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FORMULATION, CHARACTERIZATION AND EVALUATION OF REPAGLINIDE MUCOADHESIVE MICROSPHERES

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ABSTRACT

Aim: To formulate gastro-retentive mucoadhesive microspheres of Repaglinide to achieve controlled drug release and enhanced oral bioavailability. **Objective:** To prepare microspheres using sodium alginate with xanthan gum and guar gum via ionic gelation. To evaluate physicochemical properties, drug entrapment, swelling, release profile, and stability. **Materials and Methods:** Repaglinide, sodium alginate, xanthan gum, and guar gum were used. Calcium chloride acted as a crosslinking agent. Six formulations were prepared with varying drug-to-polymer ratios. **Preparation Methods:** Microspheres were prepared using the ionic gelation technique. The drug-polymer dispersion was dropped into calcium chloride solution under stirring, forming spherical microspheres, which were filtered, washed, and dried. **Evaluation Methods:** Microspheres were assessed for percentage yield, entrapment efficiency, particle size, swelling index, and in-vitro drug release in simulated gastric fluid. Stability studies were performed on selected formulations. **Results and Discussion:** Percentage yield ranged from 78.65 % ± 0.55% to 88.18 % ± 0.51%, while entrapment efficiency was 81.20 ± 0.60% to 95.60 ± 0.48%. Particle size increased with polymer concentration (130.6 ± 4.5µm to 320.5 ± 4.2µm). Swelling index varied from 48.12 ± 0.003% to 62.41 ± 0.06%. In-vitro studies showed a sustained release pattern; formulation XAG-III achieved 98.96±0.16% and GAG-III 96.40±0.22% release due to higher polymer content. Stability results indicated no significant changes. **Conclusion:** The prepared mucoadhesive microspheres displayed

satisfactory physicochemical and release characteristics, with potential for controlled delivery of Repaglinide in type 2 diabetes management.

INTRODUCTION

Oral controlled release drug delivery systems offer significant therapeutic advantages by maintaining consistent drug levels in plasma and improving patient compliance. However, they face several physiological challenges, particularly due to the limited gastric residence time, typically averaging 2–3 hours. This brief stay in the gastrointestinal tract (GIT)—especially within the stomach and proximal intestine, where drug absorption is most efficient—can cause incomplete drug release and lower bioavailability. Therefore, designing a controlled release system that sustains drug release at a rate sufficient to maintain a therapeutic drug level is crucial. Microsphere-based novel drug delivery systems have gained attention for enhancing controlled and targeted drug delivery by encapsulating the drug within biocompatible polymers. However, their clinical usefulness is often limited by a short residence time at the site of absorption. To overcome this challenge, Bio adhesive Drug Delivery Systems (BDDS) have been developed. BDDS utilize mucoadhesive polymers that form a close association with the gastric or intestinal mucosa, extending the formulation's residence time at the absorption site and thereby improving bioavailability. When combined with microsphere technology, mucoadhesive systems can provide localized drug delivery, minimize side effects, enable dose reduction, and achieve sustained therapeutic effects. Repaglinide is an oral antihyperglycemic agent from the meglitinide analogue class and is used in the management of type 2 diabetes mellitus. It acts by stimulating insulin release from pancreatic β-cells and mimics the body's natural insulin release mechanism following meals. Repaglinide has a relatively short biological half-life of around 1 hour and is rapidly absorbed, reaching peak plasma concentrations within 1 hour of administration. However, its short half-life and rapid elimination necessitate frequent dosing to maintain optimal glycemic control, which can result in poor patient compliance and fluctuating blood glucose levels. To address these challenges, the present study aims to develop an oral controlled release system of Repaglinide using mucoadhesive microspheres prepared with natural polymers. This formulation is intended to enhance gastric retention, prolong the drug release, minimize dosing frequency, and maintain a more consistent blood glucose-lowering effect. Natural mucoadhesive gums are exploited in different concentrations to prepare microspheres that adhere to the mucosal lining of the stomach, thereby optimizing the residence time and improving the overall therapeutic efficacy of Repaglinide. The prepared microspheres will be

evaluated for their physicochemical properties, drug release behaviour, mucoadhesive strength, and potential for controlled delivery in managing type 2 diabetes.

MATERIALS AND METHODS

MATERIALS

Repaglinide, Sodium Alginate, Calcium Chloride, Guar Gum, Xanthan Gum were was purchased from reputed company. All other chemicals and reagents used in the study were of analytical grade and used as received.

METHODS

Preparation of Mucoadhesive Microspheres of Repaglinide

Mucoadhesive microspheres of Repaglinide were prepared using varying ratios of drug, sodium alginate, guar gum, and xanthan gum. Sodium alginate was first dissolved in deionized water to form a smooth homogeneous solution (2% w/v). Separately, guar gum and xanthan gum were dispersed in deionized water to form viscous, sticky polymeric solutions. Repaglinide was then uniformly dispersed into the prepared gum solution. This drug-polymer dispersion was gradually added to the sodium alginate solution with continuous vigorous stirring to obtain a uniform blend.

The resulting mixture was extruded dropwise into 100 mL of calcium chloride solution (10% w/v) through a 23G syringe. As the droplets came into contact with the calcium chloride solution, spherical microspheres were formed instantly via ionic gelation. These formed microspheres were allowed to remain in the calcium chloride solution for 15 minutes to ensure complete cross-linking and achieve rigidity.

Afterward, the microspheres were collected by decantation, thoroughly washed with deionized water to remove any residual calcium ions, and dried at room temperature. The dried microspheres were stored in a desiccator for further characterization.

In this study, six different formulations were developed using varying ratios of Repaglinide and natural polymers, as detailed in Table 1. These formulations were then evaluated for various physicochemical and functional properties.

Table 1: Composition of Repaglinide Mucoadhesive Microspheres.

Formulations Code	Repaglinide (mg)	Sodium Alginate (% w/v)	Guar Gum (% w/v)	Xanthan gum (% w/v)	Calcium Chloride (% w/v)
GAG1	100	2	0.25	-	10
GAG2	100	2	0.5	-	10
GAG3	100	2	0.75	-	10
XAG1	100	2	-	0.25	10
XAG2	100	2	-	0.5	10
XAG3	100	2	-	0.75	10

Characterization of Mucoadhesive Microspheres

Percentage Yield

The prepared Repaglinide-loaded mucoadhesive microspheres were collected, dried thoroughly at room temperature, and weighed accurately. The percentage yield was calculated by dividing the final weight of dried microspheres by the total weight of Repaglinide and all excipients (polymers and other ingredients) used in the formulation. The result was then multiplied by 100 to determine the percentage yield.

Characterization of Mucoadhesive Microspheres

Determination of Particle Size

The particle size of the prepared Repaglinide-loaded mucoadhesive microspheres was determined using optical microscopy (Phoenix Science, India). A small sample of microspheres was randomly selected and observed under the microscope. The average particle size was calculated by measuring at least 100 microspheres from each formulation.

Micromeritic Properties

The flow properties of the microspheres were assessed by evaluating their micromeritic characteristics, including:

- Bulk Density
- Tapped Density
- Carr’s Index
- Hausner’s Ratio
- Angle of Repose

These parameters help determine the compressibility and flow behavior of the microsphere formulations.

Entrapment Efficiency

The drug entrapment efficiency of the prepared microspheres was assessed by crushing a known quantity of dried microspheres and extracting Repaglinide using 0.1N HCl (pH 1.2). The extract was transferred to a 100 mL volumetric flask and made up to volume with the same medium. The solution was filtered and analyzed using a UV-Visible spectrophotometer at a wavelength of 244 nm (λmax of Repaglinide).

In-vitro Drug Release Studies

The in-vitro release of Repaglinide from the mucoadhesive microspheres was studied in acidic medium (0.1N HCl, pH 1.2) for 10 hours using USP Type II (paddle) dissolution apparatus. Accurately weighed samples of microspheres were introduced into 900 mL of dissolution medium maintained at 37 ± 0.5°C with a paddle speed of 100 rpm. Aliquots were withdrawn at regular intervals (e.g., every hour), and the same volume of fresh medium was replaced to maintain sink conditions. The samples were filtered, appropriately diluted, and analyzed spectrophotometrically at 244 nm to determine the amount of drug released over time.

To understand the mechanism of drug release, the release data was analyzed using various mathematical models (e.g., zero-order, first-order, Higuchi, and Korsmeyer–Peppas models).

Swelling Studies

To assess the swelling behaviour, a known quantity of dried microspheres from each batch was submerged in the dissolution medium (pH 1.2) for 10 hours. After swelling, the microspheres were gently blotted with filter paper to remove excess surface water and immediately weighed.

Table 2: Percentage yield, Particle size and drug entrapment of Repaglinide Mucoadhesive Microspheres.

Formulation Code	Percentage Yield (%)	Average Particle Size (µm)	Drug entrapment (%)
GAG1	78.65 % ± 0.55	181.1 ± 2.4	81.20 ± 0.60
GAG2	82.14 % ± 0.48	204.2 ± 3.1	84.35 ± 0.80
GAG3	85.72 % ± 0.62	221.2 ± 1.9	88.40 ± 0.75
XAG1	87.10 % ± 0.51	236.0 ± 2.6	91.25 ± 0.54
XAG2	88.18 % ± 0.51	320.5 ± 4.2	93.50 ± 0.65
XAG3	87.00 % ± 0.45	130.6 ± 4.5	95.60 ± 0.48

RESULTS AND DISCUSSION

Percentage Yield, Particle Size, and Drug Entrapment

As shown in Table 2, the percentage yield of Repaglinide mucoadhesive microspheres ranged from 78.65% to 88.18%. It was noted that an increase in polymer concentration slightly improved the yield, possibly due to enhanced viscosity and droplet formation efficiency during processing.

The mean particle size of the microspheres ranged between 130.6 µm to 494 µm, showing a trend of increasing particle size with increasing polymer content. This is attributed to the higher viscosity of the polymer solution, which leads to the formation of larger droplets during extrusion into calcium chloride solution.

The entrapment efficiency of the Repaglinide microspheres varied from 61.4% to 95.6%. Formulations containing a higher concentration of xanthan gum (1:0.75 drug to polymer ratio) showed the highest entrapment. This occurs due to the formation of a denser matrix that can better encapsulate the drug.

Micromeritic Properties

As summarized in Table 3, the bulk density and tapped density of the microspheres ranged from 0.543 to 0.636 g/cm³ and 0.577 to 0.733 g/cm³, respectively. The Carr's Index (5.82% to 12.32%) and Hausner's Ratio (0.869 to 0.949) values indicated excellent compressibility and flow characteristics. The angle of repose for all formulations was below 40°07', confirming acceptable powder flow behaviour, suitable for unit dosage formulation.

Table 3: Micromeritic Properties data of Repaglinide Mucoadhesive Microspheres.

Formulation Code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
GAG1	0.781 ± 0.054	0.434 ± 0.016	17.62 ± 1.98	40.58 ± 1.76	35°55' ± 0.85'
GAG2	0.776 ± 0.064	0.443 ± 0.023	17.82 ± 1.57	38.76 ± 1.76	33°56' ± 1.82'
GAG3	0.769 ± 0.034	0.418 ± 0.009	17.34 ± 1.45	45.43 ± 1.54	40°07' ± 0.53'
XAG1	0.748 ± 0.024	0.420 ± 0.006	18.34 ± 2.32	43.45 ± 1.54	38°46' ± 0.82'
XAG2	0.734 ± 0.023	0.425 ± 0.005	16.48 ± 2.12	42.4 ± 1.43	34°65' ± 0.59'
XAG3	0.748 ± 0.017	0.439 ± 0.01	17.32 ± 1.23	39.38 ± 1.52	32°21' ± 1.82'

Swelling Index (SI)

From Table 4, formulation GAG-I exhibited the lowest swelling percentage (48.12 ± 0.003%), while XAG-III exhibited the highest swelling (57.83 ± 0.03%) after 10 hours. The higher swelling of xanthan-based formulations is attributed to the stronger hydration

capability and porous structure of xanthan gum compared to guar gum. This indicates that polymer concentration and type influence the swelling behaviour and, consequently, the drug release dynamics.

Table 4: Swelling Index of Repaglinide Mucoadhesive Microspheres.

Formulation Code	Swelling Index (%)
GAG1	48.12 ± 0.003
GAG2	55.64 ± 0.05
GAG3	62.41 ± 0.06
XAG1	44.25 ± 0.04
XAG2	50.37 ± 0.02
XAG3	57.83 ± 0.03

In-vitro Drug Release Studies

In-vitro drug release studies were performed in simulated gastric fluid (pH 1.2) for 10 hours. The formulations XAG-III and GAG-III showed prolonged and controlled releases of 98.96% and 96.40% Repaglinide, respectively, by the end of the study (see Figure 3 & 4). Higher polymer concentrations led to slower drug release due to increased matrix density and decreased drug diffusion.

Drug Release Kinetics

The drug release data were analyzed using various kinetic models:

Zero-order: Best fit with correlation coefficients ® ranging from 0.9910 to 0.9964 for all formulations.

Higuchi model: r values indicated a good linear fit (0.9779 to 0.9843), confirming the matrix diffusion mechanism.

Korsmeyer–Peppas model: The diffusion exponent (n) ranged from 0.9763 to 0.9907, indicating Non-Fickian (anomalous) diffusion — a combination of swelling-controlled and diffusion-controlled release.

These observations suGAGest that drug release from Repaglinide-loaded mucoadhesive microspheres follows zero-order kinetics and is released via Non-Fickian diffusion, ensuring a prolonged and nearly constant release rate over time.

Table 5: Kinetic analysis data of Repaglinide Mucoadhesive Microspheres.

Formulation Code	Zero Order (R)	Zero Order (S)	First Order (R)	First Order (S)	Higuchi's (R)	Higuchi's (S)	Korsmeyer-Peppas (R)	Korsmeyer-Peppas (S)
GAG1	0.9964	13.529	0.9751	-0.19	0.9843	34.47	0.9852	0.8256
GAG2	0.9949	12.598	0.9624	-0.14	0.9824	33.67	0.9890	0.8287
GAG3	0.9957	9.8207	0.9778	-0.10	0.9801	27.07	0.9763	0.8475
XAG1	0.9910	13.82	0.9788	-0.16	0.9832	33.60	0.9885	0.8309
XAG2	0.9953	11.99	0.9517	-0.13	0.9847	32.26	0.9907	0.8576
XAG3	0.9912	10.04	0.9702	-0.10	0.9779	28.44	0.9907	0.8105

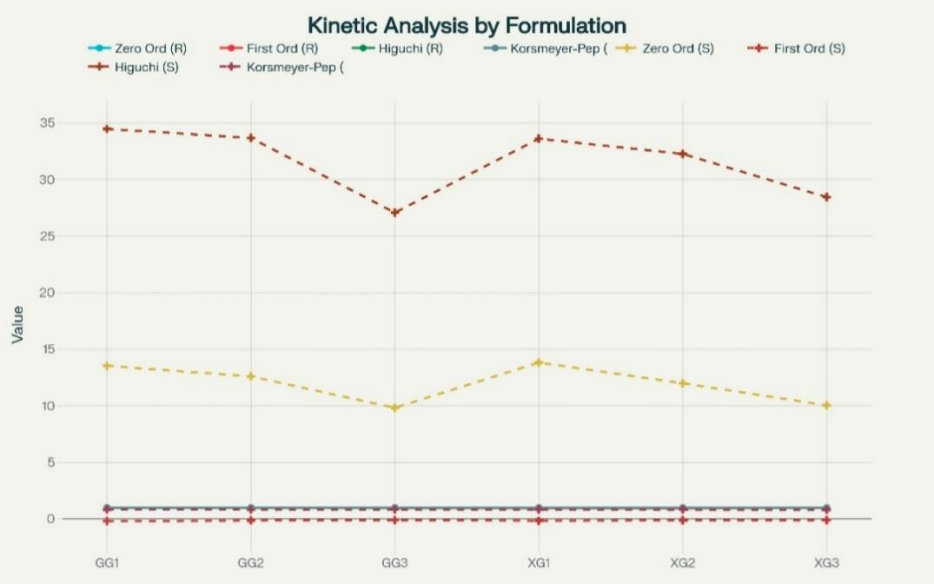

Fig. 1: Kinetics analysis data of Repaglinide Mucoadhesive Microspheres.

CONCLUSION

Repaglinide mucoadhesive microspheres were successfully formulated using natural mucoadhesive polymers, namely xanthan gum and guar gum, in different ratios. The prepared microspheres exhibited favourable physicochemical properties, with high drug entrapment efficiency, satisfactory swelling behaviour, and prolonged drug release in gastric conditions. The best formulation (XAG-III) demonstrated sustained drug release up to 10 hours and followed zero-order kinetics with a Non-Fickian diffusion mechanism, making it a promising candidate for gastro-retentive controlled drug delivery of Repaglinide.

This delivery approach may significantly enhance the bioavailability of Repaglinide, reduce dosing frequency, and provide consistent glycemic control in patients with type 2 diabetes mellitus.

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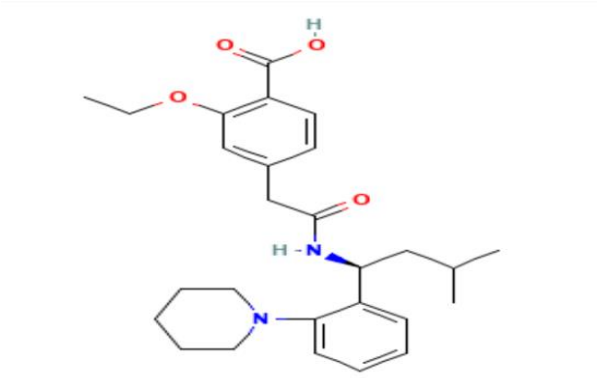

Fig. 2: Structure of Repaglinide.

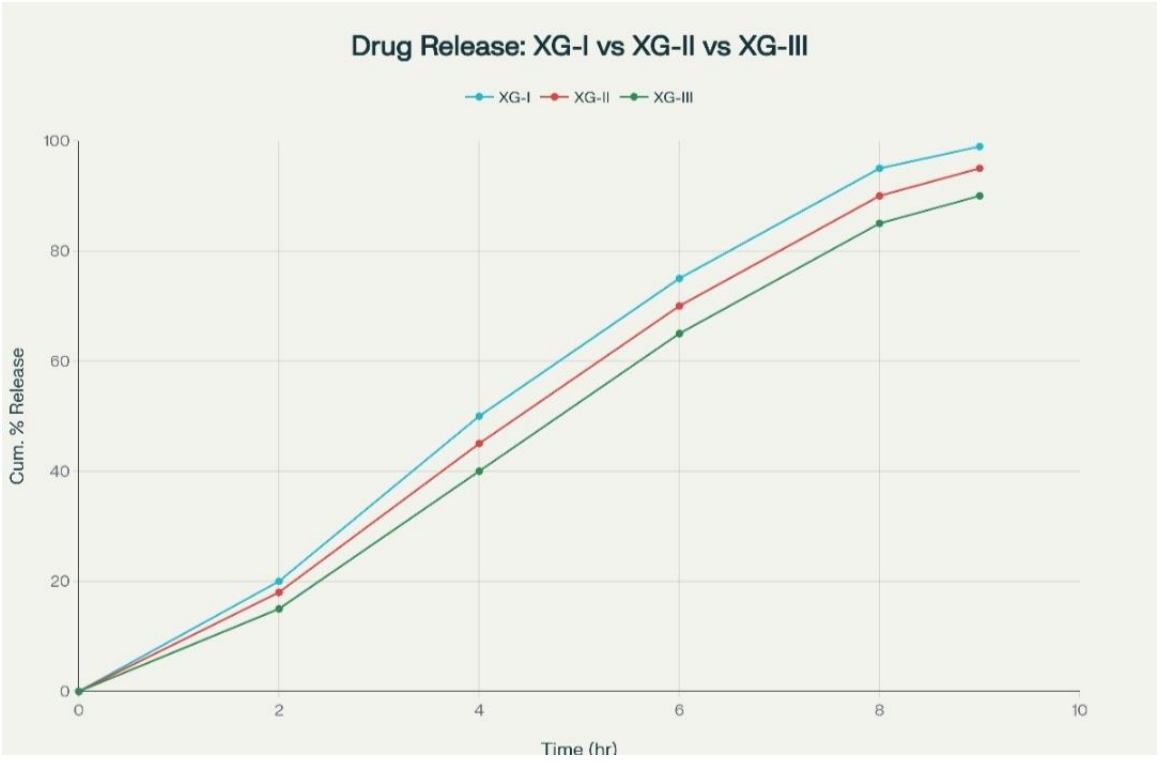

Fig. 3: Comparative in-vitro drug release plot of Repaglinide Mucoadhesive Microspheres. (XAG-I to XAG-III).

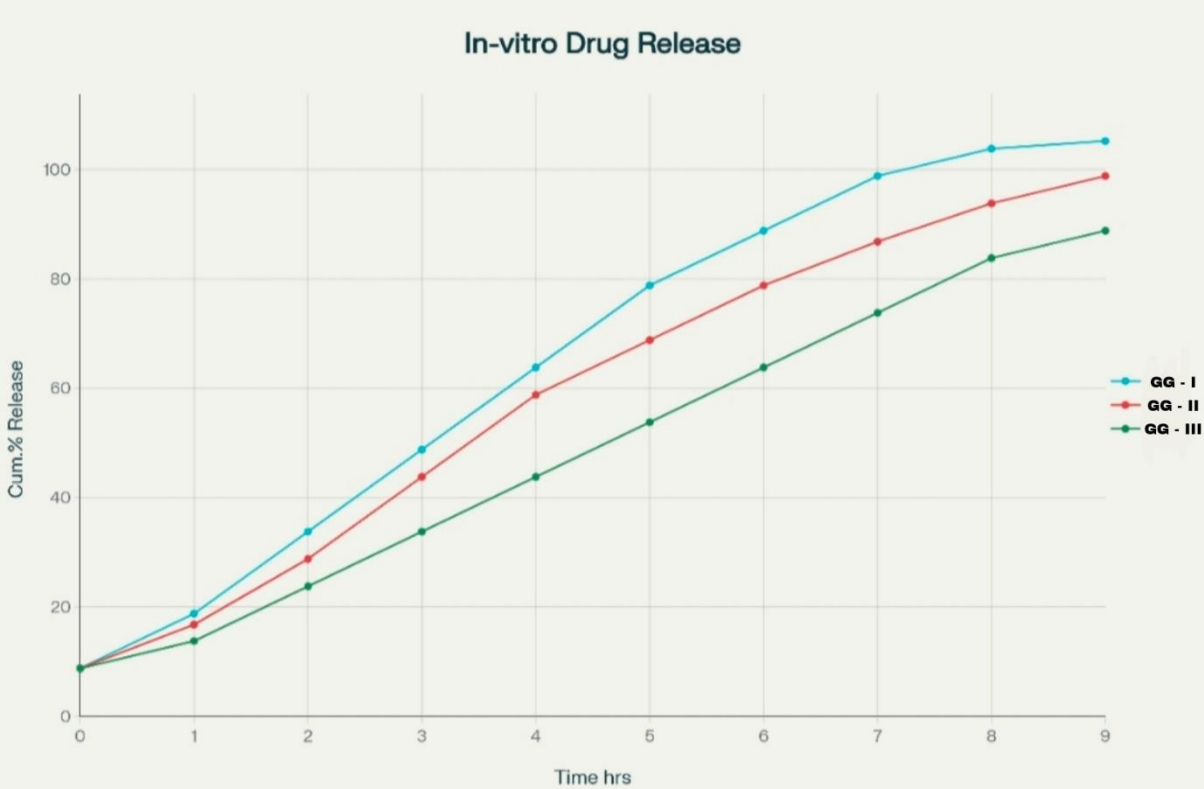

Fig. 4: Comparative in-vitro drug release plot of Repaglinide Mucoadhesive Microspheres. (GAG-I to GAG-III).

Limitations

- The study focused only on in vitro evaluation parameters; in vivo bioavailability and pharmacokinetic studies were not performed to confirm enhanced oral bioavailability in a biological system.
- Particle size range variability was relatively broad, and the effect of this size heterogeneity on drug release and mucoadhesion was not extensively explored.
- Stability studies under different environmental conditions (temperature, humidity) were not included to assess long-term storage viability.
- The study used only specific concentrations of polymers (sodium alginate, guar gum, xanthan gum) and crosslinking agent (calcium chloride); optimization with a broader range could have provided a more comprehensive understanding.
- Potential scale-up challenges of the microsphere formulation process for industrial manufacturing were not addressed.
- The mucoadhesive strength and residence time on gastrointestinal mucosa were not quantified, which are crucial for confirming gastroretentive efficacy.
- Toxicological or safety evaluation of the mucoadhesive microspheres was not conducted

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