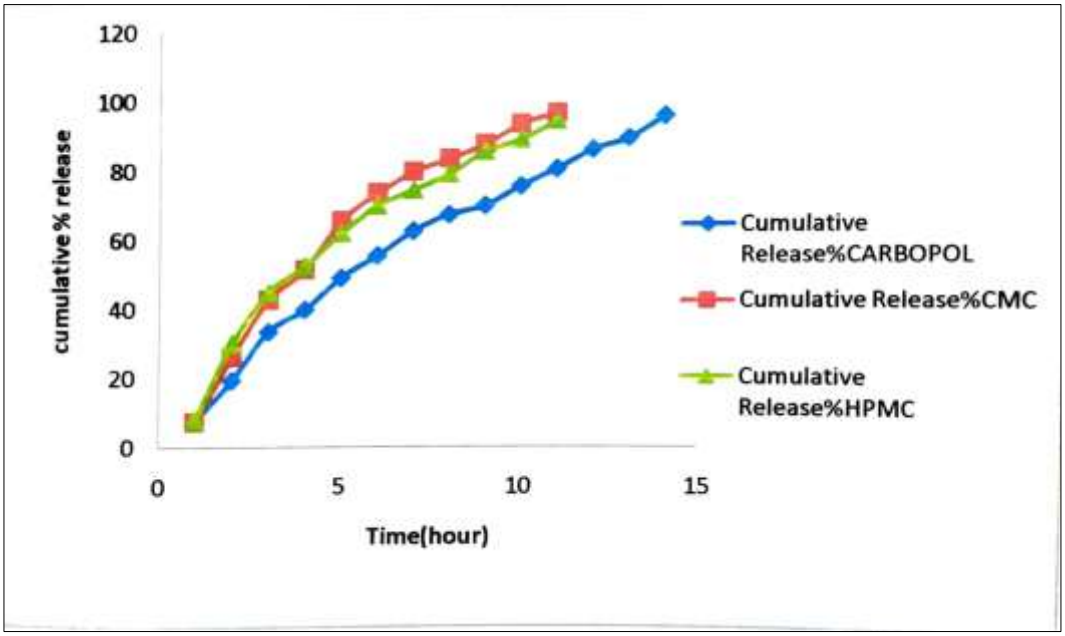
Table 6: Comparative Cumulative % Drug Release of F4 -F6 at pH 7.4 (9:1)

Time (hours)	F4: Alginate + Sodium CMC (%)	F5: Alginate + HPMC (%)	F6: Alginate + Carbopol (%)
1	7.51	8.2	7.56
2	26.29	30.28	19.56
3	42.99	45.32	33.68
4	51.87	53.02	40.19
5	66.15	62.62	49.5
6	74.32	70.74	56.03
7	80.58	75.28	63.23
8	84.44	80.12	68.1
9	88.69	86.59	70.76
10	94.64	90.17	76.52
11	97.77	95.68	81.5
12	-	-	87.15
13	-	-	90.47
14	-	-	96.89



The comparative graphs illustrate the *In Vitro* drug release profiles of glibenclamide from various mucoadhesive microsphere formulations. These graphs depict the cumulative percentage of drug released over time under different pH conditions (pH 1.2 and pH 7.4) and drug-to-polymer ratios (9:1 and 1:1).

All formulations generally exhibit extended-release behavior, meaning the drug is released gradually over an extended period rather than all at once. For instance, in 0.1 N HCl (pH 1.2), release extends up to 10 hours for the 9:1 ratio, and in phosphate buffer (pH 7.4), it extends up to 15 hours for the 9:1 ratio. Similarly, for the 1:1 ratio, release continues for 5 hours at pH 1.2 and 8 hours at pH 7.4.

The release profiles show sensitivity to pH. For example, formulations tested in phosphate buffer (pH 7.4) generally exhibit more sustained release over a longer duration than those tested in 0.1 N HCl (pH 1.2) at the same drug-to-polymer ratio. This suggests that the polymers used (CARBOPOL, HPMC, CMC) may swell or erode differently at different pH levels, thereby affecting drug diffusion.

Different polymers (CARBOPOL, HPMC, CMC) show distinct release characteristics. While all provide sustained release, their individual curves suggest variations in release rates, indicating the impact of polymer properties on drug diffusion and matrix integrity.

Comparing the 9:1 and 1:1 ratios, it's evident that the drug-to-polymer ratio influences the release duration and rate. Higher polymer content (lower drug-to-polymer ratio, e.g., 1:1) often leads to prolonged release due to a denser matrix or a longer diffusion path length. Conversely, a higher drug load (e.g., 9:1) might lead to faster initial release if the drug is less entrapped.

Overall, the comparative study highlights the significant influence of both the polymer type and the drug-to-polymer ratio on the release kinetics of glibenclamide microspheres. CARBOPOL consistently provided a more sustained release profile across both acidic and neutral pH conditions, likely due to its pH-dependent swelling properties, which are more pronounced at higher pH but still provide a barrier at lower pH. HPMC and SODIUMCMC/CMC generally exhibited faster release rates, which could be attributed to their different hydration and erosion characteristics. Furthermore, a higher polymer content

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(9:1 drug-to-polymer ratio) consistently resulted in more sustained drug release than a lower polymer content (1:1 ratio), demonstrating a direct correlation between polymer matrix integrity and drug diffusion control. These findings are critical for tailoring glibenclamide microsphere formulations to achieve specific release kinetics for optimal.

A sustained release pattern, as observed in these graphs, is generally highly suitable for mucoadhesive microspheres. Mucoadhesion aims to prolong the residence time of a drug delivery system at a specific mucosal site (e.g., gastrointestinal tract, nasal cavity, buccal cavity). By adhering to the mucosa, the microspheres can maintain a local drug concentration for an extended period, which is precisely what sustained-release formulations aim to achieve. This prolonged contact and gradual drug release can lead to enhanced bioavailability by extending the time the drug is available for absorption at the mucosal surface, reducing dosing frequency, which may allow patients to take the medication less often, improving compliance, and targeted delivery by maintaining drug levels at the site of adhesion, potentially reducing systemic side effects. The observed pH-dependent release could also be advantageous, particularly for oral delivery, where microspheres might need to withstand the acidic environment of the stomach (pH 1.2) and then release the drug more effectively in the less acidic intestinal environment (pH 7.4). The ability to control release via polymer type and ratio further enhances suitability, enabling customization of release profiles to match therapeutic needs.

In summary, the sustained and modulated drug release profiles shown in the graphs are highly desirable characteristics for mucoadhesive microspheres, as they align with the primary goals of mucoadhesive drug delivery: prolonged local action and improved therapeutic outcomes.

3.5 5.4 *In Vitro* Mucoadhesive Properties

The formulated microspheres demonstrated excellent mucoadhesive properties, indicating their suitability for prolonged residence time at the site of absorption. The mucoadhesive properties of the microcapsules were evaluated using an *In Vitro* wash-off test on freshly excised goat intestinal mucosa. The results indicated that the microspheres containing sodium alginate and a mucoadhesive polymer exhibited good mucoadhesive properties.

The environmental pH played a significant role in adhesion. The wash-off was observed to be faster at intestinal pH (7.4) than at gastric pH (1.2). Formulations F3 and F6—both containing Carbopol—demonstrated particularly good mucoadhesive properties.

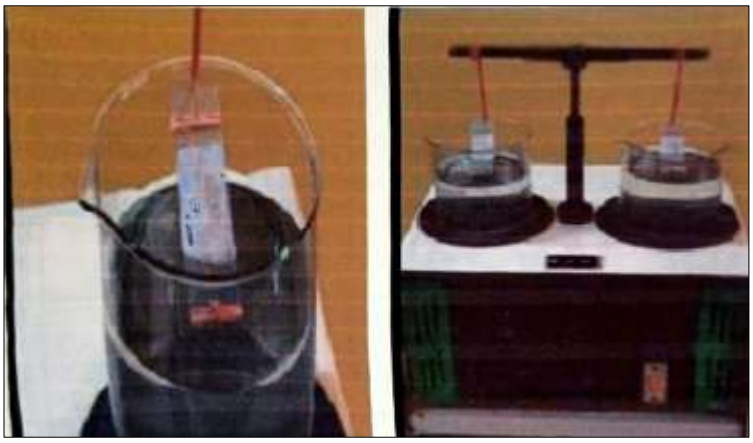

Fig 4: Mucoadhesive Testing.

This table details the percentage of microspheres remaining adhered to goat intestinal tissue over time in a simulated gastric fluid (0.1N HCl).

Table 7: *In Vitro* Wash-Off Test for Mucoadhesion (pH 1.2)

Time (Hours)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
1	71.66±1.52	83.33 ± 1.52	80.00 ± 1.58	74.33 ± 2.08	77.66 ± 1.53	82.33 ± 2.05
2	68.66 ± 3.21	79.33 ± 1.52	76.66 ± 1.15	70.66 ± 2.08	67.33 ± 1.53	69.66 ± 2.08
4	64.00 ± 1.00	74.33 ± 0.57	74.00 ± 1.00	56.33 ± 1.53	59.00 ± 1.00	60.00 ± 1.00
6	54.33 ± 2.08	68.00 ± 2.00	71.33 ± 1.53	36.00 ± 3.46	36.33 ± 1.53	33.00 ± 2.00
8	48.66 ± 1.54	62.00 ± 2.64	66.66 ± 1.53	18.33 ± 1.15	22.66 ± 1.53	18.33 ± 0.58

This table details the percentage of microspheres remaining adhered to tissue over time in simulated intestinal fluid (Phosphate Buffer).

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Table 8: *In Vitro* Wash-Off Test for Mucoadhesion (pH 7.4)

Time (Hours)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
1	62.66±2.08	66.66±1.52	69.00±1.73	71.00±1.00	68.33±3.05	70.00±2.00
2	54.66±1.52	63.00±1.00	61.66±3.51	55.33±1.52	61.00±3.00	54.33±1.527
4	22.33±1.52	19.33±1.15	25.33±3.05	21.66±1.527	35.00±1.00	30.33±1.527
6	12.33±2.08	11.66±2.52	19.66±1.27	1.66±2.08	17.33±1.527	8.33±3.51
8	3.66±3.214	6.66±0.57	10.00±1.00	-	6.00±3.00	2.66±3.055

The pH-dependent mucoadhesive behaviour indicates that the polymeric carriers maintain a stronger interaction with the mucosal tissue in acidic environments. The sustained adhesion of F2 and F6 formulations at pH 1.2 demonstrates superior mucoadhesive properties, which can extend residence time and enhance drug absorption in the gastrointestinal tract. The reduced adhesion at pH 7.4 may be attributed to changes in polymer ionization and loss of electrostatic interactions between the negatively charged polymers and the mucosal surface.

5. Conclusion

This research study successfully demonstrated the development and evaluation of mucoadhesive microspheres for the delivery of Glibenclamide. The formulations exhibited morphological characteristics suitable for pharmaceutical applications, with discrete spherical particles and good size uniformity achieved through the orifice-ionic gelation method.

Drug entrapment efficiency values ranging from 80-90% 15 confirmed the effectiveness of the encapsulation process. The *In Vitro* release studies clearly demonstrated that microspheres provided prolonged release, resulting in predictable drug availability. The polymer compositions significantly influenced release rates, with sodium alginate:carbopol combinations providing superior sustained-release profiles.

Importantly, the mucoadhesive microspheres of Glibenclamide proved suitable for oral extended-release delivery, offering significant advantages by reducing dosing frequency, improving patient compliance, and maintaining stable plasma drug levels. The successful development of these formulations provides a promising approach to improving the therapeutic efficacy of Glibenclamide in diabetes management.

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