**Journal of Neonatal Surgery**
***ISSN(Online): 2226-0439***
***Vol. 14, Issue 15s (2025)***
*https://www.jneonatalsurg.com*

OPEN ACCESS

# Design And Development Of Mucoadhesive Microspheres Of Chlorpheniramine Maleate For Nasal Delivery

**Riya Pathak[1], Prof. Jaideo Pandey[*2]**

[1, 2*] Rajarshi Rananjay Sinh College of Pharmacy, Amethi, Sultanpur, U.P.-227405

***Corresponding author:**

Prof. Jaideo Pandey

*Head, Department of Pharmaceutics, Rajarshi Rananjay Sinh College of Pharmacy, Amethi, Sultanpur, U.P., 227405

Email ID: jaideo.p@gmail.com

Cite this paper as: Riya Pathak, Prof. Jaideo Pandey, (2025) Design And Development Of Mucoadhesive Microspheres Of Chlorpheniramine Maleate For Nasal Delivery. *Journal of Neonatal Surgery*, 14 (15s), 2446-2456.

**ABSTRACT**

Drug delivery methods that allow for prolonged, close contact between the drug and the mucosa are known as mucoadhesive drug delivery systems. In order to prevent hepatic first-pass metabolism, increase residence time, and improve therapeutic efficacy, the current study aimed to produce mucoadhesive microspheres for nasal delivery. In our work, we used the Emulsification cross linking approach to create Chlorpheniramine maleate mucoadhesive microspheres with conjugation of chitosan. The microspheres were assessed in terms of their stability, in vitro drug release, in vitro mucoadhesion, percentage yield, particle size, entrapment efficiency, and swelling properties. Using SEM and FTIR technologies, microspheres were characterised. Each batch's average microsphere's particle size was found compiling with in the desired/recommended range, ensuring that every batch had appropriate handling qualities. It was discovered that the range of drug encapsulation efficiency, percentage yield & percentage for mucoadhesion for all formulations were observed to justify the recommended range. When all of the formulations were tested for In-vitro drug release using phosphate buffer 6.8 pH, microspheres showed regulated drug release for up to six hours. According to the results gathered, mucoadhesive microsphere technology represents a very promising nasal delivery for improving patient compliance and delivering medication over an extended period of time.

***Keywords:*** *Nasal Delivery, Mucoadhesion, Microsphere, Chlorpheniramine maleate, Chitosan, Emulsification-cross linking.*

## 1. INTRODUCTION

**Nasal administration** has been used historically for both local and systemic conditions. Because of its quick absorption and potency, it is a desirable alternative to needle-based systemic drug delivery for immunizations. Furthermore, it has become well-known as a stable way to distribute drugs widely, which is particularly helpful for injectable drugs that are inefficient when taken orally because of digestive system breakdown.

**Nasal Delivery and Overcoming Challenges:** By avoiding liver metabolism, nasal administration helps to mitigate problems like sluggish absorption, low bioavailability, and drug degradation. Not for administering medication or vaccines, though; rather, it's important to remember that the nose tube serves mainly to protect the lungs from dangerous substances.

**Perks of Drug Absorption through the Nasal Cavity**: A well-vascularized epithelium, effective absorption, a porous endothelium, a large surface area, improved blood flow, and neutral pH mucus are benefits of medications absorbed through the nasal cavity. These advantages are obtained without undergoing early metabolism in the stomach or pancreas. **Chlorpheniramine Maleate** is an antihistamine used primarilys to treat allergic conditions such as hay fever, rhinitis, urticaria (hives), and other allergic reactions. It works by blocking the effects of **histamine**, a substance produced by the body during an allergic response. Nasal delivery of CPM via mucoadhesive microspheres can enhance bioavailability, prolong drug residence time, and improve therapeutic efficacy by adhering to the nasal mucosa. Nasal distribution of the drug is one possible substitute delivery technique for people who have trouble swallowing, especially those who are nauseous. One strategy that has been investigated to improve drug absorption through the nasal route is the use of bio adhesive polymers. Bio adhesive polymers increase the absorption of nasal medications by extending the duration of the drug in the nasal cavity and promoting the formation of tight connections between epithelial cells. Mucoadhesive medication administration technique, particularly for usage in the nose and other mucosal areas, are made of bio adhesive polymers

known as carbomers. Using absorption enhancers, such as cyclodextrins, fusidate derivatives, fatty acids, phospholipids, surfactants, and bile salts, is another technique.

**Chitosan microspheres** are becoming more and more well-liked as efficient nasal medication delivery devices. Biocompatible, non-toxic, and biodegradable, chitosan is a polymer that adheres well to biological surfaces. Because of its amino group, it has a positive charge and is created by de-acetylating chitin. With the nasal epithelium's negatively charged mucus layer, chitosan's positive charge enables it to create robust connections.

## 2. SUPPLIES & METHODS

### Substances, Equipment, and Chemicals:

Ultra Drugs Pvt. Ltd. sent me a gift of Chlorpheniramine Maleate. The supplier of chitosan was Sisco Research Laboratories Pvt Ltd. The remaining chemicals were analytical grade and used exactly as it is, no further purification was needed. The Shimadzu Pharma Spec 1700 double-beam UV spectrophotometer, located in Kyoto, Japan, was used for the spectrophotometric studies.

### The Process of Creating Mucoadhesive Microspheres:

### Method Of Preparation By W/O Emulsion Cross Linking Method

- Step-1: Taken a 10 ml of 2% aqueous acetic acid solution.
- Step-2: Now taken a given quantity of (0.1/0.2/0.3 gm) of chitosan was dissolved in a 10 ml of 2% aqueous acetic acid solution by continuously stirring until a homogenous solution was obtained.
- Step-3: Then added the drug (0.1 gm) slowly with stirring in prepared chitosan solution. Dispersed phase was prepared.
- Step-4: Now we prepared stabilizing agent DOSS (0.2%). Given quantity (about 50 mg) of DOSS was dissolved in 25 ml glycerine continuously stirring by glass rod.
- Step-5: Then 50 ml heavy and 50 ml light liquid paraffin was taken in 500ml pvc beaker, place under electronic stirring machine for 15 min at 1500-1600 rpm.
- Step-6: Added DOSS (stabilizing solution) as per the given quantity (2 ml or 3 ml) constant stirring at 1500-1600 rpm for 15 minutes. External Phase was prepared.
- Step-7: The dispersed phase (drug + chitosan + acetic acid) was added slowly to the above prepared external phase under constant stirring at 1500 -1600 rpm for 15 minutes.
- Step-8: Added Glutaraldehyde was added to above solution using continuously stirring for next 2 or more hours at 1500-1600 rpm.
- Step-9: Microspheres was prepared and filtered using vacuum filtration.
- Step-10: Firstly, washed with the n-hexane and then washed with the water. Kept for air drying about 24 hours and then stored in desiccator until next use.

**TABLE 1: Different Microspheres Variables:**

| Formulation | PROCESS VARIABLES | | | CONSTANT PARAMETERS | | |
|---|---|---|---|---|---|---|
| | Drug polymer Ratio | DOSS (ml) | GLA (ml) | Phase Ratio (Aqueous to Oil) | Stirring Rate (rpm) | Cross Linking Period (hours) |
| **FCM1** | 1:1 | 2 | 2 | 10:100 | 1500 – 1600 | 2 |
| **FCM2** | 1:2 | 2 | 2 | | | |
| **FCM3** | 1:3 | 2 | 2 | | | |
| **FCM4** | 1:1 | 3 | 4 | | | |
| **FCM5** | 1:2 | 3 | 4 | | | |
| **FCM6** | 1:3 | 3 | 4 | | | |

# Mean ± Std. Deviation whereas n=3

**Characteristion of Chlorpheniramine Maleate Loaded Microspheres:**

**Particle Size:**

Each microsphere was assessed in terms of its dimensions and form. The microsphere-prepared slide was inspected using an optical microscope, and the microspheres size were measured using the Olympus Master camera and modified Magnus Pro 3.0 software on the microscope (OLYMPUS). Average particle size of dried microspheres suspended in glycerine was calculated.

**Production Yield:**

By comparing the weight of the finished product after drying to the initial total weight of the medication and polymer used to make the microspheres, the percentage yield of prepared microspheres was calculated. After that, the dried microspheres were gathered and precisely weighed. Next, the formula below was used to compute the % yield. (10)

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

**Entrapment Efficiancy:**

An ultrasonic stirrer was used to crush and dissolve an exact measurement equal to 5 mg of Chlorpheniramine Maleate microspheres in 100 ml of ethanol, which was then left overnight. Whatmann filter paper No. 41 was used to filter the final mixture. The appropriate dilutions (10, 20, 30, 40 & 50 mcg/ml) were made. By means of a UV spectrophotometer at 262 nm, the drug content of the samples was examined. The following equations (1) were used to calculate entrapment efficiency.

$$\textbf{Entrapment efficiency} = \frac{\textbf{Actual amount of drug in microspheres}}{\textbf{Theoretical amount of drug in microspheres}}$$

Eqn……1

**SEM Analysis:**

Using scanning electron microscopy, the surface properties of the updated formulation (F3) were examined (JSM 6100, Jeol Ltd, Japan). Images were captured with a 100X magnification and an acceleration voltage of 10 kv.

**FTIR Analysis for Interactions**

An FTIR spectrophotometer (model – Spectrum Two, PerkinElmer, US) was used to analyse Chlorpheniramine maleate, chitosan, and the improved formulation (f3). The test sample was put into the device after being diluted with KBr until it reached a final dilution of 1:10. Measurements were made in transmittance mode against the pure KBr background spectrum, in the 400–4000 cm-1. The resolution of the instrument was set at $4cm^{-1}$, and every measurement was taken 50 times.

**UV Spectrophotometric Studies:**

Using distilled water, ethanol, and phosphate buffer with a pH of 6.8, standard curves were created for values ranging from 10 to 25 mcg/ml. Within a particular range of 261 nm, the absorbance was measured and recorded.

**Swelling Capacity:**

Precisely balance After being weighed, 50 mg microspheres (W) were incubated for 24 hours at pH 6.8 in phosphate buffer saline. Whatman filter paper was used to separate the enlarged microspheres after a 24-hour period. After gathering the microspheres and blotting them to remove extra water, their weights were recorded. It was also discovered that the swelling index depended on the particle's surface area. It was discovered that the swelling index rose along with the particle surface area.

$$\text{Swelling index} = \frac{(D2 - D1)}{D1} \text{ X } 100$$

Eqn…..2

Where,

$D_1$ = Microspheres' Final Diameter after swelling.

$D_2$ = Microspheres' Initial Diameter before swelling.

**Drug Release Studies and Research Procedures in Vitro:**

The drug release investigation was conducted using the USP XXIV basket apparatus, rotating the basket at 50 rpm and 37°C

± 0.5°C. 900 mL of phosphate buffer with a pH of 6.8 was utilized as the dissolve media in accordance with the USP XXVI dissolving standards. Microspheres containing Chlorpheniramine Maleate (5 mg) were utilized in the experiment. The sample solution was extracted in a quantity of 5ml at predetermined intervals, passed through a Whatmann filter paper, diluted appropriately, and then analyzed using spectrophotometry. A new batch of dissolving medium was quickly added in an equivalent volume after the test sample was removed. Based on absorbance measurements at 262 nm, the percentage of medication dissolved at different time periods was computed.

**Drug Release Mechanism and Kinetics:**

Regression analysis of the afore mentioned plots was used to calculate the coefficient of correlation ($r^2$) values for the linear curves in the drug release data from the in-vitro dissolution study using a variety of kinetic models, including zero order, first order, Higuchi's, Peppa's and others. This allowed for a better understanding of the mechanism and kinetics of drug release. In summary, four kinetics models of data treatment were used to plot the findings from in-vitro release investigations.

**Stability:**

For stability investigations, the formulation (FCM3) 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. Percentage drug content for the same composition was also examined.

## 3. RESULTS & DISCUSSIONS

**Preparation of Mucoadhesive Microsphere:**

This work showed that the emulsification-cross linking approach (described below) was a suitable and simple way for loading Chlorpheniramine maleate into chitosan microspheres. A polar organic solvent was used as the "aqueous phase" to produce water-in-oil (w/o) emulsion.

**Characterisation of Chlorpheniramine maleate loaded Mucoadhesive microspheres:**

**Size of Particle:**

Table 2 displays the average particle sizes of the formulas. The microspheres had mean particle sizes ranging from 10 to 29 µm. Mucoadhesive polymer concentration gradually affects the particle size, and stirring rate is the main factor influencing it. Regardless of polymer concentration levels, it is clear that increased stirring speeds lead to smaller particle sizes. On the other hand, there is an inverse link between particle size and mucoadhesive polymer concentration.

**Production Yield:**

The emulsion cross-linking approach produced microspheres with production yields ranging from 91.23% to 94.97%. For Chlorpheniramine maleate, as shown in Table 2. The study showed that the microspheres with a 1:3 (drug to polymer) ratio produced a higher production yield.

**Entrapment Efficacy:**

The entrapment consistently exceeded 75%, high encapsulation values. It was noted that increased drug to polymer ratios were associated with higher entrapment efficiencies.

**TABLE 2: Characterisation of Chlorpheniramine Maleate Loaded Microspheres:**

| Sr. No. | Formulation Code | Particle Size (µm) | Production yield (%) | Encapsulation Efficiency (%) | Mucoadhesion (%) | % Drug's Content | Swelling index (%) |
|---|---|---|---|---|---|---|---|
| **1.** | FCM1 | 29 ± 3.98 | 85.20 | 83.21 | 60.17 ± 0.396 | 81.89 | 0.89 |
| **2.** | FCM2 | 25 ± 4.16 | 88.51 | 86.93 | 66.17 ± 0.431 | 82.93 | 1.07 |
| **3.** | FCM3 | 20 ± 2.01 | 94.97 | 91.56 | 71.45 ± 0.921 | 91.39 | 1.35 |
| **4.** | FCM4 | 27 ± 2.92 | 86.72 | 84.43 | 62.72 ± 0.325 | 84.42 | 0.84 |
| **5.** | FCM5 | 26 ± 3.51 | 91.23 | 87.11 | 67.98 ± 0.584 | 87.21 | 0.98 |
| **6.** | FCM6 | 21 ± 1.96 | 93.16 | 89.32 | 68.87 ± 0.123 | 89.9 | 1.27 |

Mean ± Std. Deviation whereas n=3

**Scanning Electon Microscopy i.e SEM:**

The optimized formulation, FCM3, produced spherical shaped microspheres with a smooth surface, according to SEM examination.

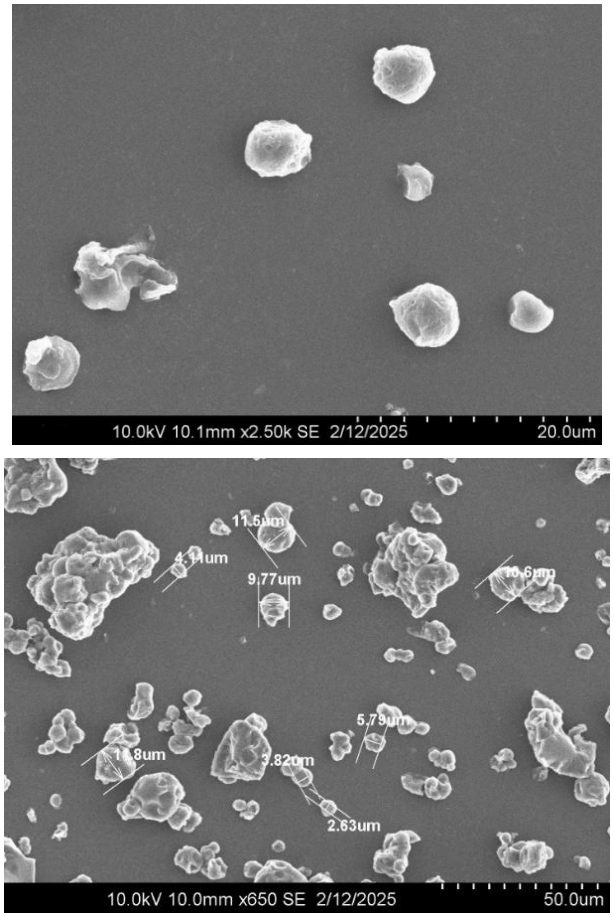


**Fig. 1: FCM3's SEM**

**FTIR:**

With FTIR spectroscopy, potential interactions between the crosslinking agent, chitosan, and Chlorpheniramine Maleate were investigated. The drug is preserved within the formulation and there is no drug-polymer interaction, the drug-loaded microspheres' spectrum indicated. Variations in peak intensity suggest that the drug-polymer interaction is not significant. The results of the FTIR for the FCM3 Formulation, Chlorpheniramine Maleate and Chitosan are displayed below as Figures 2, 3, and 4 respectively.

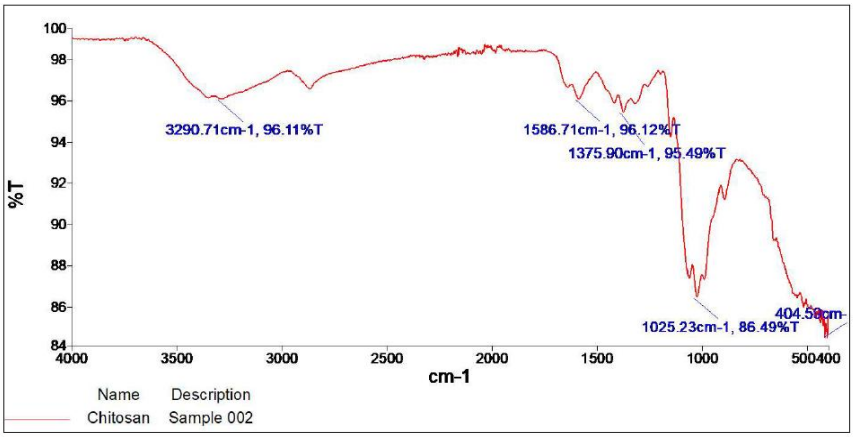


**Fig. 2: FTIR of Chitosan**

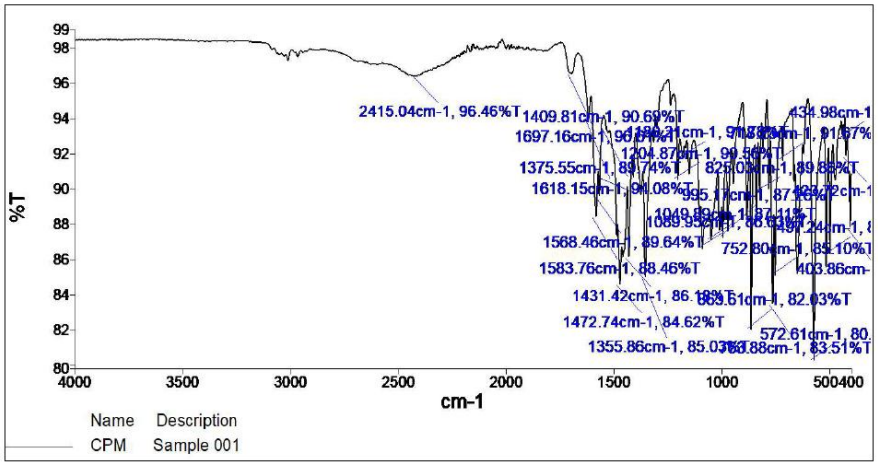


**Fig. 3: Pure Drug Chlorpheniramine Maleate's FTIR**

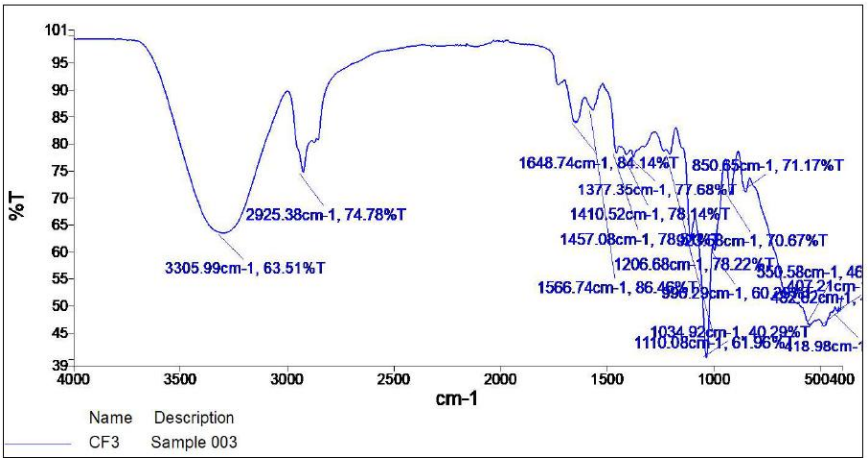


**Fig. 4: FCM3's FTIR**

**Assessment of Pure API by UV Spectrophotometre:**

By following the application of Beer-Lambert's Law over the concentration range of 10–50 µg/ml and using three different solvents - distilled water, ethanol and phosphate buffer with a pH of 6.8 the absorbance at 262 nm was measured (table 3) and calibration curves were produced (figure 5).

**TABLE 3: STANDARD CALIBRATION OF CHLORPHENIRAMINE MALEATE:**

| Sr. No. | Concentration (µg/ml) | Absorbance | | |
|---|---|---|---|---|
| | | Distilled Water | Ethanol | Phosphate Buffer (6.8 pH) |
| 1. | 10 | 0.183 | 0.195 | 0.257 |
| 2. | 20 | 0.365 | 0.365 | 0.502 |
| 3. | 30 | 0.548 | 0.587 | 0.769 |
| 4. | 40 | 0.732 | 0.783 | 1.021 |
| 5. | 50 | 0.925 | 0.975 | 1.277 |
| $R^2$ Value | | 0.9999 | 0.9992 | 0.9998 |

Mean ± Std. Deviation whereas n=3

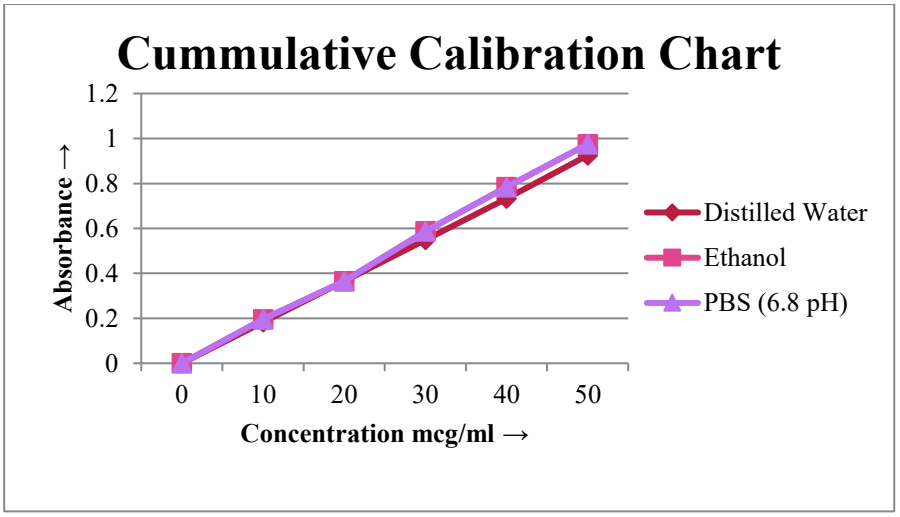


**Fig. 5: Cumulative Calibration Curve for Pure Chlorpheniramine maleate in Different Solvents.**

**Swelling Ability of Microspheres Prepared:**

Table 2 displays the swelling index for each formulation. The microspheres' degree of swelling varied amongst formulations, ranging from 0.84% to 1.35%. It is noted that as mucoadhesive polymer concentrations rise, the degree of swelling tends to significantly increase.

**In-Vitro Mucoadhesion:**

Based on polymer content, the mucoadhesion of nasal microspheres loaded with Chlorpheniramine Maleate varied from 60.17±0.396 % to 71.45±0.921 % (Table 2).

**In-Vitro Release Investigations:**

Table 4 provided an overview of each formulation's in vitro release profiles. Figure 6 shows the release characteristics of chitosan microspheres loaded with Chlorpheniramine Maleate. It became evident that the polymer concentration and stirring rate had a big influence on the drug's release.

**TABLE 4: In-Vitro Drug Release of Pure CHLORPHENIRAMINE MALEATE & Formulations of Microspheres loaded with DrUG:**

| Time in Hours | Cumulative % drug release ± SD | | | | | | |
|---|---|---|---|---|---|---|---|
| | Pure drug | FCM1 | FCM2 | FCM3 | FCM4 | FCM5 | FCM6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 3.27 | 4.87 | 6.34 | 9.46 | 7.17 | 8.45 | 8.73 |
| 1 | 10.92 | 14.47 | 17.13 | 20.53 | 15.68 | 18.03 | 18.95 |
| 2 | 18.65 | 23.23 | 25.43 | 34.17 | 26.41 | 27.53 | 31.67 |
| 3 | 25.78 | 34.54 | 38.36 | 43.56 | 34.99 | 36.51 | 40.47 |
| 4 | 32.83 | 44.77 | 48.72 | 53.63 | 45.82 | 47.11 | 49.93 |
| 5 | 55.98 | 60.69 | 64.97 | 72.89 | 61.79 | 63.54 | 66.31 |
| 6 | 64.13 | 73.26 | 79.56 | 89.69 | 75.63 | 78.05 | 84.23 |

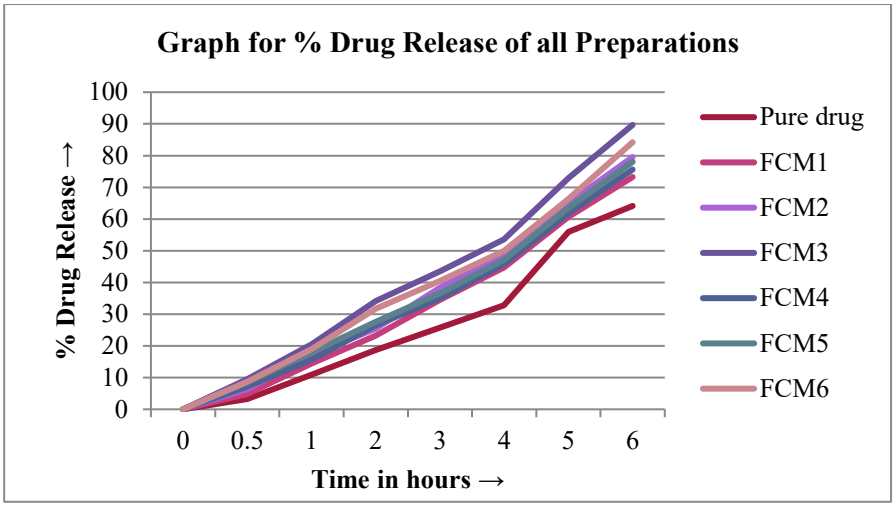


**Fig. 6: In-Vitro Drug Release of All 6 Formulations**

**Drug Release Kinetic Studies in Vitro Using Different Models:**

The Higuchi Equation, the Korsemeyer-Peppas model, the Zero-order, and the First-order models were used to analyze the in vitro drug release properties of each formulation. Table 5 displays the outcomes.

**TABLE 5: The diffusion coefficient (N) values of the Peppas equation and regression coefficient ($r^2$) values, used in the analysis of microspheric release data according to different kinetic models.**

| Formula code | Zero order | First order | Higuchi's | Korsmeyer-Peppas | |
|---|---|---|---|---|---|
| | R | R | R | n | R |
| FCM1 | 0.9656 | 0.9492 | 0.9653 | 0.6254 | 0.9744 |
| FCM2 | 0.9678 | 0.9802 | 0.9673 | 0.6575 | 0.9836 |
| FCM3 | 0.9887 | 0.9838 | 0.9844 | 0.6644 | 0.9892 |
| FCM4 | 0.9732 | 0.9738 | 0.9793 | 0.6378 | 0.9797 |
| FCM5 | 0.9757 | 0.9766 | 0.9811 | 0.6456 | 0.9804 |
| FCM6 | 0.9798 | 0.9816 | 0.9834 | 0.6623 | 0.9884 |

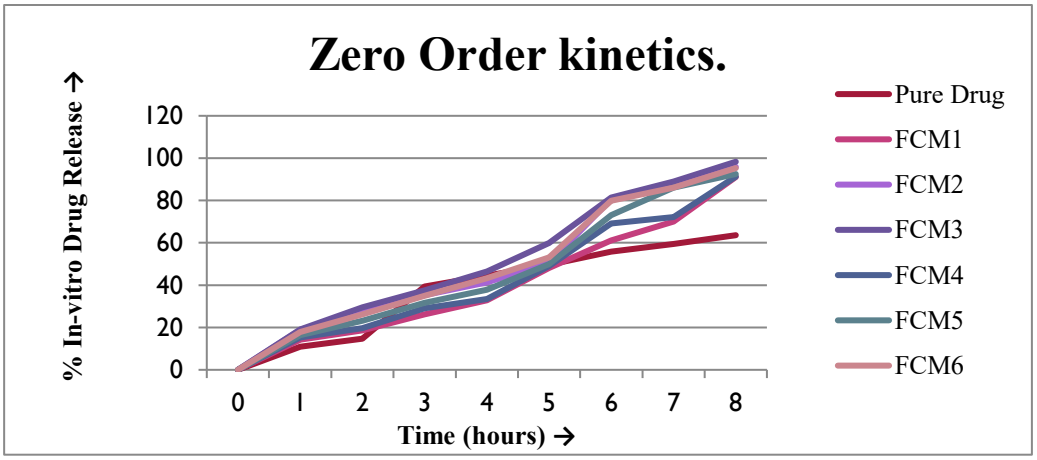


**Fig. 7: Chlorpheniramine Maleate Microsphere Formulations: Zero Order Release Kinetics.**

**Stability Assessment of Chlorpheniramine Maleate Microspheres:**

For the purpose of evaluating the stability of the formulated Chlorpheniramine Maleate microspheres, the ideal formulation FCM3 was stored for six months under the following conditions: 4±1˚C, 25±2˚C with 60±5˚C RH, and 37 ± 2˚C with 65 ± 5% RH displayed in Table 6. It's interesting to note that formulations kept at 25±2˚C with 60±5˚% RH showed the highest percentage levels of entrapment, followed by formulations kept at 4±1˚C and 37±2˚C with 65±5% RH conditions. These findings may be explained by the facts that point to a partial erosion of the polymer matrix during storage.

**TABLE 6: STABILITY STUDIES OF FCM3, THE OPTIMISED FORMULATION:**

| Sr. No. | Time in Months | 4±1°C | | 25±2°C with 60±5% RH | | 37±2°C with 65±5% RH | |
|---|---|---|---|---|---|---|---|
| | | Z | Y | Z | Y | Z | Y |
| 1 | 1 | 85.9 | 84 | 85.9 | 84.05 | 85.93 | 84.03 |
| 2 | 2 | 85.8 | 83.6 | 85.8 | 84.03 | 85.62 | 84.01 |
| 3 | 3 | 85.7 | 83.6 | 85.7 | 84 | 85.1 | 83 |
| 4 | 4 | 85.0 | 83.5 | 85.5 | 83.9 | 84.7 | 82.8 |
| 5 | 5 | 84.7 | 83.4 | 85.3 | 83.8 | 84.3 | 82.5 |

# Z= % Entrapment Efficacy & Y= % Cumulative Drug Release

## 4. CONCLUSION

It is clear from the ongoing studies that Chlorpheniramine Maleate microspheres, which are made with chitosan using emulsification cross-linking technique, have potential for use in nasal delivery. As a result, the created microsphere becomes a potential candidate for an intranasal controlled medication delivery system.

## REFERENCES


[1] Adimoodlam S, Chavda GA, Patel JN, Jimson J, and Narayana SVB: Formualation and Evaluation of Tinazidine Hydrochloride Microspheres by using 32 Full Factorial Designs. *Internation research journal of pharmacy*.2011; 2 (9):110-115.

[2] Al-Helw AA, Al-Angary AA, Mahrous GM, Al-Dardari MM: Preparation and Evaluation of Sustained Release Cross-linked Chitosan Microspheres Containing Phenobarbitone. *Journal of Microencapsulation*. 1998; 15: 373– 382

[3] Ali, Huma, Muhammad Harris Shoaib, and Rabia Bushra. "Formulation development of pheniramine maleate tablet by direct compression." *Jordan Journal of Pharmaceutical Sciences* 4.1 (2011): 1-8.

[4] Bhoi, Ganesh S., et al. "Formulation and evaluation of medicated chewing gum containing chlorpheniramine maleate." *Indo Am J Pharm Res* 4.3 (2014): 1309-1319.

[5] Callens, Catherine, and Jean Paul Remon. "Evaluation of starch–maltodextrin–Carbopol® 974 P mixtures for the nasal delivery of insulin in rabbits." *Journal of controlled release* 66.2-3 (2000): 215-220.

[6] Chintagunta P, Kavitha K and Anil KSN: Formulation and Evaluation of Trimetazidine Hydrochloride Loaded Chitosan Microspheres. *International Journal of Applied Pharmaceutics*. 2010; 2; 11-14.

[7] Chowdary KPR, and Rao YS: Mucoadhesive Microspheres and Micro Capsules: Current Status. *Indian Journal of Pharmaceutical Sciences*. 2005; 67(2):141-150.

[8] Desai S, Gali Vidyasagar G, Shah V, Desai D: Preparation and in vitro Characterization of Mucoadhesive Microspheres of Midazolam: Nose to Brain Administration, *Asian Journal of Pharmaceutical and Clinical Research*. 2011; 4: 100-102.

[9] Deshmukh T, Deshmukh V, Jadhav P, Kasat K and Patil R: Formulation and Evaluation of Mucoadhesive Microspheres of Ziprasidone Hydrochloride for Oral Controlled Release. *Journal of Current Pharma Research*, 2012; 497- 502.

[10] Gavini E and Hegg AB: Nasal Administration of Carbamazepine using Chitosan Microspheres in-vitro / in-vivo studies. *International Journal of Pharmceutical Science.* I, 2006; 307: 9-15.

[11] Gavini E, Rassu G, Sanna V, Cossu M and Giunchedi P: Mucoadhesive Microsphere for Nasal

Administration of an Antiemetic Drug, Metoclopramide: In-vitro/Ex-vivo Studies. *Journal of Pharmacy and Pharmacology*. 2005; 57: 287-294

[12] Ghosh PK: Thernoreversible- Mucoadhesive Gel for Nasal Delivery of Sumatriptan. *AAPS Pharm Sci Tech*, 2006; 7: 100-102.

[13] Hardenia SS, Jain A, Patel R and Kaushal A: Formulation and Evaluation of Mucoadhesive Microspheres of Ciprofloxacin. *Journal of Advanced Pharmacy Education and Research.* 2011; 214-222.

[14] Jadhav KR, Gambhire MN, Shaikh IM, Kadam VJ and Pisal SS: Nasal Drug Delivery System-Factor Affecting and Applications. *Current Drug Therapy*, 2007; 27-38.

[15] Jameela SR, Kumary TV, Lal AV and Jayakrishnan A: Progesterone-Loaded Chitosan Microspheres: A Long Acting Biodegradable Controlled Delivery System. *Journal of Controlled Release*. 1998; 52: 17–24.

[16] Jain AJ, Chauk DS, Mahajan HS, Tekade AR and Gattani SG: Formulation and Evaluation of Nasal Mucoadhesive Microspheres of Sumatriptan Succinate. *Journal of Microencapsulation*, 2009; 26(8): 711–721.

[17] Kavita K and Rajas NJ: Sustained Opthalmic Delivery of Levofloxacin Hemihydrate from an Ion Activated In-situ Delling System. *International Journal of PharmTech Research* 3, 2011; 702-706.

[18] Krishnamoorthy R and Mitra AK: Prodrugs for Nasal Drug Delivery. *Advanced Drug Delivery Rev* 29, 1998; 135-46.

[19] Kumar, Manish, et al. "Chlorpheniramine maleate containing chitosan-based nanoparticle-loaded thermosensitive in situ gel for management in allergic rhinitis." *Drug Delivery and Translational Research* 9.6 (2019): 1017-1026.

[20] Mahajan H, Gattani S and Surana S: Spray Dried Mucoadhesive Microspheres of Ondansetron for Nasal Administration. *International Journal of Pharmaceutical Sciences and Nanotechnology,* 1 2008; 267-274.

[21] Mahalaxmi R and Kumar S: Preparation of Mucoadhesive Microspheres for Nasal Delivery by Spray Drying. *Indian Journal of Pharmaceutical Sciences,* 2007; 9: 651–657.

[22] Mahmood, Sura Zuhair, et al. "Optimization and evaluation of chlorpheniramine maleate oral strip for pediatric use." *Optimization* 11.12 (2018).

[23] Mainardes RM, Cocenza urban MC, Cinto PO, Chaud MV and Evangelista RC: Liposomes and Micro / Nanoparticles as Colloidal Carriers for Nasal Drug Delivery. *Current Drug Delivery* 3, 2006; 275-85.

[24] Martin A, Bustamante P, Chun AH and Eds: Physical Pharmacy, 4th Edn, B.J. Waverly Pvt. Ltd; New Delhi, 1996; 423-432.

[25] Martinac A and Pavelic A: Spray Dried Chitosan / Ethyl Cellulose Microspheres for Nasal Drug Delivery: Swelling Study and Evaluation of in vitro Drug Release Properties. *Journal of Microencapsulation*, 2005, 5: 549-561.

[26] Merkus, F. W. H. M., et al. "Cyclodextrins in nasal drug delivery." *Advanced drug delivery reviews* 36.1 (1999): 41-57.

[27] Mishra S, Patel NS, Kumar M and Pathak K: Cross-linked Mucoadhesive Microspheres Based on Anionic Eteropolysaccharide for Nasal Delivery of Felodipine: Optimization and in-vitro Evaluation. *Drug Delivery Letters*. 2013; 3, 136-148.

[28] Pandey JD & Tripathi P, Formulation and Evaluation of Levocetrizine Loaded Mucoadhesive Microspheres for Nasal Delivery. *International Journal of Pharmaceutical Sciences and Research (IJPSR)* (2016), vol 7, Issue 5, 2242-2251.

[29] Pandey JD & Tripathi P, Mucoadhesive Microspheres of Anti-allergic Agent for Nasal Delivery. *Asian Journal of Pharmaceutical Technology and Innovation* (2016), vol 4, Issue 18, 48-58.

[30] Patel D, Patel N, Thakkar V, Modi A and Gandhi T: Development and Characterization of Mucoadhesive Microspheres of Levosalbutamol Sulphate. *International Journal of Pharmaceutical Sciences and Research*. 2013; 4(5): 1838-1851.

[31] Patel, AMIT A., Rajesh H. Parikh, and Tejal A. Mehta. "Development optimization and evaluation of effervescent tablets of chlorpheniramine maleate using Box Behnken design." *Int J Pharm Pharm Sci* 7.8 (2015): 317-23.

[32] Patil SB & Sawant K: Chitosan Microspheres as a Delivery System for Nasal Insufflations. *Colloids and Surfaces, Biointerfaces*. 2011; 84; 384–389.

[33] Prajapati RK, Mahajan HS and Surana SJ: PLGA Based Mucoadhesive Microspheres for Nasal Delivery: In vitro/Ex vivo Studies. *Indian Journal of Novel Drug Delivery*. 2011; 3 (1):9-16.

[34] Rajalakshmi AN and Bhuwaneshwari B: Short Review on Pharmaceutical Microspheres: *Interantional Journal of Universal Pharmacy and Life Sciences*. 2012; 2(2): 2449- 6793.

[35] Ramachandran S, Nandhakumar S and Dhanaraju MD: Formualtion and Characterization of Glutaraldehyde Cross Linked Chitosan Biodegradable Microspheres Loaded with Famotidine. *Tropical Journal of Pharmaceutical Research.* 2011; 10(3): 309-316.

[36] Rao JV, Gangadi JR, Kumar SM, Venu K and Rao KNV: Formulation and Evaluation of Mucoadhesive Microspheres for Intra-nasal Delivery. *International Journal of Pharmacy & Technology*. 2010; 2(4): 1158-1198.

[37] Rathan M, Kumar DS, Shirwaikar A, Ravi Kumar D, Sampath Kumar and Prasad RS: Preparation of Mucoadhesive Microspheres for Nasal Delivery by Spray Drying. *Indian Journal of Pharmaceutical Sciences* , 2007; 69: 651-657.

[38] Sanchez-Gonzalez, Marcos, et al. "A randomized controlled pilot trial to test the efficacy of intranasal chlorpheniramine maleate with xylitol for the treatment of allergic rhinitis." *Cureus* 13.3 (2021).

[39] Shwetha, S., K. Kamath, and S. K. Kumar. Design and evaluation of floating microspheres of Rabeprazole sodium. *International Journal of Pharmacy and Pharmaceutical Sciences* 4.3 (2012): 104-120.

[40] Sinha VR, Singla AK, Wadhwan S, Kaushik R, Kumaria R, Basal K, and Dhawan S: Chitosan Microspheres as a Potential Carrier for Drugs. *International Journal of Pharmaceutics*. 2004; 274: 1-33.

[41] Soane RJ, Frier M, Perkins AC, Jones NS and David SS: Evaluation of the Clearance Characteristics of Bio adhesive System in Human. *international Journal of Pharmaceutics*. 1999; 178: 55-65

[42] Soliman, Iman I., Nadia A. Soliman, and Ebtsam M. Abdou. "Formulation and stability study of chlorpheniramine maleate nasal gel." *Pharmaceutical Development and Technology* 15.5 (2010): 484-491.

[43] Swamy NGN and Abbas Z: Preparation and In-vitro Characterization of Mucoadhesive Polyvinyl Alcohol Microspheres Containing Amlodipine Besylate for Nasal Administration. *Indian Journal of Pharmaceutical Education and Research*. 2012; 46: 52-58.

[44] Taş, Çetin, et al. In vitro and ex vivo permeation studies of chlorpheniramine maleate gels prepared by carbomer derivatives. *Drug development and industrial pharmacy* 30.6 (2004): 637-647.

[45] Tatiya GD and Basarkar GD: Formulation Development and In-vitro Evaluation of Mucoadhesive Microspheres of Simvastatin for Nasal Delivery. *International Journal of Pharmaceutical Sciences Review and Research*. 2013; 21(2): 334-341.

[46] Thanoo BC, Sunny MC and Jayakrishnan A: Cross-linked Chitosan Microspheres: Preparation and Evaluation as a Matrix for the Controlled Release of Pharmaceuticals. *Journal of Pharmacy and Pharmacololgy*. 1992; 44: 283– 286

[47] Ugwoke M, Agu R, Verbeke N, and Kinget R: Nasal Mucoadhesive Drug Delivery: Background, Applications, Trends and Future Perspectives. *Advance Drug Delivery Review*.2005; 57: 1640–1665.

[48] Ugwoke, Michael Ikechukwu, et al. Intranasal bioavailability of apomorphine from carboxymethylcellulose-based drug delivery systems. *International journal of pharmaceutics* 202.1-2 (2000): 125-131.

[49] Viswanadhan Vasantha, Prasanth, et al. "Combination of cellulose derivatives and chitosan-based polymers to investigate the effect of permeation enhancers added to in situ nasal gels for the controlled release of loratadine and chlorpheniramine." *Polymers* 15.5 (2023): 1206.

[50] Wamorkar V, Manjunath SY and Verma MM: Development and Validation of UV Spectroscopic Method for Determination of Metoclopramide Hydrochloride in Bulk and Tablet Formulation. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2011; 3(3); 171-174.

[51] Yetkin, G., et al. "The effect of dimethyl-beta-cyclodextrin and sodium taurocholate on the nasal bioavailability of salmon calcitonin in rabbits." *STP pharma sciences*, 1999; 9(3): 249-252.

[52] Yuvraj S, Dangi, and Kamta PN: Preparation, Optimization and Characterization of Controlled Release Mucoadhesive Microspheres Containing Highly Variable Drug Itraconazole in Reducing Gastric Variability as Compared to Innovator Formulation. *Scholar Research Library*. 2010: 37-51.

[53] Zuheir A, Samein LH and Alash N: Preparation and In-vitro Evaluation of Metoclopramide HCL Hollow-Type Suppository. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2013, 660-666.