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GLECAPREVIR SUSTAINED RELEASE MUCOADHESIVE MICROSPHERE FORMULATIONS: DEVELOPMENT AND PHARMACEUTICAL CHARACTERIZATION

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ABSTRACT

Background: Conventional drug delivery systems often face limitations such as poor bioavailability and lack of site-specific action. To overcome these challenges, mucoadhesive microspheres have emerged as a promising approach for controlled and targeted drug delivery. The present study aims to develop and evaluate Glecaprevir-loaded mucoadhesive microspheres using spruce gum to enhance drug retention, bioavailability, and sustained release. **Methods:** Mucoadhesive microspheres were prepared using a cross-linking method with calcium chloride. Pre-formulation studies were conducted using FTIR, DSC, and XRD to assess drug-polymer compatibility. The formulations (F1-F4) were evaluated for production yield, drug loading, entrapment efficiency, particle size, swelling index, and mucoadhesion. Surface morphology was analyzed using SEM, and in vitro drug release studies were performed using a Franz diffusion cell. **Results:** The prepared microspheres showed a production yield of 40.26-55.93% and drug loading of 49.21-74.60%. Particle size ranged from 14.3-18.3 µm. Swelling (82-91%) and mucoadhesion (45.6-79.6%) increased with polymer concentration. The optimized formulation (F2) exhibited maximum drug release of 98.26% within 300 minutes. FTIR confirmed compatibility, while DSC and XRD indicated conversion of the drug into an amorphous form, enhancing solubility. **Discussion:** The study demonstrates that polymer concentration plays a crucial role in controlling drug release, swelling behavior, and mucoadhesion. The transformation of

Glecaprevir from crystalline to amorphous form improved its dissolution characteristics. The optimized formulation (F2) showed a balanced profile of drug release and mucoadhesion, making it suitable for sustained drug delivery. **Conclusion:** Glecaprevir-loaded mucoadhesive microspheres were successfully formulated and evaluated. The optimized formulation exhibited desirable physicochemical properties, sustained drug release, and enhanced mucoadhesion. This system can serve as an effective approach for controlled drug delivery and improved therapeutic efficacy.

KEYWORDS: Control Drug Delivery, Glecaprevir, Mucoadhesive Microsphere, Spruce Gum etc.

INTRODUCTION

Drug Delivery System

The drug administration through oral route is most commonly used method due to its convinces and flexibility in drug dosage form design. Drug release system that release the drug molecules over a extended period of time after the single dose it's called as sustained, prolonged, modified release system.[1] Recent years have witnessed growing interest in innovative dosage forms capable of controlling drug release and delivering active molecules to specific sites. A well-designed controlled drug delivery system can overcome limitations of conventional therapy and improve therapeutic efficacy.[2,3] Among these, mucoadhesive microsphere drug delivery systems have gained attention due to their ability to adhere to mucosal surfaces and release drugs near the absorption site. This close contact enhances drug bioavailability and produces both local and systemic effects. Mucoadhesive microspheres can adhere to mucosal tissues of the eye, nasal cavity, urinary tract, and gastrointestinal tract, enabling targeted and controlled drug delivery.[1-4]

Mucoadhesive Microsphere

There has been extensive research into developing innovative dosage forms of medication, many of which are capable of regulating the release rate and targeting the active medication molecule to a specific location.[11] One such innovative technology for delivering medication is the use of microspheres comprised of a variety of polymers and having multiple potential applications. Microspheres (often referred to as microparticles) are microscopic (1 μm to 1000 μm) spherical particles.[3,8] The microspheres can be constructed from either natural or synthetic polymers. Adding mucoadhesive properties to the microspheres will provide the added benefit of improved absorption and bioavailability of the medication aside from their

ability to regulate and target the delivery of the medication via multiple methods.[9] Mucoadhesive microspheres contain various agents (ex. monoclonal antibodies, bacterial piles, plant lectins, etc.) that can promote an increase in the adhesion of the drug to the site of absorption as well as enhancing proximity to the mucus layer at the site of absorption. Mucoadhesive microspheres can be custom-built to adhere to mucosal surfaces of the mouth, nose, eye, urinary tract, gastrointestinal tract allowing for localization of drug release in a regulated manner.[12]

MATERIALS AND METHODS

MATERIALS

Alembic® India Limited of Ahmedabad, India was contacted and asked to provide us with pharmaceutical grade Glecaprevir and spruce gum. Analytical grade calcium chloride, Span-80, n-octanol, and dichloromethane were all provided by Sigma Aldrich® Limited, Mumbai, India.

METHODS

Drug and polymer interaction studies

Glecaprevir and spruce gum were tested for compatibility with an FT-IR spectrometer (GX-FT-IR, Perkin Elmer®, USA) to determine whether or not the polymer was appropriate for the microsphere manufacturing process. Scanning was done between 4000 cm^{-1} and 500 cm^{-1} using KBr discs containing the drug, polymer, and physical combination samples.

Preparation of mucoadhesive microsphere

Mucoadhesive microspheres were prepared using a cross-linking method without emulsification. Initially, spruce gum was dissolved in double-distilled water with mild heat, then Glecaprevir was incorporated into this solution, which was homogenized at 40°C.[54] A mixture of 2% w/v span-80 and a n-octanol:water system (99:1) was prepared with continuous agitation at 1700 rpm. This emulsion was generated by injecting the spruce gum solution, followed by stirring for 30 minutes. Subsequently, a 4% CaCl2 solution was gradually added while agitating the dispersion for 5 minutes. The microspheres were filtered through Whatman filter paper no. 41, washed with isopropyl alcohol, and desiccated at room temperature after drying them in a hot air oven at 40°C.

Table 1: Formulation batches of spruce gum microspheres of Glecaprevir.

Formulation code	Drug (mg)	Spruce gum (mg)
F1	20	20
F2	20	40
F3	20	60
F4	20	80

Evaluation of mucoadhesive microspheres

1. Production yield

The proportion of the original Glecaprevir and spruce gum polymer weight that was recovered after drying the end product (formulation) was used to calculate the manufacturing yield of several batches of microsphere formulation.

2. Drug loading

For 24 hrs, each formulation's microspheres were extracted in double-distilled water using a mechanical shaker, releasing all of the Glecaprevir that had been encapsulated within. No. 41 Whatman filter paper was used to filter the solution. 1 mL sample was taken and diluted to 10 mL using 10 times as much double-distilled water. We measured the concentration of the medication in this solution using a UV-Vis spectrophotometer (Shimadzu® UV-1800, Japan) set to 313 nm.

3. Entrapment efficiency

For 24 hrs, each formulation's microspheres were extracted in double-distilled water using a mechanical shaker, releasing all of the Glecaprevir that had been encapsulated within. No. 41 Whatman filter paper was used to filter the solution. 1 mL sample was taken and diluted to 10 mL using 10 times as much double-distilled water. We measured the concentration of the medication in this solution using a UV-Vis spectrophotometer set to 313 nm.

4. Particle size analysis

A Motic digital microscope (DMW2-223, Motic® Instruments Inc., Canada) equipped with a 1/3" CCD camera imaging attachment and computer-controlled image analysis software was used for microscopic image analysis for the assessment of particle size. The produced microspheres were evenly spread out on a standard-sized microscope slide, and the video camera was used to scan the microscopic field. Within the scanned area, the programme evaluated the photos.

5. Degree of swelling

Allowing the formulations to swell in the phosphate buffer pH 6.6 established the Glecaprevir microspheres' swellability in the physiological medium. For twenty-four hrs, a measured volume of microspheres was submerged in a phosphate buffer with a pH of 6.6 and then completely rinsed.

***6. In-vitro* mucoadhesive study**

The falling liquid film method evaluated the mucoadhesive quality of microspheres using goat nasal mucosa. A 2 cm^2 section was prepared and placed over a polyethylene plate, onto which 100 mg of microspheres was added alongside 100 µL of a simulated nasal electrolyte solution. The setup was incubated for 15 minutes in a desiccator at 90% relative humidity. The membrane was positioned at a 45° angle, with a phosphate buffer (pH 6.6, 37±1°C) pumped through at 1 mL/min. The drug concentration in the perfusate was measured spectrophotometrically after 1 hour.

7. Differential scanning calorimetry (DSC)

We used a differential scanning calorimeter (Mettler Toledo®, USA) to investigate the thermal properties of the pure drug, polymer, physical mixture, and optimised microsphere formulation by heating them at a rate of 10°C/min from 30-300°C while maintaining an inert nitrogen atmosphere with a flow rate of 20 mL/min.

8. X-Ray diffraction study (XRD)

Samples of pure medication, polymer, physical mixture, and optimised formulation were irradiated with Cu-K radiation (monochromatized) in the 2θ range of 3-60° on an X-ray diffractometer (Ultima-III, Rigaku®, Japan) and analysed for X-ray diffraction patterns.

9. Scanning electron microscopy (SEM)

The surface morphology of the microspheres was examined using a scanning electron microscope (Jeol®, JSM-5610 LV, Japan) at 400x and 2000x magnifications. To assess the surface morphology, gold-coated (4A° thickness) microspheres were powdered and then sifted over double-sided tape on the aluminum stub of the SEM chamber. At a working accelerating voltage of 6 kV, photomicrographs of the microspheres in development were captured.

10. In-vitro drug release study

The investigation utilized manufactured microspheres for in vitro drug release through a Franz diffusion cell. The experiment employed a dialysis membrane with a molecular cut-off of 12,000 to 14,000, ensuring careful distribution of the mucoadhesive microspheres in the donor compartment. A pH 1.2 phosphate buffer solution filled the receptor well, with the donor chamber in contact with the receptor's diffusion medium, maintained at 37±1°C using a circulating water bath. Samples were periodically collected from the receptor section, with measurements taken at 313 nm using a UV-Vis spectrophotometer while maintaining a constant sink state.

Statistical analysis

Statistical analysis evaluated variations in Glecaprevir-loaded mucoadhesive microspheres, with data expressed as mean ± standard deviation. One-way ANOVA and Tukey's post-hoc test were used for comparisons, with $p < 0.05$ as the significance threshold. The correlation of polymer concentration with yield, drug loading, entrapment efficiency, swelling behavior, and in vitro drug release was analyzed via Pearson's correlation coefficient. Regression analysis assessed the impact of polymer concentration on drug release kinetics, with data visualized through histograms, scatter plots, and line graphs. GraphPad Prism and SPSS software were employed for accurate and reproducible results.

RESULTS

Drug-polymer compatibility study

FTIR spectroscopy was employed to investigate the interaction between Glecaprevir and the polymer spruce gum. The spectra showed that the peaks of the pure drug and those of the polymer were similar in both the physical mixture and the optimized formulation F2, indicating no significant chemical interactions such as covalent bonding or molecular degradation. The retention of characteristic peaks confirms the absence of substantial drug-polymer interaction, which is critical for pharmaceutical development, ensuring the stability and efficacy of the formulation. The findings validate spruce gum as a suitable excipient, supporting the therapeutic application of Glecaprevir without compromising its efficacy.

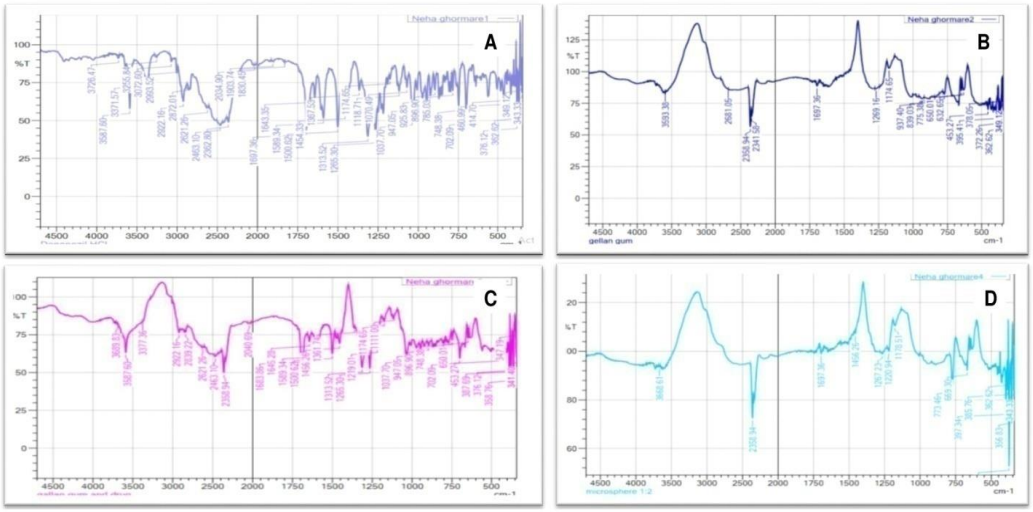

Figure 1: Drug compatibility studies: (A) pure Glecaprevir; (B) spruce gum; (C) physical mixture; and (D) optimized formulation F2.

Characterization of mucoadhesive microspheres

1. Production Yield

The production yield ranged from 40.26-55.93% and increased with higher polymer concentration due to improved microsphere formation and reduced loss. However, excess polymer may cause aggregation. The polymer concentration significantly affects yield.

Table 2: Results of Characterization Parameters for Mucoadhesive Microspheres. The results are shown in table 2.

2. Drug Loading

Drug loading ranged from 49.21-74.60% (Display in table 2). It was highest at 1:1 ratio and decreased with increasing polymer concentration due to reduced surface area and drug entrapment.

2. Particle Size

Particle size ranged from 14.3-18.3 µm (Table 2), suitable for intravenous delivery. Polymer concentration had minimal effect, while higher stirring rate reduced particle size. The image of particle displayed in figure 2.

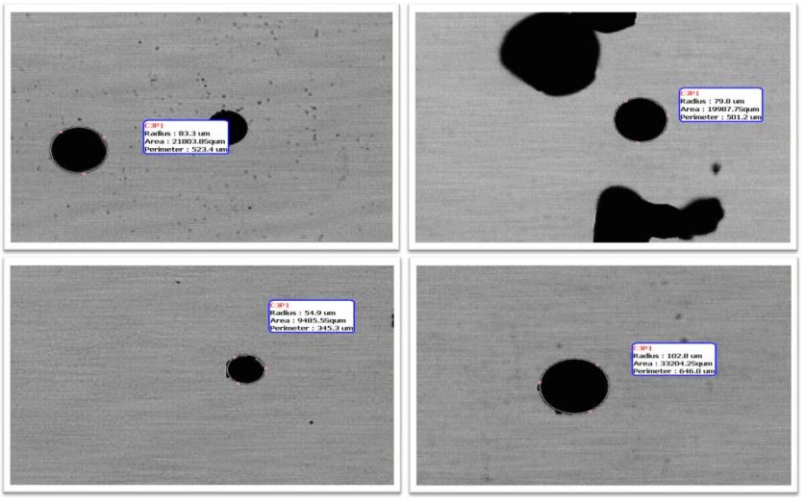

Figure 2: Microscopic Image of Microspheres.

4. Swelling Property

Swelling ranged from 82%-91% (Table 2). Swelling increased with higher polymer concentration due to greater water absorption, enhancing mucoadhesion.

5. Mucoadhesion Potential

Mucoadhesion ranged from 45.6%–79.6%. It increased with polymer concentration due to enhanced hydrogen bonding and interaction with nasal mucosa. Higher polymer content improved swelling and adhesion, resulting in better retention at the absorption site. However, excessive adhesion may affect comfort, so optimization is necessary.

Formulation code	Production yield (% ± SD)	Drug loading (% ± SD)	Entrapment efficiency (% ± SD)	Particle size (µm ± SD)	% Swelling (% ± SD)	Mucoadhesion (% ± SD)
F1	40.26 ± 0.1	74.60 ± 0.01	34.5 ± 1.02	17.3 ± 0.3	82 ± 0.1	45.6 ± 0.1
F2	44.83 ± 0.3	64.62 ± 0.01	40.5 ± 0.15	14.3 ± 0.2	83 ± 0.2	57.6 ± 0.2
F3	50.45 ± 0.2	57.77 ± 0.02	42.3 ± 0.15	17.6 ± 0.1	88 ± 0.1	62.2 ± 0.1
F4	55.93 ± 0.1	49.21 ± 0.03	53.6 ± 0.21	18.3 ± 0.5	91 ± 0.1	79.6 ± 0.1

6. Thermal Characteristics

DSC analysis showed pure drug exhibited a sharp peak at 225°C, confirming crystallinity. In the optimized formulation (F2), the peak disappeared, indicating amorphous dispersion of

drug in polymer matrix. This transformation enhances solubility, dissolution, and bioavailability, confirming successful drug-polymer interaction.

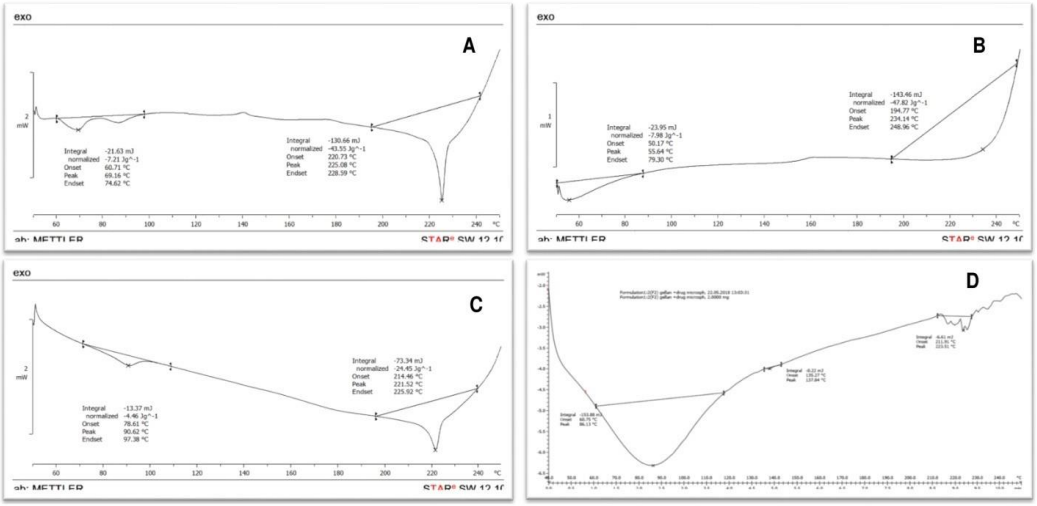

Figure 3: DSC thermograms: (A) pure Glecaprevir; (B) spruce gum; (C) physical mixture; and (D) optimized formulation F2.

8. Physical State Examination (Results)

XRD analysis showed that pure Glecaprevir exhibited sharp peaks at 2θ values of 6.64°, 6.87°, and 13.00°, confirming its crystalline nature. Spruce gum displayed a broad halo pattern, indicating its amorphous structure. In the optimized microspheres (F2), the characteristic crystalline peaks of Glecaprevir disappeared, suggesting conversion to an amorphous form. This indicates successful molecular dispersion of the drug within the polymer matrix, which may enhance solubility and dissolution.

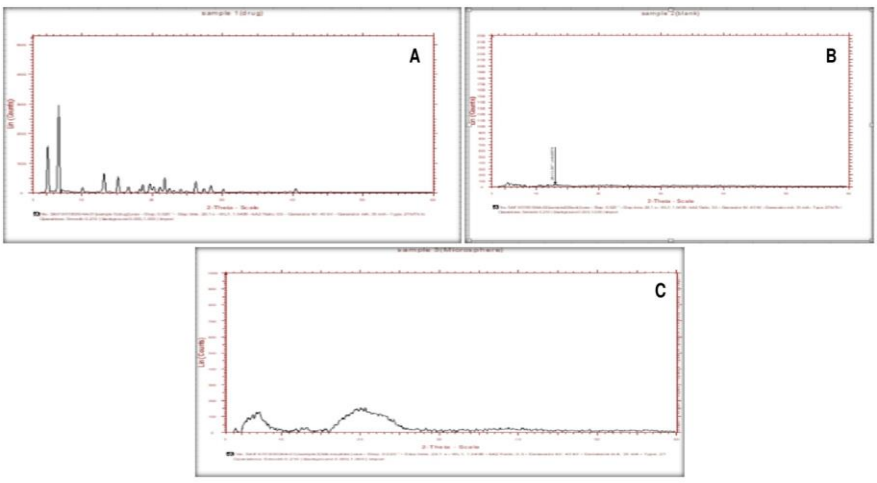

Figure 4: Powder X-Ray diffractogram: (A) pure Glecaprevir; (B) spruce gum; and (C) optimized formulation F2.

9. Morphological Examination (Results)

SEM analysis showed that the microspheres were spherical and uniform in shape, indicating suitability for nasal drug delivery. The surface was mostly smooth with slight roughness, likely due to formulation conditions. No pores, cracks, or ruptures were observed, confirming good structural integrity and controlled drug release. Additionally, no drug crystals were visible on the surface, indicating efficient drug encapsulation within the polymer matrix. These characteristics support improved stability, mucoadhesion, and sustained drug release.

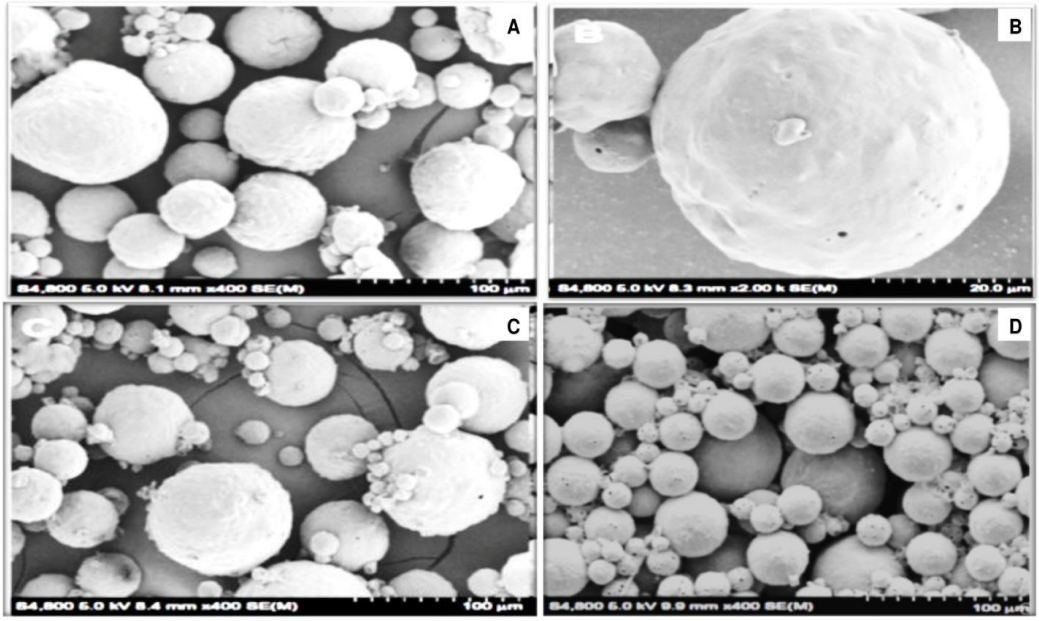

Figure 5: Scanning electron photomicrographs: (A) 400x maginification; (B) 2000x maginification; (C) 400x maginification; and (D) 400x maginification.

10. *In-vitro* Release

In-vitro drug release studies showed that polymer concentration significantly affected Glecaprevir release from microspheres. Among all formulations, F2 exhibited the highest cumulative drug release (98.26%) within 300 minutes, indicating an optimal balance between drug diffusion and polymer content. In contrast, F4 showed the lowest release due to higher polymer concentration, which restricted drug diffusion and provided a sustained release effect.

Table 3: *In vitro* drug release profile of Glecaprevir mucoadhesive microsphere formulations.

Time (min)	F1	F2	F3	F4
15	15.52 ± 0.1	19.69 ± 0.1	9.78 ± 0.3	12.07 ± 0.2
30	31.93 ± 0.1	41.20 ± 0.1	25.67 ±0.2	25.55 ± 0.1
60	38.07 ± 0.2	47.92 ±0.3	37.71 ± 0.1	31.29 ± 0.1
90	44.43± 0.1	54.48 ± 0.1	44.16 ± 0.2	36.39 ± 0.5
120	50.39 ± 0.1	62.94 ± 0.1	49.11 ± 0.1	44.05 ± 0.1
150	53.72± 0.2	67.94 ± 0.2	53.93 ± 0.4	50.09 ± 0.2
180	57.81± 0.2	72.86 ± 0.1	55.93 ± 0.4	53.61 ± 0.1
210	63.06± 0.2	79.03 ± 0.1	59.58 ± 0.5	59.27 ± 1.1
240	66.41± 0.1	85.07± 0.2	64.79 ± 0.1	65.31 ± 0.1
270	72.62 ± 0.2	92.87 ± 0.3	71.97 ± 0.2	68.16 ± 0.2
300	78.24 ± 0.1	98.26 ± 0.1	77.21 ± 0.1	76.92 ± 0.1

6. CONCLUSION

The present study successfully developed and evaluated Glecaprevir-loaded mucoadhesive microspheres for sustained drug delivery. The optimized formulation demonstrated desirable characteristics such as uniform particle size, good encapsulation efficiency, and strong mucoadhesion. Characterization studies (SEM, FTIR, DSC, and XRD) confirmed the stability and compatibility of the drug within the polymer matrix. *In vitro* release studies indicated a controlled and sustained drug release pattern, influenced by polymer concentration and drug–polymer interactions. The microspheres also exhibited good structural integrity and stability, supporting their suitability for drug delivery applications.

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