RESEARCH PAPER

Design And Development Of Mucoadhesive Microspheres Of Anti-Vertigo Agent For Nasal Delivery

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ABSTRACT

Mucoadhesive drug delivery systems are made to keep a formulation in close contact with the mucosal surface, this allows the drug to remain at the site of absorption for an extended period of time. The goal of this study is to create and assess mucoadhesive microspheres for the nasal delivery of Betahistine, as an antivertigo medication. The study's objectives were to reduce hepatic first-pass metabolism, increase therapeutic efficacy, and extend the duration of drug residency in the nasal cavity. Using chitosan as the mucoadhesive polymer and the emulsification cross-linking process, Betahistine-loaded mucoadhesive microspheres were created. Particle size distribution, percentage yield, drug entrapment efficiency, swelling index, in-vitro drug release, and in-vitro mucoadhesive strength were among the physicochemical and performance characteristics that were assessed for the produced microspheres. In order to evaluate formulation integrity over time, stability experiments were also carried out. Surface morphology and structural compatibility were examined using FTIR and SEM.

The produced microspheres showed particle sizes between 10 and 50 µm, suggesting that they were suitable for nasal delivery and had acceptable handling qualities. A regulated release profile lasting up to six hours was shown in in vitro drug release experiments conducted in phosphate buffer with a pH of 6.8. The release kinetics indicates that all formulations shows zero order release kinetics that is controlled release pattern. According to the results, the produced mucoadhesive microsphere system offers a great deal of promise as a nasal delivery method for Betahistine, providing better therapeutic treatment of vertigo and extended drug retention at the absorption site.

Keywords: Betahistine, Mucoadhesive Microspheres, Nasal's Administration, Anti-Vertigo Agent, Chitosan, Emulsification Cross-linking Method, Controlled Release.

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1. INTRODUCTION

Vertigo is a common vestibular disorder characterized by a sensation of spinning, dizziness, and loss of balance, which can significantly impair the quality of life of affected individuals. It is frequently associated with inner ear disorders such as Ménière's disease and vestibular dysfunction. Effective management of vertigo is essential to reduce the frequency and severity of symptoms and improve patient well-being. Betahistine, a histamine analogue, is widely used in the treatment of vertigo and Ménière's disease due to its ability to improve microcirculation in the inner ear and reduce vestibular disturbances. However, betahistine undergoes extensive first-pass metabolism following oral administration, resulting in low bioavailability and reduced therapeutic efficiency.

To overcome the limitations associated with conventional oral dosage forms, alternative drug delivery systems have been extensively investigated. Among these, nasal drug delivery has emerged as a promising approach because of its unique anatomical and physiological characteristics. The nasal cavity possesses a highly vascularized mucosal membrane that facilitates rapid drug absorption into the systemic circulation. Furthermore, the nasal route bypasses hepatic first-pass metabolism and gastrointestinal degradation, thereby enhancing drug bioavailability and providing a faster onset of therapeutic action. These advantages make nasal administration particularly suitable for drugs such as betahistine that exhibit low oral bioavailability. Despite these benefits, nasal drug delivery is challenged by the rapid clearance of formulations from the nasal cavity due to the mucociliary clearance mechanism. This physiological defense system reduces the residence time of administered formulations and may limit drug absorption. Consequently, the development of delivery systems capable of prolonging drug retention within the nasal cavity is essential for improving therapeutic outcomes.

Mucoadhesive microspheres have attracted considerable attention as carriers for nasal drug delivery. These multiparticulate systems adhere to the mucus layer covering the nasal epithelium, thereby

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increasing the residence time of the formulation at the absorption site. Extended contact with the nasal mucosa promotes enhanced drug permeation and improved bioavailability. In addition, microspheres offer several advantages, including controlled drug release, protection of the incorporated drug, uniform distribution across the mucosal surface, and reduced dosing frequency.

The mucoadhesive properties of these systems are achieved through the use of polymers capable of interacting with mucin present on mucosal surfaces. Chitosan is one of the most widely used mucoadhesive polymers due to its biocompatibility, biodegradability, non-toxic nature, and excellent adhesive properties. Its positive charge facilitates interaction with negatively charged mucosal surfaces, resulting in prolonged retention and enhanced drug absorption. Moreover, chitosan has been reported to improve epithelial permeability, further promoting drug transport across the nasal membrane. Considering the therapeutic importance of betahistine and the advantages offered by nasal mucoadhesive drug delivery systems, the development of betahistine-loaded mucoadhesive microspheres represents a promising strategy for improving treatment outcomes in vertigo. Such a formulation may increase residence time within the nasal cavity, enhance drug absorption, improve bioavailability, and provide sustained therapeutic action while minimizing the limitations associated with oral administration.

Therefore, the present study was undertaken to design and develop mucoadhesive microspheres of betahistine for nasal delivery. The prepared microspheres were evaluated for their physicochemical characteristics, drug entrapment efficiency, mucoadhesive properties, swelling behavior, and in vitro drug release performance to determine their suitability as an effective nasal drug delivery system.

2. MATERIALS AND METHODS

2.1 Materials:

Betahistine dihydrochloride was obtained as a gift sample from a reputed pharmaceutical company. Chitosan was used as the mucoadhesive polymer, while sodium tripolyphosphate (TPP) served as the cross-linking agent. All other chemicals, solvents, and excipients used in the formulation were of analytical grade and procured from authorized suppliers. Double-distilled water was used throughout the study, and all materials were utilized without further purification.

2.2 Method Of Preparation By W/O Emulsion Cross Linking Method[8&44]

1. 2% aqueous acetic acid solution was prepared by dissolving 2 mL of glacial acetic acid in 100 mL of distilled water.
2. An accurately weighed quantity of chitosan (0.1, 0.2, or 0.3 g) was added to 10 mL of the prepared 2% acetic acid solution. The mixture was stirred continuously until a clear and homogeneous solution was obtained.
3. A weighed amount of betahistine (0.1 g) was slowly added to the chitosan solution with continuous stirring to obtain a uniform drug–polymer dispersion.
4. A stabilizing solution was prepared by dissolving approximately 50 mg of dioctyl sodium sulfosuccinate (DOSS) in 25 mL of glycerine with continuous stirring.
5. A mixture of light liquid paraffin (50 mL) and heavy liquid paraffin (50 mL) was taken in a 500 mL beaker and stirred using an electric stirrer at 1250 rpm for about 15 minutes to obtain a uniform oil phase.
6. The prepared DOSS solution (2–3 mL) was added to the paraffin mixture under continuous stirring at 1150–1350 rpm for approximately 15–20 minutes to form a stable external phase.
7. The previously prepared drug–chitosan solution was slowly added dropwise into the external oil phase with constant stirring at 1250–1450 rpm. Stirring was continued for about 15 minutes to form a stable emulsion.
8. Glutaraldehyde was added slowly to the emulsion while maintaining constant stirring (1250–1450 rpm). The mixture was further stirred for about 2 hours to allow complete cross-linking and formation of microspheres.
9. The formed microspheres were separated from the mixture by vacuum filtration.
10. The collected microspheres were cleaned using distilled water to get rid of any unreacted compounds and n-hexane to get rid of any remaining oil. After a day of air drying, the microspheres were kept in a desiccator for further use.

Table 1: **Formulation Variables and Process Optimization:**

Formulation Code	Ratio of Drug to Polymer	Dioctyl Sodium Sulfosuccinate (mL)	Glutaraldehyde (mL)	Aqueous : Oil Phase proportion	Mixing Speed (rpm)	Cross-linking Time (hrs)
BF1	1 : 1	2	2	10 : 100	1640 ± 10	2
BF2	1 : 2	2	2	10 : 100	1640 ± 10	2
BF3	1 : 3	2	2	10 : 100	1640 ± 10	2
BF4	1 : 1	3	4	10 : 100	1640 ± 10	2
BF5	1 : 2	3	4	10 : 100	1640 ± 10	2
BF6	1 : 3	3	4	10 : 100	1640 ± 10	2

2.2 Characterization & Evaluation

2.2.1 Determination of Percentage Yield of Microspheres:

The production yield of the microspheres was evaluated by measuring the weight

of the dried product obtained after formulation and comparing it with the theoretical weight of the starting materials. The dried microspheres were carefully collected, weighed, and the percentage yield was calculated using the following formula:

$$\% \text{ yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer}} \times 100$$

2.2.2 Determination of % Drug Content and % Entrapment Efficiency: Accurately weighed microspheres (100 mg) were crushed and dispersed in 100 mL of ethanol. The dispersion was sonicated to facilitate complete drug extraction and kept undisturbed for 12 h. The solution was subsequently filtered through Whatman No. 41 filter paper, and the drug content in the filtrate was quantified spectrophotometrically at 210 nm using a UV–Visible spectrophotometer.

2.2.3 Particle Size Analysis: The particle size of the prepared Betahistine-loaded mucoadhesive microspheres was determined using an optical microscope equipped with a digital imaging system. A small quantity of dried microspheres was dispersed in glycerine and mounted on a glass slide. The microspheres were observed under the microscope, and their images were captured using an Olympus digital camera. The diameter of selected microspheres was measured using Magnus Pro 3.0 image analysis software, and the average particle size was calculated and expressed as mean particle diameter. The shape and surface characteristics of the microspheres were also examined during microscopic observation.

2.2.4 Shape and Surface Characterization: The surface morphology and shape of the prepared Betahistine-loaded mucoadhesive microspheres were evaluated using Scanning Electron Microscopy (SEM). A small amount of microspheres was mounted on an aluminum stub using double-sided adhesive tape and coated with a thin layer of gold under vacuum conditions. The samples were then examined under a scanning electron microscope at appropriate magnifications. Micrographs were recorded to assess the surface texture, shape, and structural integrity of the microspheres.

2.2.5 Degree of Swelling: The swelling index of the prepared Betahistine-loaded mucoadhesive microspheres was determined by immersing 50 mg of microspheres in phosphate buffer (pH 6.8) for 24 h. After the incubation period, the swollen microspheres were separated, gently blotted to remove excess surface moisture, and weighed (Wt). The swelling index was then calculated using the initial and final weights of the microspheres.

2.2.6 Mucoadhesive Property by Wash-Off Test: The mucoadhesive properties of the prepared Betahistine-loaded microspheres were evaluated using the wash-off method. Fresh goat nasal mucosa was mounted on a glass slide using cyanoacrylate adhesive, and approximately 25 microspheres were uniformly distributed over the hydrated mucosal surface. The slide was attached to the arm of a USP disintegration apparatus and immersed in phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. The apparatus was operated with a regular up-and-down movement, and the number of microspheres remaining adhered to the mucosal tissue was recorded at predetermined intervals up to 6 h to assess the mucoadhesive strength of the formulation. The percentage Mucoadhesion was calculated from the number of microspheres retained on the tissue surface. The following formula was used to display the adherent percentage:

$$\text{Mucoadhesion} = \text{No. of microspheres adhered} / \text{No. of microspheres applied} \times 100$$

2.2.7 In-Vitro Drug Release or Dissolution Studies: The in vitro drug release of the prepared Betahistine-loaded mucoadhesive microspheres was evaluated using a USP dissolution apparatus (basket method). The study was performed in 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C and stirred at 50 rpm. Microspheres equivalent to the required dose of Betahistine were placed in the dissolution medium. Samples were withdrawn at predetermined time intervals and replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The collected samples were analyzed using a UV–Visible spectrophotometer at the predetermined λmax of Betahistine, and the cumulative percentage drug release was calculated.

2.2.8 Kinetics of Drug Release: The in vitro drug release data of the prepared Betahistine-loaded mucoadhesive microspheres were analyzed using various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The release data were fitted to the respective equations, and the correlation coefficient (R^2) values were determined through regression analysis. This kinetic evaluation was performed to understand the mechanism and pattern of drug release from the microspheres and to identify the model that best described the release behavior of the optimized formulation.

2.2.9 Stability Study: For stability investigations, the formulation (NGN3) was created from the produced microspheres. Three sample sets of the formulation were separated and stored at 4±1°C, 25±2°C & 60±5%RH and 37±2°C & 65±5%RH. After 30 days, the samples were tested for drug release. Entrapment effectiveness for the same composition was also examined.

3. RESULTS AND DISCUSSION

3.1 FTIR Spectra: FTIR spectroscopy was carried out to assess the compatibility between Betahistine and the excipients used in the formulation. The infrared spectrum of pure Betahistine was recorded using the KBr pellet method. The characteristic absorption peaks of the drug were identified and compared with those of the optimized formulation to evaluate any potential drug–excipient interactions

and to confirm the stability of the formulation.

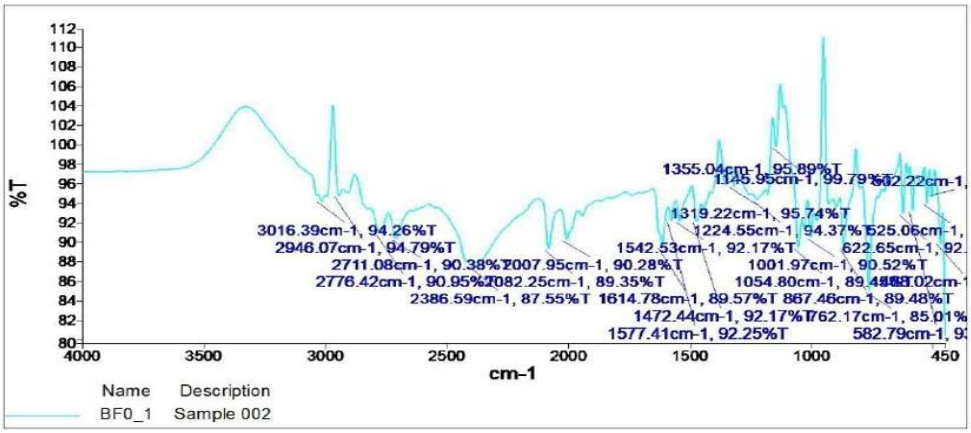


Figure 1 FTIR Spectra of Betahistine

3.2 Compatibility Study: Drug–polymer compatibility was evaluated using FTIR spectroscopy. The infrared spectra of pure Betahistine, chitosan, and the optimized formulation (CP0) were recorded and compared. The characteristic peaks of betahistine were retained in the formulation spectrum without any significant shift, disappearance, or formation of new peaks, indicating the absence of chemical interaction between the drug and polymer. The FTIR spectra of chitosan and the optimized formulation (CP0) are presented in Figures 2 and 3, respectively.

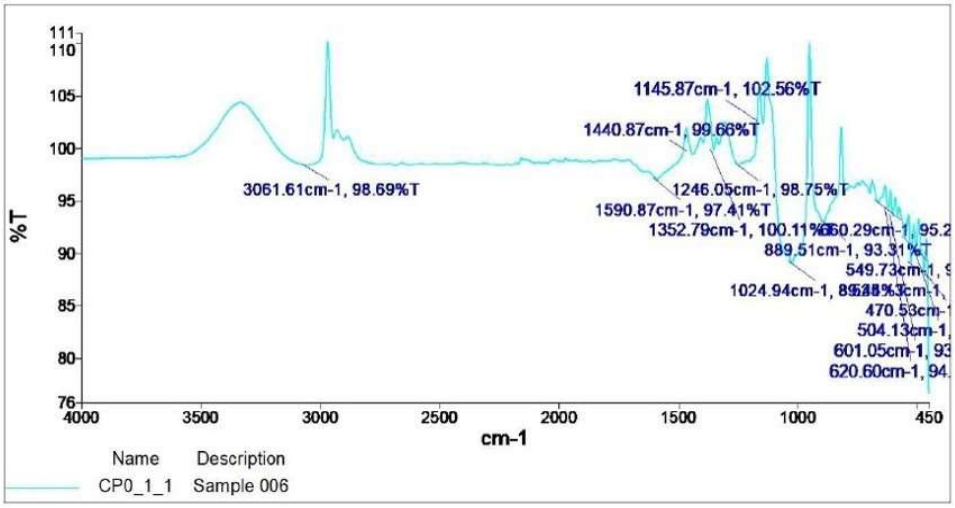


Figure 2: FTIR Spectra of Chitosan

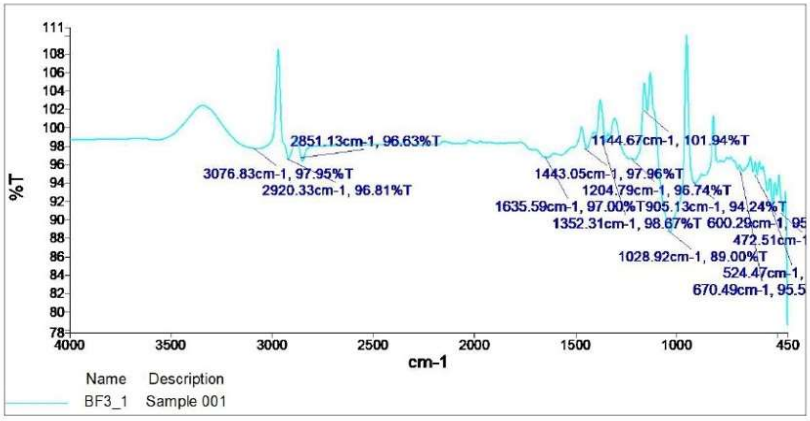


Figure 3: FTIR Spectra of Formulation BF-3

The FTIR spectra of chitosan and the optimized formulation (BF3) were compared to evaluate drug–polymer compatibility. The characteristic absorption peaks of Betahistine and chitosan were retained in the formulation spectrum without any significant shift, disappearance, or emergence of new peaks. These results indicate the absence of chemical interaction between Betahistine and chitosan, confirming their compatibility and the stability of the optimized formulation.

Optimization of Process and Formulation Variables

i) Emulsification Cross Linking Method: In the current work, the emulsification cross- linking approach was used to create microspheres. As the aqueous phase, polar organic solvent was used to prepare the w/o kind of emulsion.

ii) Selection of Internal phase

Selection of dispersing agent: The results of this study demonstrated that liquid paraffin was the exterior phase, and DOSS-which is soluble in both liquid paraffin and cone—was employed. It was discovered that 0.2% w/v was adequate for the creation of microspheres. DOSS appears to have shielded organic polymer droplets from one another and kept them from clumping together.

Selection of Washing Solvent: In order to get rid of any last residues of liquid paraffin, microspheres were cleaned. Hexane was tested, in which liquid paraffin is soluble but polymers are not, in an attempt to find a washing solvent that will only dissolve liquid paraffin and not polymers. The resulting microspheres were distinct in character.

3.3 Characterization and Evaluation

Production Yield: The percentage yield of the prepared betahistine-loaded mucoadhesive microspheres ranged from 86.58% to 92.68%. Among all formulations, BF3 showed the highest yield (92.68%), indicating efficient microsphere formation. Variations in yield may be attributed to processing losses, microsphere aggregation, and adhesion of polymer to the preparation vessel and stirring equipment..

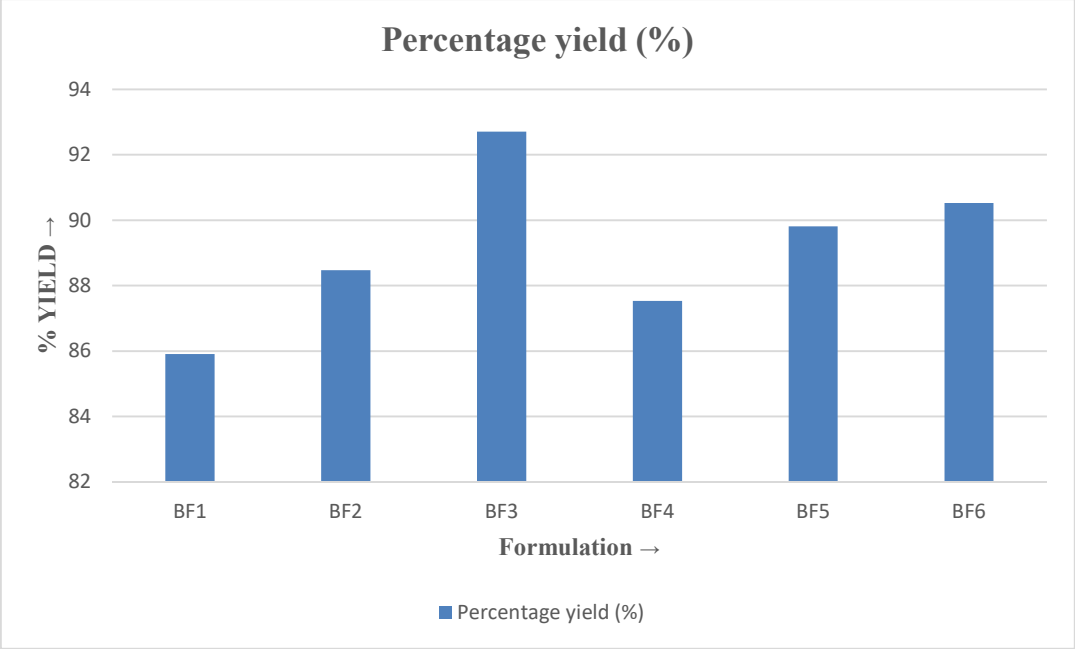
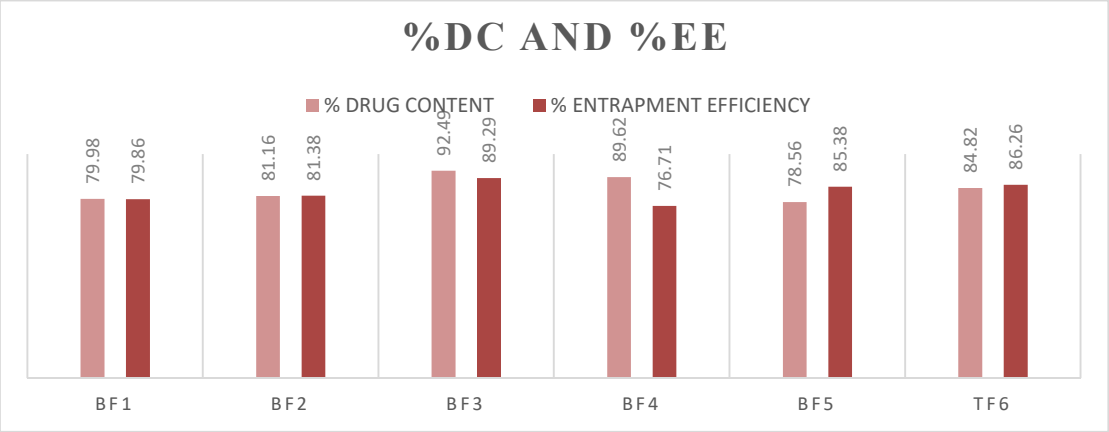


Table 4. Data For Percentage Yield of Mucoadhesive Microsphere Betahistine

Drug Content and Entrapment Efficiency: The drug content study indicated that the selected preparation method was effective in producing mucoadhesive microspheres of Betahistine with satisfactory drug loading, even when the polymer concentration was varied. The percentage drug content (% w/w) for different formulations was found to be in the range of 81.20% to 90.80%.

Among all batches, BF3 exhibited the highest DC (90.80% w/w), followed by BF1, BF2, BF4, BF5, and BF6. This suggests that the formulation technique allowed efficient incorporation of the drug into the matrix(polymer).

The entrapment efficiency of the prepared microspheres is illustrated in Figure 3.8. The % entrapment efficiency was observed in the range of 76.30% to 88.60%, with BF3 showing the maximum entrapment efficiency among all formulations.



Percentage drug content of prepared microspheres

Particle Size Analysis of Microspheres: An optical microscope (OLYMPUS INEA) was has been used to assess the size of the betahistine mucoadhesive microspheres that were created. Table 3.8 summarizes the mean particle size values for various formulations. The microspheres were determined to be between 10.42 ± 1.12 µm and 52.76 ± 2.15 µm in size. It was observed that the particle size was more significantly affected by the concentration of the cross-linking agent than by the polymer concentration. An increase in chitosan concentration up to an optimum level resulted in comparatively smaller and more uniform microspheres. This may be due to the availability of more ionic sites, which promotes effective cross-linking and leads to the formation of compact particles. Among all formulations, BF3 showed an optimum particle size of 10.42 ± 1.12 µm, which is considered suitable for nasal drug delivery, as it supports better deposition and retention in the nasal cavity.

Table : Mean Particle Size Analysis of BF

S. No.	Formulation	Average particle size in µm
1	BF1	18.09±1.12
2	BF2	21.09±1.73
3	BF3	10.42±1.12
4	BF4	32.78±2.62
5	BF5	52.76±2.15
6	BF6	20.56±1.82

Surface Morphology by Scanning Electron Microscopy (SEM): SEM was used to assess the surface properties of the produced mucoadhesive microspheres of Betahistine. The dried microspheres were carefully placed on a brass stub for examination, and in order to increase conductivity, a small coating of gold was applied using an ion sputtering process. Figure SEM picture of the improved formulation (BF3) showed that the microspheres had a smooth, uniform surface and were almost spherical in shape. There were no noticeable surface imperfections or fissures, and the particles looked well-formed. These findings show that the formulation technique was successful in creating microspheres that were structurally stable. Because they provide superior flow characteristics, less aggregation, and enhanced contact with the nasal mucosa, the uniform shape and smooth surface are beneficial for nasal medication administration.

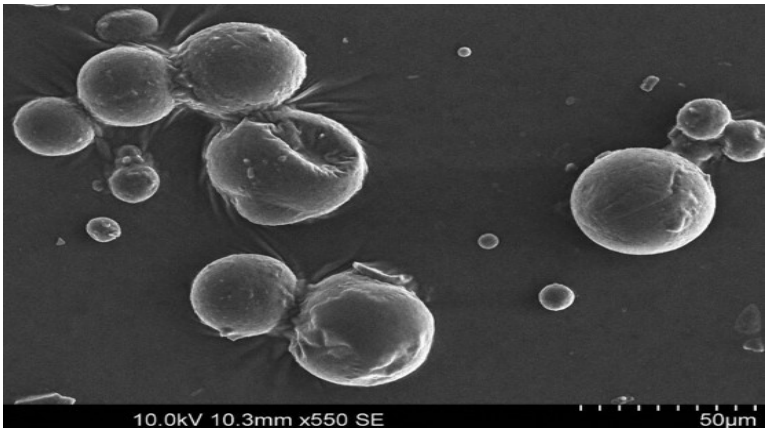


Figure 6: SEM image of Formulation BF3

Swelling Property: The swelling behaviour of the prepared mucoadhesive microspheres of Betahistine was evaluated to understand their hydration capacity and structural stability. The swelling index values for different formulations are presented in Figure.
With a higher polymer content (3% w/v), formulations BF3 and BF6 demonstrated a better capacity for swelling and were able to preserve their structural integrity for an extended period of time (up to about 4 hours). In contrast, formulations with lower polymer content, such as BF1 and BF4 (1% w/v) and BF2 and BF5 (2% w/v), began to lose their structure after approximately 3 hours.
The increased polymer content in BF3 and BF6, which creates a denser and more stable matrix that permits progressive medium penetration and extended swelling, is responsible for this behavior. It was also observed that particle surface area plays an important role in swelling behaviour, as an increase in surface area led to an increase in the swelling index.
Overall, higher polymer content contributed to improved swelling and stability of the microspheres.

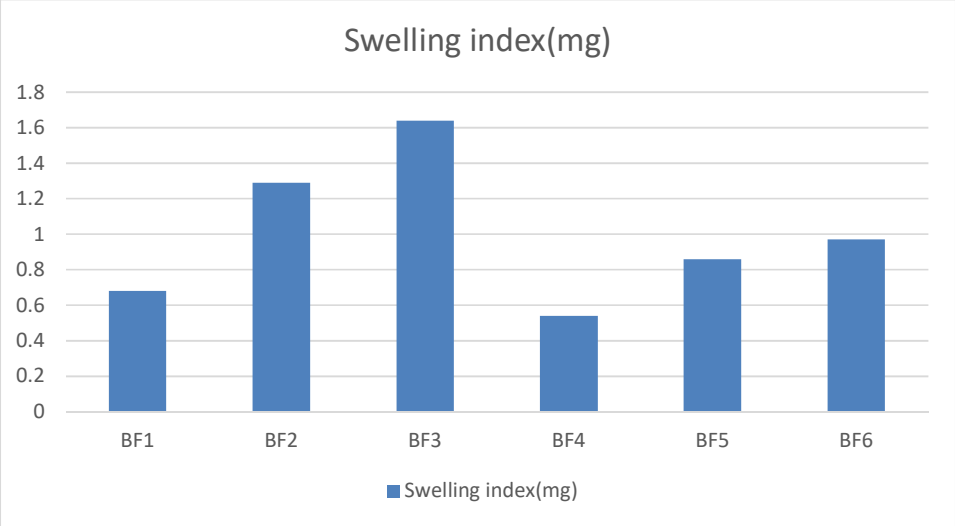


Figure 7: Swelling index of Microspheres

In-vitro mucoadhesion Test for Microspheres: The mucoadhesive behaviour of the prepared microspheres of Betahistine was evaluated to determine their ability to adhere to the nasal mucosa. The results obtained are summarized in Table. The study indicated that mucoadhesive strength increased with an increase in polymer concentration. Formulations containing higher chitosan content, such as BF3 and BF6 (3% w/v), exhibited stronger mucoadhesion compared to formulations with lower polymer concentration like BF1 and BF2 (1% w/v). This enhanced mucoadhesion may be due to the presence of more functional groups in the polymer, which interact with the mucosal surface and improve adhesion. It was also observed that particle surface area plays a significant role in mucoadhesion, as microspheres with larger surface area showed better adhesion properties.
Overall, increased polymer concentration and appropriate particle characteristics contributed to improved mucoadhesive performance of the microspheres.

Table 3: Data for in-vitro wash off test for mucoadhesion in Phosphate buffer pH 6.8

SR. No.	Formulation code	Mucoadhesion (%)
1	BF1	63.18 ± 0.367
2	BF2	65.19 ± 0.921
3	BF3	73.47 ± 0.124
4	BF4	64.71 ± 0.255
5	BF5	66.39 ± 0.174
6	BF6	68.49 ± 0.723

In-vitro Release Studies: Figure 3.12 shows the in-vitro release profile of betahistine from various microsphere formulations. According to the research, formulations BF1 through BF6 exhibited a regulated and sustained release pattern, with around 70–78% of the medication being delivered within 6 hours.
The findings unequivocally indicate that drug release is significantly influenced by both polymer concentration and stirring speed. A more regulated and marginally improved release profile resulted from an increase in polymer concentration, possibly as a result of better swelling and hydration of the polymer matrix. It was also observed that higher stirring speed resulted in increased drug release. This can be explained by the formation of smaller microspheres at higher speeds, which provide a larger surface area and shorter diffusion

path, thereby facilitating faster drug release. The polymer chitosan played an important role in the release mechanism by forming a hydrophilic network, allowing easy penetration of the dissolution medium. This leads to swelling of the matrix and promotes drug diffusion.

Overall, the medication was released from microspheres via a combination of polymer erosion and diffusion, which allowed for regulated drug administration throughout time.

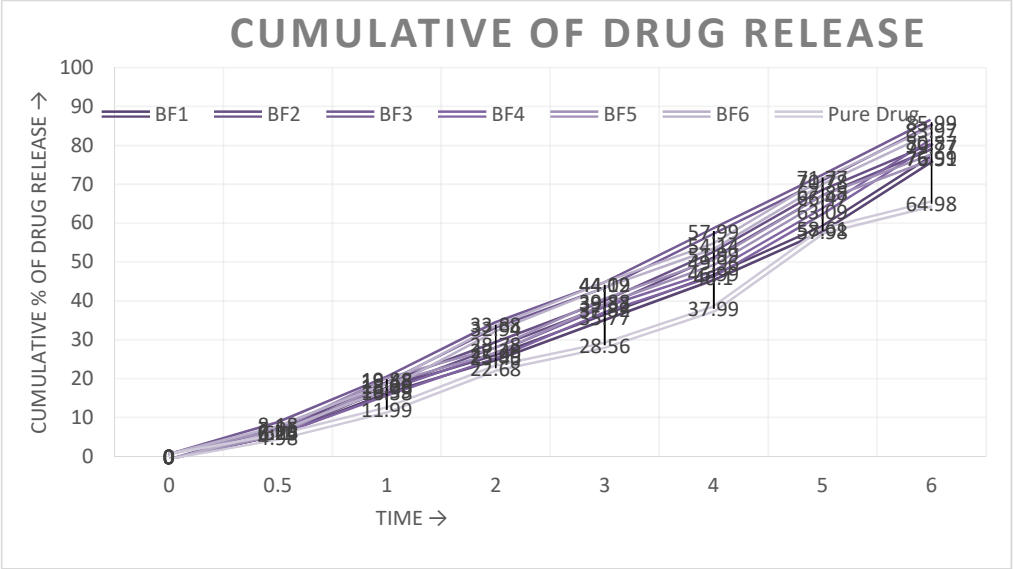


Figure 8: In-vitro drug release of prepared microspheres formulations

In-vitro drug release kinetics: Several kinetic models were used to examine the drug release data. The regression coefficient values, which ranged from 0.9724 to 0.9949, indicate that the drug release follows zero-order kinetics. The Korsmeyer-Peppas model's diffusion exponent (n value) was found to be 0.9888. This result indicates that non-Fickian diffusion is the mechanism of drug release. This indicates that diffusion and polymer relaxation mechanisms work together to release drugs from microspheres. Among them, it was discovered that the primary mechanism for drug release from the drug-loaded chitosan microspheres was drug diffusion. Table displays the kinetic analysis's complete findings.

Table 3.11: In-Vitro Release Kinetic Data for Betahistine Formulation (TF)

Formula code	Zero order		First order		Higuchi's	Korsmeyer-Peppas	
	K_0	R	K_1	R	R	N	R
BF1	3.0218	0.9741	0.0346	0.9868	0.9857	0.6154	0.9650
BF2	3.0322	0.9724	0.0319	0.9868	0.9877	0.6679	0.9681
BF3	2.9993	0.9949	0.0313	0.9857	0.9903	0.6359	0.9888
BF4	2.9888	0.9827	0.0288	0.9767	0.9917	0.6777	0.9762
BF5	2.9589	0.9878	0.0285	0.9904	0.9958	0.6628	0.9814
BF6	2.9758	0.9881	0.0197	0.9894	0.9942	0.6634	0.9729

$_0$= Zero order constant K_1= First order rate constant r= Coefficient correlation n= diffusion exponent

Stability Study: For six month, stability tests were conducted on the BF3 formulation at various temperatures and humidity levels, including 4 ± 1°C, 25 ± 2°C/60 ± 5% RH, and 37 ± 2°C/65 ± 5% RH.
The samples were examined for drug content and entrapment efficiency percentage following the research period. The findings demonstrated that the medication content of the BF3 formulation had not changed significantly.
This shows that the formulation held steady under the specified storage conditions. The polymer matrix, which aids in safeguarding the medication and preserving its integrity over time, may be the cause of the formulation's stability.

Table 3.12: BF3 Stability studies

Sr. No.	Time in Months	4±1ºC		25±2ºC with 60±5% RH		37±2ºC with 65±5% RH	
		Z	Y	Z	Y	Z	Y
1	**1**	86.7	84.9	87.9	86.2	86.3	84.3
2	**2**	86.5	84.6	86.8	86.1	86.2	84.1
3	**3**	84.7	84.6	86.7	86.0	86.1	83.2

4	**4**	84.0	84.1	86.5	85.5	85.7	82.5
5	**5**	83.8	83.2	84.4	85.4	84.1	82.1
6	**6**	83.7	83.1	84.3	85.3	84.0	82.1

CONCLUSION

Betahistine-loaded mucoadhesive microspheres were successfully formulated using chitosan as the mucoadhesive polymer by the W/O emulsion cross-linking technique. The prepared microspheres exhibited satisfactory physicochemical characteristics, drug entrapment efficiency, mucoadhesive strength, swelling behavior, and sustained drug release properties. Among the developed formulations, BF3 was found to be the optimized formulation based on its overall performance.

The enhanced mucoadhesion and prolonged residence time observed for the optimized formulation indicate its potential to improve nasal drug absorption. Furthermore, nasal delivery of Betahistine may overcome the limitations associated with oral administration, particularly extensive first-pass metabolism and low bioavailability. Therefore, the developed mucoadhesive microsphere system represents a promising strategy for improving the therapeutic effectiveness of betahistine in the management of vertigo and related vestibular disorders.

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