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Formulation and Evaluation of Mucoadhesive Microspheres Loaded with Antidiabetic Agents

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Abstract

Mucoadhesive microspheres have emerged as a promising drug delivery system for enhancing the bioavailability and therapeutic efficacy of antidiabetic agents. This study focuses on the formulation and evaluation of mucoadhesive microspheres loaded with antidiabetic drugs to achieve controlled and sustained drug release. The microspheres were prepared using the solvent evaporation technique with biocompatible polymers such as chitosan and polycarbophil, which provide enhanced mucoadhesion and prolonged gastrointestinal retention. Various physicochemical parameters, including flow properties, particle size, drug entrapment efficiency, swelling behavior, and mucoadhesive strength, were assessed to determine the suitability of the formulations. Scanning Electron Microscopy (SEM) confirmed the spherical shape and smooth surface morphology of the microspheres, contributing to their controlled-release profile. The in vitro drug release studies revealed a sustained release pattern over six hours, with formulation F6 exhibiting the highest drug release (56%) and superior mucoadhesive strength (84.11%). The swelling studies indicated significant expansion of the microspheres in pH 6.8 phosphate buffer, enhancing drug retention at the absorption site. The results demonstrate that the formulated microspheres offer a potential drug delivery approach for improving the bioavailability and therapeutic effectiveness of antidiabetic agents. Further in vivo studies are required to confirm their pharmacokinetic and pharmacodynamic performance for clinical application in diabetes management.

Keywords: Mucoadhesive microspheres, antidiabetic agents, controlled release, drug entrapment efficiency, polymer-based delivery, gastrointestinal retention.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to insufficient insulin production or impaired insulin utilization. The prevalence of diabetes has increased globally, making it a major public health concern. Conventional oral hypoglycemic agents often suffer from limitations such as poor bioavailability, rapid drug elimination, and frequent dosing, leading to poor patient compliance. To address these challenges, novel drug delivery systems, such as mucoadhesive microspheres, have gained significant attention. Mucoadhesive microspheres are designed to adhere to the mucosal surfaces of the gastrointestinal tract, prolonging drug residence time and enhancing absorption. This approach not only improves drug bioavailability but also reduces dosing frequency, thereby enhancing therapeutic efficacy and patient adherence. The development of mucoadhesive drug delivery systems is particularly beneficial for antidiabetic agents, as it ensures controlled and sustained drug release, minimizing fluctuations in blood glucose levels. The formulation of mucoadhesive microspheres involves techniques such as ionic gelation, solvent evaporation, and spray drying, which help in encapsulating antidiabetic agents within biocompatible polymers. These polymers, including chitosan, alginate, and carbopol, exhibit excellent mucoadhesive properties, ensuring prolonged contact with the intestinal mucosa. Characterization of these microspheres is crucial to assess parameters such as particle size, surface morphology, encapsulation efficiency, swelling behavior, and in vitro drug release. The effectiveness of mucoadhesive microspheres is further evaluated through in vivo studies to determine their pharmacokinetic and pharmacodynamic profiles. This research aims to optimize the formulation of mucoadhesive microspheres loaded with antidiabetic agents, ensuring a sustained and effective drug delivery system. By overcoming the limitations of conventional therapy, mucoadhesive microspheres have the potential to improve glycemic control and enhance the quality of life for diabetic patients.

Literature Survey

Livet et al (2021) The effects of alogliptin and imigliptin on diabetes and beta-cell function were studied in Chinese patients with type 2 diabetes. Over a 13-day period, 37 participants were administered either 25 mg of imigliptin, 50 mg of imigliptin, a placebo, or 25 mg of alogliptin (as a positive control). Oral glucose tolerance tests were conducted at both the beginning and the end of the study, utilizing the oral minimal model (OMM) for analysis. Both imigliptin and alogliptin were associated with improved beta-cell function, as indicated by

enhanced jess and jot metrics. Additionally, reductions in glucose area under the curve (AUC) and postprandial glucose levels were observed. The AUC for the glucose appearance rate between 0 and 120 minutes also showed a decline in the imigliptin and alogliptin groups. However, fasting glucose-based insulin resistance remained unchanged. The transplantation index's secretory units of islets (SUIT) and homeostatic model assessment parameters (HOMA-b and HOMA-IR) exhibited minimal significant differences between or within treatment groups. After 13 days of treatment, both alogliptin and imigliptin demonstrated potential in reducing hyperglycemia by enhancing beta-cell function. Notably, glucose stimulation proved to be a more sensitive indicator of beta-cell activity changes compared to HOMA or SUIT measurements.

Mishra et al., (2021) Using the emulsification solvent evaporation method, amethopterin-loaded floating microspheres were developed using ethyl cellulose, polyvinyl alcohol, and polyvinyl pyrrolidone-K90. These microspheres were evaluated for various properties, including surface morphology (SEM), flow characteristics, flexibility, yield, drug loading efficiency, in vitro dissolution, pH stability, and FTIR analysis. The microspheres exhibited smooth, spherical shapes with sizes ranging from 256.02 to 362.84 µm, depending on polymer concentration. Among the formulations, F2 showed optimal drug entrapment and buoyancy, with in vitro drug release ranging from 58.15% to 96.28% after six hours. The newly formulated floating microspheres of amethopterin proved to be a viable approach for prolonging drug release, enhancing oral bioavailability, improving therapeutic efficacy, and ensuring better patient compliance.

Prajapati et al., (2021) Baclofen floating microspheres were developed and evaluated to enhance gastric retention, as Baclofen primarily acts in the upper gastrointestinal tract. The microspheres were formed through liquid evaporation, and a factorial design (Y5) was used to assess the impact of two variables on multiple factors, including particle size (Y1), percent drug loading (Y2), total buoyancy percentage (Y3), in-vitro oral bioavailability at one hour (Y4), and in-vitro drug release at six hours (Y5). Multiple linear regression analysis revealed that higher concentrations of Eudragit RL100 and Eudragit RS100 increased particle size, cumulative drug-controlled release, and floating percentage while reducing the in-vitro therapeutic effect. The optimized formulation demonstrated 90.76% buoyancy, 90.06% drug entrapment, and a particle size of 115.96 µm, ensuring sustained drug release over 24 hours.

Gupta et al., (2020) Nizatidine, an H2-receptor antagonist used for treating stomach and intestinal ulcers, was formulated using a floating drug delivery strategy to prolong its gastrointestinal retention. Researchers employed the flush distribution disappearance technique with HPMC and MCC polymers to enhance its therapeutic efficacy. Various evaluations, including antibacterial properties, yield, encapsulation efficiency, floating behavior, particle geometry, specific surface area, in vitro dispersion duration, particle density, and electrochemical impedance testing, were conducted. The optimized formulation (F4) had a suspended microsphere size of 178.5 nm, a zeta potential of -33.6 mV, and percent recovery ranging from 75.65% to 82.3%. Encapsulation efficiency varied between 65.56% and 75.65% w/w, while surface morphology was examined under different magnifications. The highest correlation coefficient (r = 0.969) in zero-order kinetics indicated that drug release followed a non-Fickian dispersion mechanism, ensuring prolonged release. The formulation exhibited superior bactericidal effectiveness, with clear solutions free from turbidity, demonstrating better infection control compared to conventional treatments at similar doses. As a gastro-retentive (GR) dosage form, Nizatidine floating microspheres play a crucial role in optimizing drug release at targeted sites, significantly improving therapeutic outcomes.

Tiwari et al., (2019) Famotidine, a histaminic drug widely used for treating stomach and intestinal ulcers, Zollinger-Ellison syndrome, and reflux esophagitis, works by reducing swelling and constricting blood vessels in the gastrointestinal tract, aiding in gastritis treatment. Floating microspheres, a gastro-retentive drug delivery system, were developed to prolong gastric retention, ensuring faster absorption and action due to rapid dissolution. These free-flowing granules allow for sustained drug release as they remain in the stomach while saliva aids absorption through the mouth, throat, and esophagus, potentially enhancing bioavailability compared to conventional dosage forms. Various formulations using different ratios of sodium alginate and ethyl cellulose were designed to maintain a consistent release profile over 24 hours. Each formulation was evaluated for in-vitro floating behavior, drug entrapment efficiency, and drug release properties. Results indicated over 70% buoyancy after 24 hours, with microsphere sizes ranging from 102.33 to 420.53 µm. The H1 formulation was identified as the most effective, achieving a continuous and consistent famotidine HCl release of 98.84% over 24 hours.

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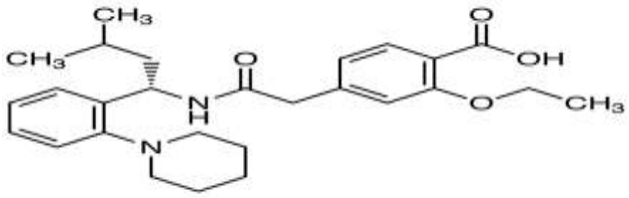
DRUG PROFILE

Repaglinide

IUPAC Name

(S)-2-Ethoxy-4-(1-[2-{piperidin-1-yl}phenyl]-3-methylbutylcarbamoylmethyl)benzoic acid

Chemical structure



Molecular Formula: - C27H36N2O4

Molecular Weight: - 452.6 g/mol

Solubility: - 67.9 [ug/mL] (The mean of the results at pH 7.4)

Description: - Repaglinide is a member of piperidines.

Repaglinide, an oral antihyperglycemic drug, is used to manage non-insulin-dependent diabetes mellitus (NIDDM). As a short-acting insulin secretagogue from the meglitinide class, it binds to pancreatic cells to enhance insulin release, helping to reduce postprandial blood glucose levels by triggering an early insulin response to meals. It should only be taken with meals, and any missed doses should be skipped if a meal is not consumed. A noticeable reduction in fasting blood glucose levels typically requires a month of treatment. Meglitinides may lead to slight weight gain or have no significant effect, with new users of oral diabetes medications experiencing mild weight gain, which is generally lower than that caused by sulfonylureas and insulin. The risk of hypoglycemia is lower with meglitinides compared to sulfonylureas, as their action is glucose-dependent. They effectively reduce glycosylated hemoglobin (HbA1c) levels, reflecting glucose control over the past 8 to 10 weeks, and are more efficient in lowering postprandial blood glucose than metformin, sulfonylureas, and thiazolidinediones. Repaglinide undergoes extensive hepatic metabolism before being excreted in the bile, with its metabolites having no significant hypoglycemic activity. Approximately 90% of a single oral dose is eliminated through feces, while around 8% is excreted via urine.

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Mechanism of action

Repaglinide lowers blood glucose levels by stimulating insulin release from pancreatic beta islet cells. It accomplishes this by inhibiting ATP-dependent potassium channels in the membrane of beta cells. By depolarizing the beta cells and activating their calcium channels, the resulting calcium influx stimulates insulin synthesis.

Uses

- Repaglinide is a drug used in the treatment of diabetes mellitus type 2.
- It belongs to a class of antihyperglycemic agents known as meglitinides, along with nateglinide.
- Meglitinides work to reduce blood glucose levels by stimulating endogenous insulin production.

Adverse effects

Common adverse events include:

Metabolic

- Hypoglycemia (31%)

Respiratory

- Upper respiratory infection (16%)
- Sinusitis (6%)
- Rhinitis (3%)

Gastrointestinal

- Nausea (5%)
- Diarrhea (5%)
- Constipation (3%)
- Vomiting (3%)

Musculoskeletal

- Arthralgia (6%)
- Back Pain (5%)

Other

- Headache (11%)
- Paresthesia (3%)

Contraindications

Repaglinide is contraindicated in people with:

- Diabetic ketoacidosis, with or without coma
- Type 1 diabetes
- Co-administration with gemfibrozil
- Known hypersensitivity to drug or inactive ingredients

Drug interactions

Repaglinide is a significant substrate of the CYP3A4 enzyme, requiring caution when used alongside certain medications such as gemfibrozil, clarithromycin, or azole antifungals like itraconazole and ketoconazole. Co-administration with these drugs can elevate repaglinide plasma levels, increasing the risk of hypoglycemia. Another critical interaction occurs with clopidogrel, a CYP2C8 inhibitor, which can significantly lower blood glucose due to drug-drug interactions. Even a single day of concurrent use can lead to a substantial rise in repaglinide levels and an increased risk of hypoglycemia. Additionally, since repaglinide and sulfonylureas share a similar mechanism of action in lowering blood glucose, their combination is generally not recommended due to the heightened risk of hypoglycaemias. To prevent potentially harmful interactions, careful medication management and consultation with a healthcare provider are essential for individuals with diabetes.

Special populations

Pregnancy category C: Pregnant women are unknown for their safety. There is only one case report that notes no issues with repaglinide use during pregnancy, and there is a dearth of data. Caution should be taken in people with liver disease and decreased kidney function when using this medication.

MATERIALS AND METHODS

Torrent Pharmaceutical Ltd. in Gujarat, India provided a free sample of repaglinide. Dichloromethane, light liquid paraffin, Tween 80, and Span 80 were provided as gifts by Research Laboratories in Hyderabad, India.

PREFORMULATION STUDIES

The preformulation studies are the first step in the rational development of any formulation. "Investigation of the physical and chemical properties of the drug substance alone and combined with the excipients" is one way to put it.

The primary aim of preformulation testing is to provide the formulator with valuable data for the development of dosage forms that are both stable and bioavailable, suitable for large-scale production. The specific objectives of this study include:

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1. To establish physical characteristics.
2. Ascertaining its compatibility with the excipients.
3. Determine the kinetic rate profile.

1.Preparation of Mucoadhesive Microspheres

The mucoadhesive microspheres were created utilizing a double-emulsion process with oil, water, and oil (O/W/O). The first emulsion, 50.0 g of aqueous polymer solution, was made with repaglinide diluted in dichloromethane. The quantity and concentrations used are summarized in Table 1.

To help with the emulsification process, Tween 80 (0.15 mL) was added. Using a Silverson homogenizer, the emulsions were immediately blended for fifteen minutes. The first emulsion (25 ml) was applied dropwise to 250 ml of light liquid paraffin containing 1% Span 80. The resulting double emulsion was agitated at 800 rpm. To enhance water evaporation, the samples were heated to between 60 and 70 degrees Celsius. The solid polymer microspheres were then centrifuged to remove the oil, washed with hexane, and dried in a vacuum oven for twenty-four hours at 40oC.

Results And Discussion

1.Method

Table 01: Composition of formulations

Formulation code	Repaglinide (g)	Dichloromethane	Span 80(%)	Liquid Paraffin(ml)	Hexane (ml)
F1	0.500	10	1	250	50
F2	0.500	10	1	250	50
F3	0.500	10	1	250	50
F4	0.500	10	1	250	50
F5	0.500	10	1	250	50
F6	0.500	10	1	250	50

2.Particle size

The table presents six distinct formulations (F1 to F6) developed for the preparation of repaglinide, a medication used in the treatment of type 2 diabetes. Each formulation maintains a consistent repaglinide concentration, with 0.500 grams of the active ingredient. Additionally, all formulations include 10 ml of dichloromethane, a commonly used pharmaceutical solvent,

along with 1% Span 80, a surfactant and emulsifier. Liquid paraffin, an essential pharmaceutical excipient, is present in a volume of 250 ml across all formulations, while hexane, another widely used solvent in pharmaceutical preparations, is included at 50 ml.

These formulations are likely designed for pharmaceutical research and development, where researchers explore varying combinations of solvents, surfactants, and excipients to optimize repaglinide's formulation. The consistency in drug concentration while adjusting other components suggests an investigative approach aimed at enhancing the medication's efficacy, stability, or other desirable characteristics. These formulations may undergo further testing and analysis to assess their suitability for pharmaceutical applications in diabetes management.

Table:02 Results of particle size analysis of all formulations (Mean ± SD, n=3)

Formulation Code	Volume Mean diameter (um)
F1	95.73±0.75
F2	98.13±0.65
F3	103.02±0.77
F4	82.13±0.33
F5	88.20±0.57
F6	97.13±0.65

An essential finding was that to achieve a stable emulsion, a minimum concentration of 1% Span 80 was necessary.

Furthermore, it is important to mention that the emulsification was performed with a stirring speed that affected the average particle size of the microspheres. For example, below 800 rpm like speed, the microspheres tended to grow in diameter and agglomeration of particles resulted in bigger and more clustered particles. On the other hand, if the stirring speed was over 800 rpm, there were smaller and uniform particles in the microspheres.

3.Flow Properties

To evaluate the flow properties of the formulated microspheres, several parameters were analyzed, including the angle of repose, bulk density, Hausner's ratio, and Carr's index. These parameters provide insights into the powder's flow characteristics, with acceptable values typically falling within specific ranges: the angle of repose should be between 20°58' and 21°51', Carr's index should be below 20, and Hausner's ratio should range from 1.31 to 2.22. As presented in Table 3, all formulations demonstrated values for the angle of repose, Carr's

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index, and Hausner's ratio within these acceptable limits. Notably, formulations F1 to F6 exhibited angle of repose values within the desired range, confirming their favorable flow properties.

Table:03 Micromeritics properties of all formulations (Mean ± SD, n=3)

Formulation Code	Angle of repose (°)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner's Index
F1	20.58±1.10	0.5545±0.02	0.6822±0.03	22.92±1.53	1.31±0.41
F2	18.54±0.34	0.5358±0.02	0.5821±0.03	21.42±3.12	1.41±0.31
F3	19.88±0.26	0.5434±0.03	0.6352±0.03	20.88±0.95	1.36±0.37
F4	20.43±0.34	0.5655±0.01	0.6893±0.03	20.43±2.21	2.21±0.21
F5	21.11±0.53	0.4957±0.02	0.5317±0.04	21.44±1.12	2.27±0.12
F6	21.51±0.85	0.4823±0.03	0.5136±0.03	21.57±1.14	2.22±0.23

4.Encapsulation efficiency

Since inadequate drug loading can make this method economically unfeasible, achieving high drug entrapment efficiency in microspheres prepared via the solvent evaporation method is crucial. As shown in Table 5, the entrapment efficiency for various formulations ranged from 78.9% to 92.7%. Lower entrapment efficiency may be attributed to the drug's solubility in the solvent, potentially leading to its migration into the processing medium during the dichloromethane extraction and evaporation process.

Table 04. Drug entrapment efficiency of microparticles

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Formulation	Theoretical content (mg)	Actual content (mg)	Percentage Drug entrapment efficiency
F1	10	9.24	92.5
F2	10	8.43	83.5
F3	10	9.05	90.6
F4	10	8.15	81.4
F5	10	8.17	88.5
F6	10	7.82	75.4

5. Swelling index

A highly effective strategy for achieving gastro retention is the development of an in-situ expanding or swelling system. The figure illustrates the swelling percentage observed in the microspheres, revealing that all batches exhibited rapid swelling upon exposure to pH 6.8 phosphate buffer. This pronounced swelling behavior can be attributed to the high molecular weight of polycarbophil and its ability to ionize, which enables the polymer to unfold and expand significantly. Notably, formulation F1 demonstrated a remarkable swelling capacity, reaching 294%.

6. Muco-adhesion

The microspheres demonstrated significant mucoadhesive properties, effectively adhering to the intestinal mucosa, as reflected in the results. Additionally, variations in the polymer-to-drug ratio were found to directly influence the degree of mucoadhesion. Among the formulations, F6 exhibited the highest and most sustained mucoadhesion, achieving an impressive 84.11%, as shown in Table 6.

Table 5. Percentage muco-adhesion of microspheres

Formulation No	Percentage of muco-adhesion
F1	74.32
F2	77.45
F3	79.21
F4	80.43
F5	81.32
F6	82.45

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7.Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) is a highly advanced imaging technique used across various scientific disciplines to analyze the surface morphology and topography of specimens with exceptional resolution. Unlike optical microscopes, SEM employs a focused electron beam to interact with the specimen's surface, generating highly detailed images.

In SEM operation, an electron gun emits a beam of high-energy electrons that systematically scans the specimen's surface. Upon interaction, multiple processes occur, including secondary electron emission, backscattered electron generation, and specimen excitation. These interactions are detected and converted into signals, producing detailed, high-contrast images. SEM offers numerous advantages, such as a high depth of field, superior resolution at the nanometer to sub-nanometer scale, and the capability to analyze non-conductive and complex specimens. Due to its versatility, SEM is widely utilized in materials science, biology, geology, and nanotechnology for research, quality control, and failure analysis. Its ability to provide in-depth insights into the microstructure of materials makes it an essential tool in modern scientific exploration.

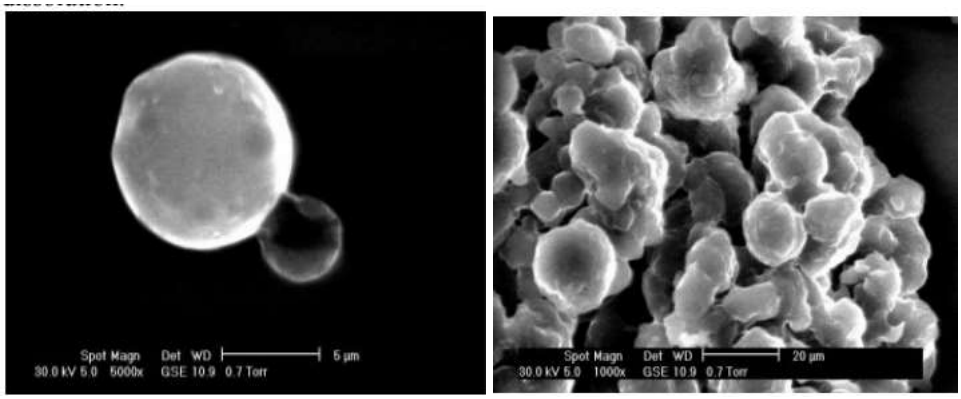

Figure1. SEM photographs of microspheres

8. Dissolution rate

Time (hr)	Cumulative Percent drug release					
	F1	F2	F3	F4	F5	F6
0.5	12±1.8	13±2.2	22±2.0	32±2.0	36±2.1	45±2.1
1	13±1.6	20±2.6	24±1.6	38±2.2	36±1.6	46±1.6
2	13±1.4	22±2.5	26±2.7	38±2.4	39±1.9	48±1.2

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3	16±1.1	22±3.2	27±3.6	42±2.2	39±2.3	48±2.2
4	16±1.6	23±4.2	34±4.8	44±1.5	41±3.2	51±1.6
5	17±1.1	23±4.6	38±4.1	45±2.4	42±3.8	52±3.2
6	18±1.5	24±1.4	42±3.2	48±2.2	47±2.5	56±2.2

The cumulative drug release profiles of formulations F1 to F6 were evaluated over a period of six hours, as presented in the data. The results indicate a progressive increase in drug release across all formulations, with variations depending on the composition. At the 0.5-hour mark, drug release ranged from 12% (F1) to 45% (F6), highlighting the differences in initial burst release. Among the formulations, F6 consistently demonstrated the highest drug release, reaching 56% at the six-hour mark, suggesting a more rapid and sustained release pattern. In contrast, F1 exhibited the slowest drug release, increasing gradually from 12% to 18% over the study duration. The intermediate formulations (F2 to F5) showed moderate drug release trends, with F3 and F4 exhibiting relatively higher release rates compared to F1 and F2. The variations observed in drug release profiles can be attributed to differences in polymer composition, drug-to-polymer ratio, and the mucoadhesive nature of the microspheres, which influence the diffusion and erosion mechanisms controlling drug release. Formulations with higher polymer content likely exhibited extended drug release due to increased matrix density and reduced porosity, leading to slower drug diffusion. The steady increase in drug release over time suggests a controlled-release mechanism, which is crucial for maintaining therapeutic drug levels while minimizing fluctuations. These findings emphasize the potential of mucoadhesive microspheres for sustained drug delivery, ensuring prolonged drug availability and improved bioavailability for antidiabetic therapy.

Conclusion

The formulation and evaluation of mucoadhesive microspheres loaded with antidiabetic agents demonstrated their potential as an effective controlled drug delivery system. The study confirmed that the prepared microspheres exhibited favorable physicochemical properties, including good flow characteristics, high drug entrapment efficiency, and strong mucoadhesive strength. The optimized formulations showed sustained drug release, with variations influenced by polymer composition and drug-to-polymer ratios. The swelling studies indicated that the microspheres expanded significantly in a pH 6.8 phosphate buffer, enhancing drug retention and absorption. Scanning Electron Microscopy (SEM) analysis revealed a uniform surface

morphology, contributing to improved drug release and mucoadhesion. The release kinetics suggested that the microspheres followed a controlled diffusion mechanism, ensuring prolonged therapeutic effects. Among all formulations, F6 exhibited the highest drug release and mucoadhesive strength, making it the most promising candidate for further development. The ability of these microspheres to adhere to the intestinal mucosa prolongs drug residence time, potentially improving bioavailability and reducing dosing frequency, thereby enhancing patient compliance. Overall, the study highlights the potential of mucoadhesive microspheres as an advanced drug delivery system for antidiabetic agents, offering a sustained and effective treatment approach. Further in vivo studies and clinical evaluations are required to validate their efficacy and optimize the formulation for commercial application in diabetes management.

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