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Formulation and Evaluation of mucoadhesive microsphere of montelukast for nasal delivery

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ABSTRACT

Mucoadhesive drug delivery systems are drug delivery techniques that enable extended, intimate contact between the medication and the mucosa. The goal of the current study was to create mucoadhesive microspheres for nasal administration in order to enhance therapeutic efficacy, prolong residence duration, and avoid hepatic first-pass metabolism. In our study, we created Montelukast mucoadhesive microspheres with chitosan conjugation using the Emulsification cross linking technique. The stability, in vitro drug release, in vitro mucoadhesion, percentage yield, particle size, entrapment efficiency, and swelling's property of the microspheres were evaluated. Microspheres were characterized using infrared spectroscopy and scanning electron microscopy. The average microsphere particle size in each batch was between 10 and 50 µm, guaranteeing that each batch had the right handling characteristics. For all formulations, the range of drug encapsulation efficiency was found to be 75.71% to 89.24%. The percentage-yield of the drug for each formulation was found to vary between 86.51% and 91.58%. The observed mucoadhesion percentages ranged from 62.17% to 73.45%. All of the formulations demonstrated controlled drug release for up to six hours when evaluated for drug release in vitro using phosphate's buffer pH 6.8. As per the collected data, mucoadhesive microsphere preparation techniques are a very promising nasal administration method that can enhance patient adherence and provide medicine over a longer duration.

Keywords: *Montelukast, Mucoadhesive Microspheres, Nasal Delivery, Anti-Asthmatic Agent, Chitosan, Emulsification Cross-linking Technique.*

1. INTRODUCTION

Parenteral injections have often been compared to nasal drug delivery as the most practical option. This is caused by the nasal epithelium's high permeability, which permits a greater molecular mass cut-off at roughly 1000 Da, a quick rate of drug absorption, and plasma drug profiles that are occasionally nearly equal to those from intravenous injections (1). Historically, medications have been administered through the nose to treat conditions like allergies, infections, and congestion of the nasal passages. Recent research has demonstrated that the nasal route can be used to distribute polar medicines—which include low molecular weight peptides and proteins—systemically. These compounds are difficult to administer by other means than injection. When compared to oral and intramuscular treatment, rapid absorption offers a quicker beginning of action from a pharmacokinetic perspective. Additionally, hepatic first-pass metabolism is circumvented, resulting in heightened and consistent bioavailability. (2)

"Nasaya Karma," or nasal therapy, has long been acknowledged in Ayurvedic medicine. Nonetheless, in 1992, the potential for nasal medication administration was identified. Historically, the nasal route has been utilised to administer medications for the treatment of local illnesses; however, in the past ten years, the nasal cavity has gained recognition as a viable drug delivery channel. Research and review publications on nasal medication delivery are becoming more and more common. The various potential benefits that the nasal cavity may offer are the source of this interest (3). Mucoadhesive microspheres are composed of a bioadhesive polymer either fully or with an exterior coating. They can also be microparticles or microcapsules (containing a drug core) with a diameter of 1.000 µm. The targeted and regulated release of drugs is a topic of ongoing research on microspheres in general. A polymeric device lowers the total amount of medication required by enabling slow, regulated, and predictable drug release over time. The coupling of bioadhesive properties to microspheres is crucial for nasal drug delivery because it offers several benefits, including improved drug bioavailability and efficient absorption, a closer bond with the mucus layer, and a decrease in the frequency of drug administration because of a decrease in mucociliary clearance of drug delivery systems that adhere to the nasal mucosa (4).

Montelukast selectively binds to and inhibits the **cysteinyl leukotriene receptor 1 (CysLT1)**.

- It blocks the action of leukotrienes (LTs), which are inflammatory mediators released by mast cells, eosinophils, and other cells.
- Leukotrienes cause:
    - Bronchoconstriction (airway narrowing)
    - Increased vascular permeability
    - Mucus secretion
    - Inflammation
- By inhibiting leukotrienes, montelukast:
    - Reduces inflammation in the airways
    - Prevents bronchoconstriction
    - Improves asthma symptoms and allergic rhinitis.

2. MATERIALS AND METHODS

2.1 Materials: Montelukast was obtained as a gift sample from Ultra Drug Pvt. Ltd., Baddi. Chitosan was procured from Sisco Research Laboratory Pvt. Ltd., Delhi. Ethanol, Glutraldehyde, DOSS, Sodium hydroxide, Sodium chloride, Light Liquid Paraffin, Heavy liquid paraffin and acetic acid were purchased from SD Fine chemicals, Mumbai.

2.2 Compatibility Study: The I.R. Spectroscopy was used to verify the compatibility study. I.R. Spectroscopy was used to get the FTIR spectra of the formulation and chitosan. The resulting FT-IR spectra were used to determine the compatibility between the pure medication and polymer. The sample was scanned over the wave number, and the 4000-400 cm^{-1} wave number was used to record the spectra. (6, 7)

2.3 Method Of Preparation By W/O Emulsion Cross Linking Method (8, 9)

- 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. Given quantity about 50 mg of DOSS was dissolved in 25 ml glycerine continuously stirring by glass road.
- 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 mins at 1550-1650 rpm.
- Step-6: Added DOSS (stabilizing solution) as per the given quantity (2 ml or 3 ml) constant stirring at 1550-1650 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 1550-1650 rpm for 15 minutes.
- Step-8: Added Glutaraldehyde was added to above solution using continuously stirring for next 2 or more hours at 1550-1650 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 variables of microspheres

Formulation and process variables				Constant parameters		
For. Code	**Drug: Polymer**	**Vol. of stabilizing agent (DOSS)**	**Vol. of cross linking agent (Glutaraldehyde)**	**Constant parameter aq. to oil phase**	**Stirring rate**	**Cross linking**

FM1	1:1	2 ml	2 ml	10 :100	1550 – 1650 rpm	2 hrs
FM2	1:2	2 ml	2 ml			
FM3	1:3	2 ml	2 ml			
FM4	1:1	2 ml	4 ml			
FM5	1:2	2 ml	4 ml			
FM6	1:3	2 ml	4 ml			

2.4 Characterization and Evaluation

2.4.1 Determination of Percentage Yield of Microspheres: 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)

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

2.4.2 Determination of % Drug Content and % Entrapment Efficiency: 100 mg of precisely weighed microspheres were crushed in a glass mortar and pestle, and with the aid of an ultrasonic stirrer, the powdered microspheres were dissolved in 100 ml of methanol. The solution was filtered through Whatmann filter paper no. 41 after 12 hours, and the filtrate's drug content was measured at 345 nm using a UV-visible spectrophotometer. (11)

2.4.3 Particle Size Analysis: Each microsphere was assessed in terms of its dimensions and form. The microsphere-prepared slide was inspected using an optical microscope, and the microsphere's size was 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. (12, 13)

2.4.4 Shape and Surface Characterisation: Microspheres' form and surface characteristics were examined using a scanning electron microscope (SEM). The Tokyo Scanning Electron Microscope, Joel model JSM 6400, was the tool utilised in this investigation. Using double-sided sticky tape, the microspheres were adhered directly to the SEM sample stub. Gold film (200 nm in thickness) was then applied under low pressure (0.001 torr) and captured on camera.

2.4.5 Degree of Swelling: 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 weight (Wt) was 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. (14, 15)

2.4.6 Mucoadhesive Property by Wash-Off Test: Microspheres' mucoadhesive properties were assessed using the wash-off method, an in vitro adhesion testing technique. “A freshly cut (2 x 2 cm) slice of goat nasal mucosa was mounted using cyanoacrylate glue on glass slides (3 x 1 inch); about twenty-five microspheres were placed on each wet-rinsed tissue specimen after two glass slides were coupled with an appropriate support and the support was then fastened to the arm of a USP tablet dissolving test machine”. “The tissue specimen was placed in the test fluid (phosphate buffer pH 6.8) at 37 ± 0.5°C for a slow, regular up-and-down instant before the disintegration test machine was turned on and the machine was stopped after 30 minutes, 60 minutes at hourly intervals, and up to 6 hours, and the number of microspheres that were still attached to the tissue was counted”. The following formula was used to display the adherent percentage:

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

2.4.7 In-Vitro Drug Release or Dissolution Studies: All of the formulations were subjected to dissolution experiments using the USP XXIV apparatus (Basket technique) with 900 ml of phosphate buffer (pH 6.8) as the dissolution medium, rotating at a constant speed of 50 rpm and at 37 ± 0.5°C. “For each test, a sample of microspheres equivalent to 10 mg of Montelukast was employed; to keep the sink condition, an aliquot of the sample was periodically taken at an appropriate time interval, and the volumes were replaced with new dissolving medium”. At 345 nm, the percentage of the medication that dissolved during various time periods was computed. (16, 17)

2.4.8 Kinetics of Drug Release: Regression analysis of the aforementioned 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. (18, 19)

2.4.9 Stability Study: For stability investigations, the formulation (TF3) was created from the produced microspheres. Three sample sets of the formulation were separated and stored at 4 ±1, 25 ±2 and 60 ±5%RH and 37 ±2 and 65±5%RH. After 30 days, the samples were tested for drug release. Entrapment effectiveness for the same composition was also examined. (20, 21)

3. RESULTS AND DISCUSSION

3.1 FTIR Spectra: The pure form of Montelukast's FTIR spectrum was captured. Figure 1 displays the sample drug's FTIR spectrum. FTIR spectroscopy was used to analyse the infrared spectra of pure drugs utilising the KBR.

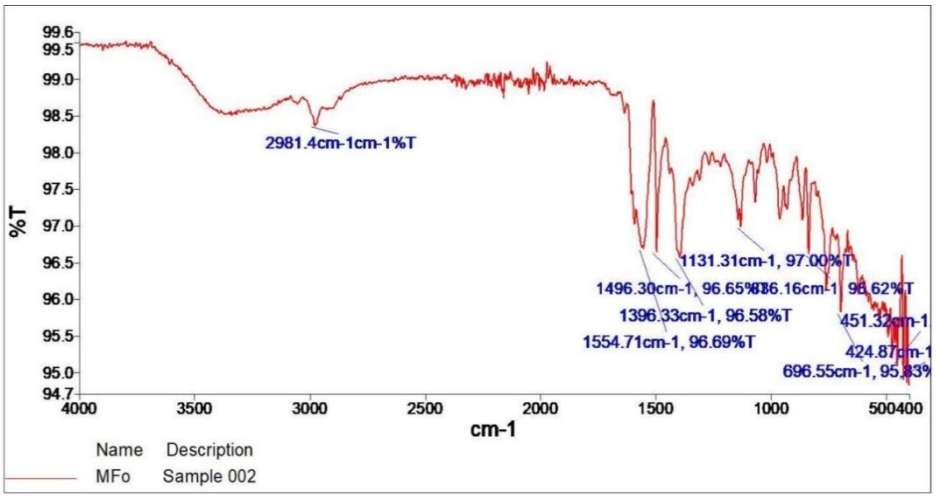

Figure 1 FTIR Spectra of Montelukast

3.2 Compatibility Study: By employing FTIR spectroscopy, the medication and polymer were found to be compatible. For the medication, chitosan, and formulation TF3, infrared spectroscopy examination was done. Figures 2 and 3 show the FTIR spectra of Formulation TF3 and chitosan.

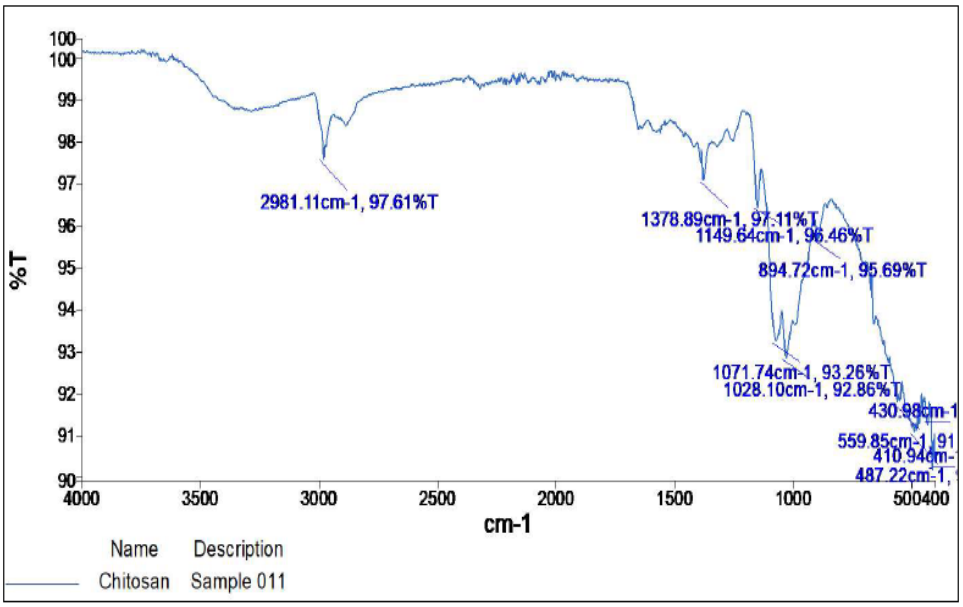

Figure 2: FTIR Spectra of Chitosan

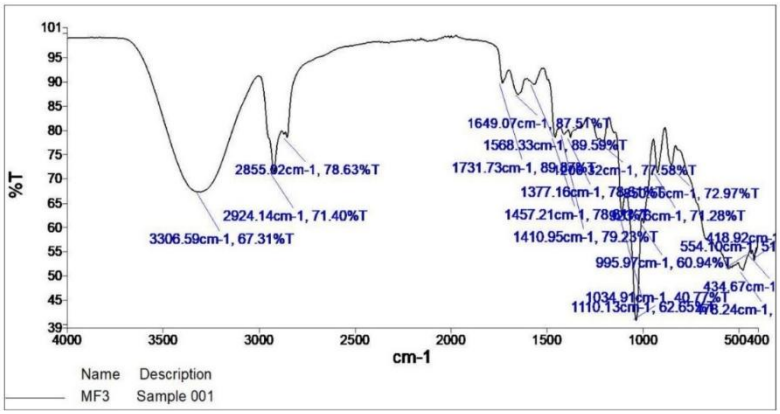

Figure 3: FTIR Spectra of Formulation FM-3

The FTIR spectra of chitosan and formulation FM3 revealed that the distinctive peaks of the medication and polymer did not move or vanish. This implies that the medication and polymer do not interact. Thus, it can be said that the medication keeps its original form without interacting chemically with chitosan.

3.3 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.

3.4 Characterization and Evaluation

3.4.1 Production Yield: Following the microspheres' preparation, the practical yield and percentage yield were determined. Figure 4 displays the % yield of several formulations. It was discovered that FM3 had the highest percentage yield, followed by FM1, FM2, FM3, FM4, FM5 and FM6. It was discovered that the percentage yield ranged from 86.51% to 91.58%. FM3 formula demonstrated the highest yield of 91.58%. Microspheres do not develop at concentrations below or beyond the optimal threshold for the polymer and crosslinking agent, according to observations. Process parameters were the cause of the material loss that occurred during the microsphere preparation. Another region for that may be agglomeration and sticking of polymer to blades of stirrer and to the wall of the beaker during microsphere formulation.

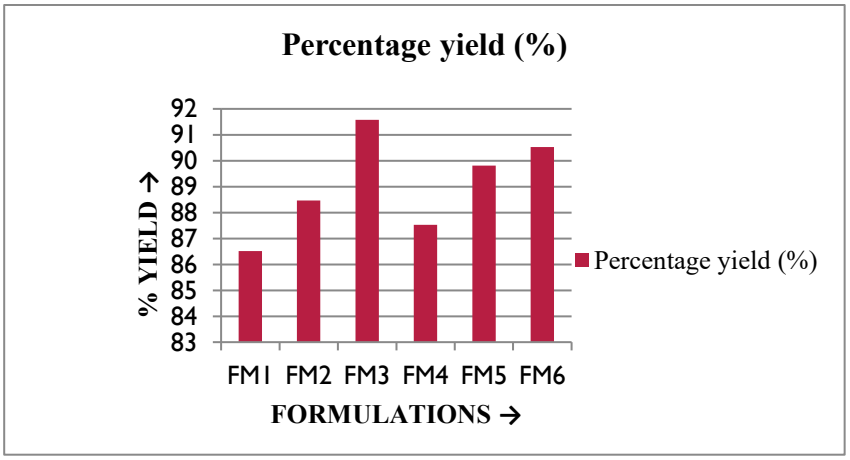

Fig 4. Percentage Yield of Mucoadhesive Microsphere Montelukast

3.4.2 Drug Content and Entrapment Efficiency:

The drug content research showed that even when the polymer composition was changed, the method was highly successful in creating microspheres with the highest potential drug content. 80.14 to 91.47% was the range of the drug content percentage (w/w). FM3, FM1, FM2, FM4, FM5, and FM6 were found to have the greatest percentage of drug content. The formulation with the highest drug content percentage, FM3, showed 91.47% w/w.

The microspheres' entrapment efficiency findings are shown in Figure 3.9. From 75.71% to 89.24%, the calculated percentage entrapment effectiveness varied for each microsphere. Maximum entrapment efficiency is found for formulation FM3. The polymer concentration, in general, affects the entrapment efficiency. Entrapment efficiency was greater in formulations containing 3%w/v chitosan (FM3 and FM6) than in formulations containing 1%w/v chitosan (FM1 and FM2). It was demonstrated that as the concentration of polymer rose, so did the entrapment efficiency.

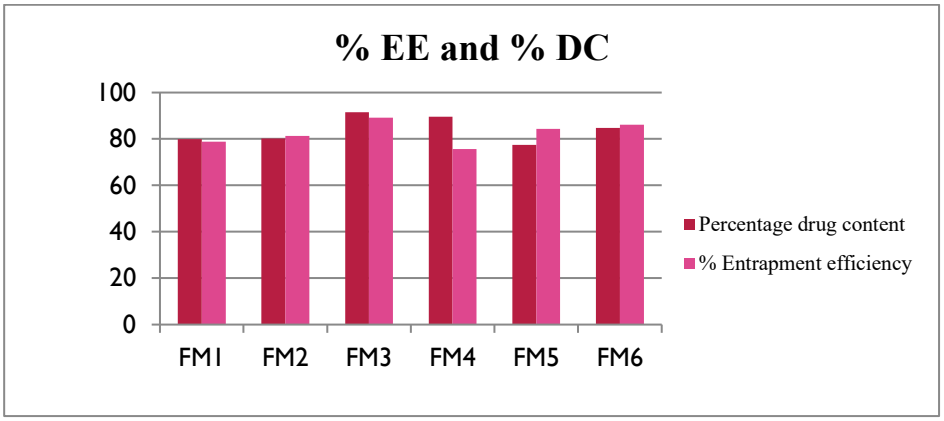

Figure 5: Percentage drug content of prepared microspheres

3.4.3 Particle Size Analysis of Microspheres:

The particle sizes of every microsphere that was created were examined using OLYMPUS INEA. The average size of the produced microspheres' particles is shown in Table 2. The size range of the microspheres was 10.28±1.12 to 50.95±1.92 µm. Particle size was found to be more affected by the concentration of the crosslinking agent than by the concentration of the polymer. Up to a certain extent, a higher chitosan cone leads to the formation of small particles, which might be the result of a high concentration of anionic. Formulation FM3 exhibited the most appropriate particle size of 31.77±2.62 µm among all the formulations, which made it appropriate for nasal administration.

Table 2: Mean Particle Size Analysis of FM

S. No.	Formulation	Average particle size in µm
1	FM1	18.09±1.12
2	FM2	20.09±1.72
3	FM3	10.28±1.12
4	FM4	31.77±2.62
5	FM5	50.95±1.92
6	FM6	20.55±1.81

3.4.4 Surface Morphology by Scanning Electron Microscopy (SEM):

The produced micropsheres' surface morphology was examined using scanning electron microscopy. Dry microspheres were coated with gold using an ion sputter after being deposited in a brass stub for a scanning electron microscope. Figure 6 displayed the formulation FM3 SEM figure. According to the batch FM3 formulation created for SEM investigation, the surface morphology of the microspheres was spherical and smooth.

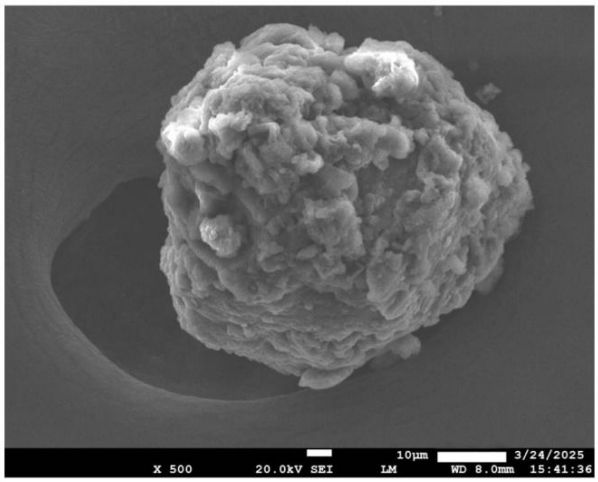

Figure 6: SEM image of Formulation FM3

3.4.5 Swelling Property:

Figure 7 displays the formulas' Swelling Index. Formulations FM3 and FM6, with a higher polymer concentration (3% w/v), showed more swelling's and maintained their integrity for 4 hours, while formulations FM l and FM4 with 1% w/v and FM2 and FM5 with 2% w/v polymer concentration lost their integrity after 3 hours. It is possible that this is because the former's greater density permitted a slower rate of solvent penetration over a longer duration than the latter. The surface area of the particle was shown to be a determining factor in the swelling's index. The swelling's index increased as the particle surface area did, it was found.

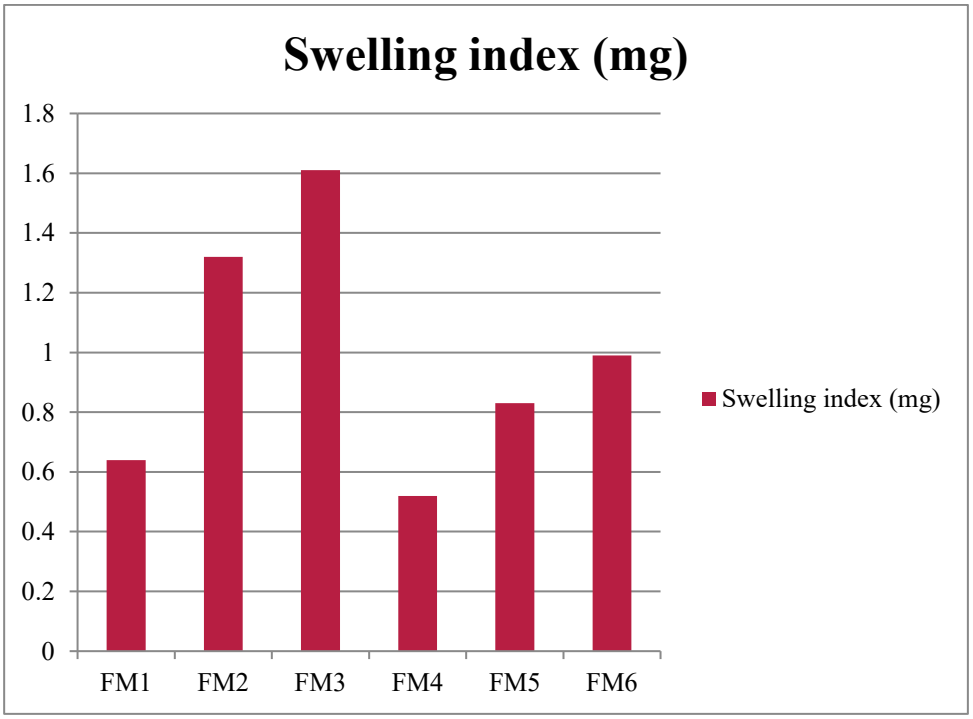

Figure 7: Swelling index of Microspheres

3.4.6 In-vitro mucoadhesion Test for Microspheres: Table 3 displays the mucoadhesion test result. The findings demonstrate that mucoadhesive strength rises with polymer content. In comparison to the 1% w/v formulations (FMl and FM2), the formulations with a 3% w/v polymer concentration (FM3 and FM6) demonstrated higher mucoadhesive strength. It was also shown that the mucoadhesion was influenced by the particle's surface area. It was shown that when particle surface area rose, so did mucoadhesion.

Table 3: Mucoadhesion test in Phosphate's buffer pH 6.8

SR. No.	Formulation code	Mucoadhesion (%)
1	FM1	62.17 ± 0.326
2	FM2	64.17 ± 0.931
3	FM3	73.45 ± 0.121
4	FM4	63.72 ± 0.225
5	FM5	66.38 ± 0.184
6	FM6	69.47 ± 0.723

In-vitro Release Studies:

Figure 8 shows a tabulation of all the formulations' in-vitro release data. 75% of the drug was expected to be released after six hours. For the FM l through FM6 formulas, respectively. Both the polymer content and the stirring rate clearly had a major effect on the drug release. With increasing polymer concentration, the release of drug exceeded the concentration of mucoadhesive polymer. Drug release increased significantly when the stirring rate was raised from a lower to a higher level. This is probably because the microspheres have smaller particles at higher stirring speeds, which means that a much larger surface area is accessible for release and that the drug has a shorter pathlength to diffuse through. The chitosan's enhanced drug release, which facilitates drug diffusion by forming a hydrophilic conduit inside the microspheres. Water was able to enter microspheres more easily thanks to the increased hydrophilic pores formed by chitosan, which also accelerated the expanding matrix's erosion and coupled the diffusion and erosion processes to release medications from mini-spheres.

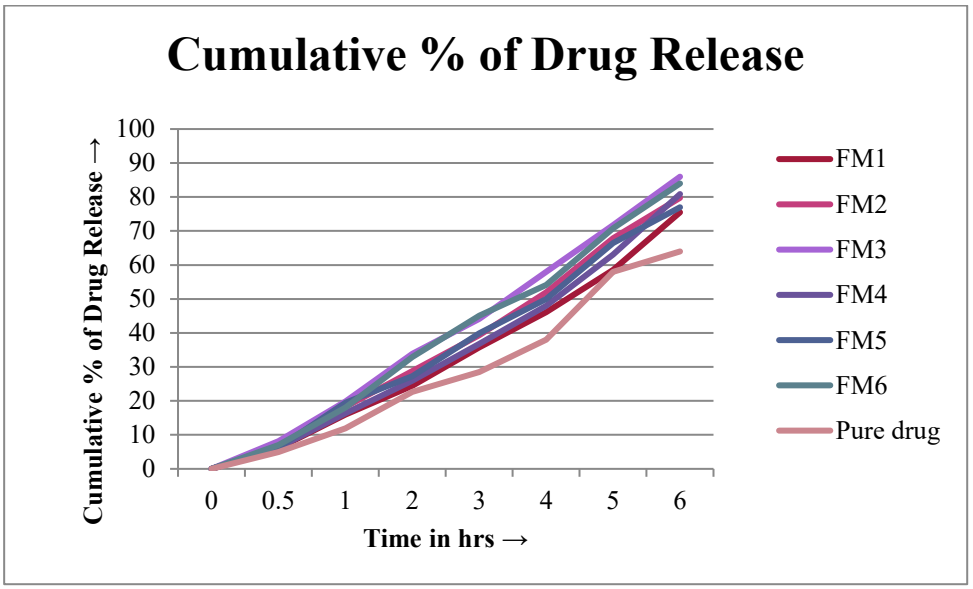

Figure 8: In-vitro drug release of prepared microspheres formulations

In-vitro drug release kinetics:

A regression analysis with a value between 0.9734 and 0.9939 showed that the medication release sequence was zero order. A value of "R" was found 0.9882 for the Korsemeyer Peppas equation. According to this, the drug release is followed by a non-fickinian diffusion. It is possible to release medications from microspheres through the diffusion process. Drug diffusion was discovered to be the primary mechanism governing the release of the FM-loaded chitosan microsphere drug delivery device. Results were shown in Table 4.

Table 4: In-Vitro Release Kinetic Data For Montelukast Mucoadhesive Microspheres

Formula code	Zero order		First order		Higuchi's	Korsmeyer-Peppas	
	K_0	R	K_1	R	R	N	R
FM1	3.0215	0.9739	0.0336	0.9866	0.9855	0.6254	0.9651
FM2	3.0312	0.9734	0.0318	0.9877	0.9876	0.6678	0.9683
FM3	2.9989	0.9939	0.0312	0.9856	0.9902	0.6356	0.9882
FM4	2.9887	0.9825	0.0286	0.9761	0.9916	0.6775	0.9761
FM5	2.9587	0.9875	0.0275	0.9901	0.9955	0.6623	0.9813
FM6	2.9756	0.9891	0.0195	0.9892	0.9939	0.6644	0.9728

K_0= Zero order constant

K_1= First order rate constant

r= Coefficient correlation

n= diffusion exponent

Stability Study:

The FM3 formulation was put through a stability study that involved temperature changes of 4 ±1 °C, 25 ± 2 °C/ 60 ±5 RH, and 37 ± 2 °C/ 65 ±5% RH for a duration of one month. A % entrapment efficiency analysis of the sample at that time revealed that the FM3 formulation's drug content had not changed significantly. According to this, FM3 stayed constant at the designated temperature. One possible explanation for these results is that the polymer matrix erodes with time.

Table 5: Stability studies of formulation FM3

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	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	83.7	83.1	84.3	84.8	84.3	82.1

4. CONCLUSION

In order to prevent first pass metabolism, increase patient compliance, employ an alternative therapy to traditional dosage forms, achieve controlled blood level profiles of the drug, and enhance the therapeutic efficacy of propranolol hydrochloride as a migraine prophylactic, mucoadhesive microspheres of Montelukast for nasal delivery were developed using the W/O emulsion cross linking method. The mucoadhesive polymer utilised was chitosan. Several metrics were used to assess the manufactured microspheres. Of the formulations created, formulation FM3 produced the best outcomes. After a thorough analysis of all the experimental findings, it was determined that microspheres made using W/O Emulsion Cross Linking procedures would be a highly promising option for the sustained release of different medications. Use also lessens drug loss and dosage frequency.

REFERENCES

[1] Ugwoke MI, Verberke N and Kigent R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol. 2001;53:3-22.

[2] Lisbeth Illum. Nasal drug delivery-Possibilities, Problems and Solutions. J Control Release. 2000;87:187-198.

[3] Ahuja A, Kar RK and Ali J. Mucoadhesive drug delivery system-Review. Drug Dev Ind Pharm.

1997;23(5):489-515.

[4] Chowdary KPR and Srinivas L. Mucoadhesive drug delivery system-A review of current status. Indian Drugs. 2000;37(9):400-406.

[5] Thanou M, Nihot MT, Jansen M, Verhoef JC, Junginger HE. Mono N- carboxymethyl chitosan (MCC), a polyampholytic chitosan derivative enhances the intestinal absorption of low molecular weight heparin across intestinal epithelia in vitro and in vivo. J Pharm Sci 2001; 90: 38- 46.

[6] Kunisawa J, Okudaira A, Tsutusmi Y, Takahashi I, Nakanishi T, Kiyono H, et al. Characterization of mucoadhesive microspheres for the induction of mucosal and systemic immune responses. Vaccine 2000; 19(4): 589-594.

[7] Chowdary KPR, Rao YS. Mucoadhesive microspheres for controlled drug delivery. Biol Pharm Bull 2004; 27(11):1717-1724.

[8] Belgamwar V, Shah V, Surana SJ. Formulation and evaluation of oral mucoadhesive multiparticulate system containing metoprolol tartarate: an in vitro, ex vivo characterization. Curr Drug Deliv 2009; 6 (1):113-121.

[9] Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: in vitro and in vivo evaluations of bilayer tablet formulations. Drug Dev Ind Pharm 2000; 26(8): 857-866.

[10] Rita JM, Pradip KG, Manish LU, Rayasa SR. 2006. Thermoreversible mucoadhesive gel for nasal delivery of sumatriptan. AAPS PharmSciTech 7:E1–7.

[11] Alagusundara M. et al; Nasal drug delivery system-an overview. Int J Res Pharm Sci 2010; 1(4): 454-465.

[12] Gavini E., Rassu G., Haukvik T., Lanni C., Racchi M., Giunchedi P. Mucoadhesive microspheres for nasal administration of cyclodextrins. J. Drug Target 2008; 17:168-179.

[13] Martinac A, Filipovic G, Perissutti B, Voinovich D, Pavelic Z. 2005. Spraydried chitosan/ethylcellulose microspheres for nasal drug delivery: Swelling study and evaluation of in vitro drug release properties. J Microencapsulation 22:549–561.

[14] Kataria S, Middha A, Sandhu P, Bilandi A, Kapoor B. Microsphere: A Review. Int J Res Pharm Chem 2011; 1(4): 1185-1198.

[15] Hameed MD, Kellaway IW. 1997. Preparation and in vitro characterization of mucoadhesive polymeric microspheres as intra-nasal delivery systems. Eur J Pharm Biopharm 44:53–60.

[16] Juan JT, Alfredo GA, Santiago TS, Luis G. 2001. Spray-dried powders as nasal absorption enhancers of cyanocobalamin. Biol Pharm Bull 24:1411–1416.

[17] Mahalaxmi R, Kumar S. 2007. Preparation of mucoadhesive microspheres for nasal delivery by spray drying. Indian J Pharm Sci 9:651–657.

[18] Michael IU, Norbert V, Renaat K. 2001. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol 53:3–22.

[19] Pereswetoff-Morath L. 1998. Microspheres as nasal drug delivery systems. Adv Drug Del Rev 29:185–194.

[20] Saraparn H, Vimolmas L, Narueporn S, Garnpimol CR. 2006. Spraydried mucoadhesive microspheres: Preparation and transport through nasal cell monolayer. AAPS PharmSciTech 7:E1–10.

[21] Ugwoke M, Agu R, Verbeke N, Kinget R. 2005. Nasal mucoadhesive drug delivery: Background, applications, trends and future perspectives. Adv Drug Del Rev 57:1640–1665.