RESEARCH PAPER

Formulation And Evaluation Of Mucoadhesive Microspheres Of Tramadol For Nasal Delivery

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ABSTRACT
The objective of the present study was to develop and evaluate mucoadhesive microspheres of Tramadol hydrochloride for nasal delivery to enhance its bioavailability and provide rapid onset of action for pain management. Tramadol, a centrally acting analgesic, undergoes extensive first-pass metabolism when administered orally. In this study, chitosan was employed as a natural mucoadhesive polymer, and microspheres were prepared by the emulsification cross-linking polymerization technique using glutaraldehyde as a cross-linking agent. The formulated microspheres were evaluated for particle size, surface morphology, drug entrapment efficiency (69.90%–80.76%), swelling index, in-vitro mucoadhesion (62.27-74.65%), and in-vitro drug release. The results indicated that the microspheres were spherical with a particle size range suitable for nasal deposition (11-39 µm). In-vitro release studies over six hours at pH 6.8, showed an initial burst followed by a controlled release pattern. The mucoadhesive property of chitosan significantly prolonged the residence time of the drug on the nasal mucosa. It was concluded that Tramadol-loaded chitosan microspheres represent a promising intranasal delivery system for systemic pain management.
KEYWORDS: Tramadol, Mucoadhesive Microsphere, Nasal Delivery, Opioid Analgesic, Chitosan, Emulsification Cross-Linking Technique.
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1. INTRODUCTION (1,8,9,18,19,36,45&46)

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. [47&48] 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.[27]

"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. [2] 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. [8,9&25]

Tramadol Hydrochloride is a centrally acting synthetic opioid analgesic used primarily to treat moderate to moderately severe pain. It possesses a dual mechanism of action: it acts as a weak agonist at µ-opioid receptors and simultaneously inhibits the neuronal reuptake of

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norepinephrine and serotonin, which modulates the descending pain pathways in the central nervous system. When administered orally, it undergoes extensive hepatic first-pass metabolism—primarily via the cytochrome P450 enzyme CYP2D6 into its active metabolite, O-desmethyltramadol—resulting in an absolute oral bioavailability of approximately 75%. Because of its distinctive dual pathway, Tramadol provides effective pain relief with a lower risk of respiratory depression compared to classical opioids, though it still requires careful clinical management due to risks of tolerance, dependence, and potential drug interactions like serotonin syndrome.

In the current study, chitosan and the W/O Emulsion Cross Linking Method are used to create microspheres.

2. MATERIALS AND METHODS

2.1 Materials: Tramadol was obtained as a gift sample from Orex Pharma Pvt. Ltd., Mumbai. Chitosan was procured from Sisco Research Laboratory Pvt. Ltd., Delhi. Ethanol, Glutaraldehyde, 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: [6,8,9,20,24,25&53] 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 4000400 cm^{-1} wave number was used to record the spectra.

2.3 Method Of Preparation By W/O Emulsion Cross Linking Method[7, 33,34,35,48&49]

- Step-1: Taken a 10 ml of 2% aqueous acetic acid solution (2 ml acetic acid dissolved in 100 ml distilled water).
- 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 with 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 beaker, place under electronic stirring machine for 15 mins at 1650 rpm.
- Step-6: Added DOSS (stabilizing solution) as per the given quantity (2 ml or 3 ml) constant stirring at 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 1650-1690 rpm for 15 minutes.
- Step-8: Added Glutaraldehyde was added to above solution using continuously stirring for next 2 or more hours at 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		
Fo. Code	**Drug: Polymer**	**Vol. of stabilizing agent (DOSS)**	**Vol. of cross linking agent (Glutaraldehyde)**	**Constant parameter aq. to oil phase**	**Stirring rate**	**Cross linking**
TRMDL1	1:1	2 ml	2 ml	10 :100	1650-1690 rpm	2 hrs
TRMDL2	1:2	2 ml	2 ml			
TRMDL3	1:3	2 ml	2 ml			
TRMDL4	1:1	2 ml	4 ml			
TRMDL5	1:2	2 ml	4 ml			
TRMDL6	1:3	2 ml	4 ml			

2.4 Characterization & Evaluation [6&20]

2.4.1 Determination of Percentage Yield of Microspheres: [40] 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.

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

2.4.2 Determination of % Drug Content and % Entrapment Efficiency: [18] 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 ethanol. The solution was filtered through Whatmann filter paper no. 41 after 12 hours, and the filtrate's drug content was measured at 273 nm using a UV-visible spectrophotometer.

2.4.3 Particle Size Analysis: [14&30] 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.

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: [22&16] 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.

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: [21&28] 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 Tramadol 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 273 nm, the percentage of the medication that dissolved during various time periods was computed.

2.4.8 Kinetics of Drug Release: [16&22] 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.

2.4.9 Stability Study: [41,55&56] For stability investigations, the formulation (TRMDL3) 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 , the samples were tested for drug release. Entrapment effectiveness for the same composition was also examined.

3. RESULTS AND DISCUSSION

3.1 FTIR Spectra: The pure form of Tramadol'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.

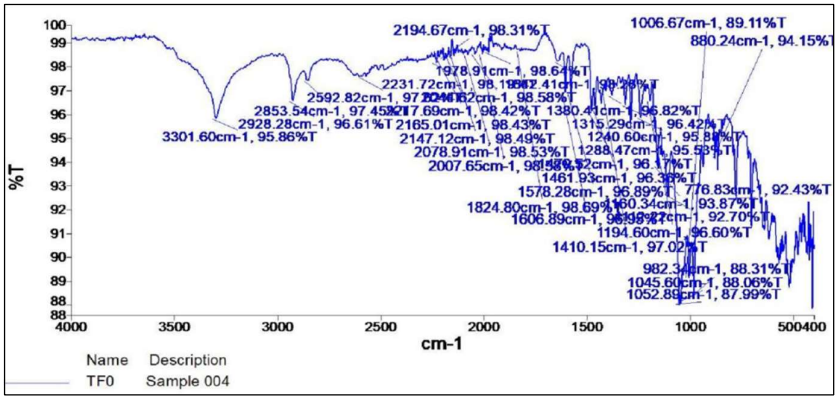

Figure 1: FTIR Spectra of Tramadol

3.2 Compatibility Study: By employing FTIR spectroscopy, the medication and polymer were found to be compatible. For the medication, chitosan, and formulation TRMDL3, infrared spectroscopy examination was done. Figures 2 and 3 show the FTIR spectra of Formulation TRMDL3 and chitosan.

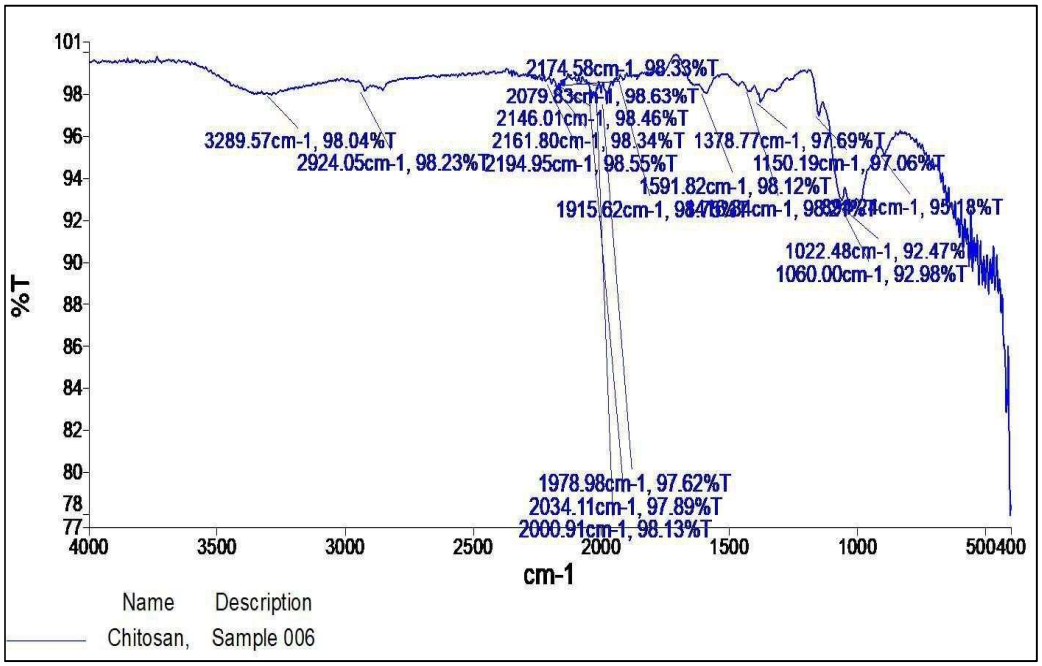

Figure 2: FTIR Spectra of chitosan

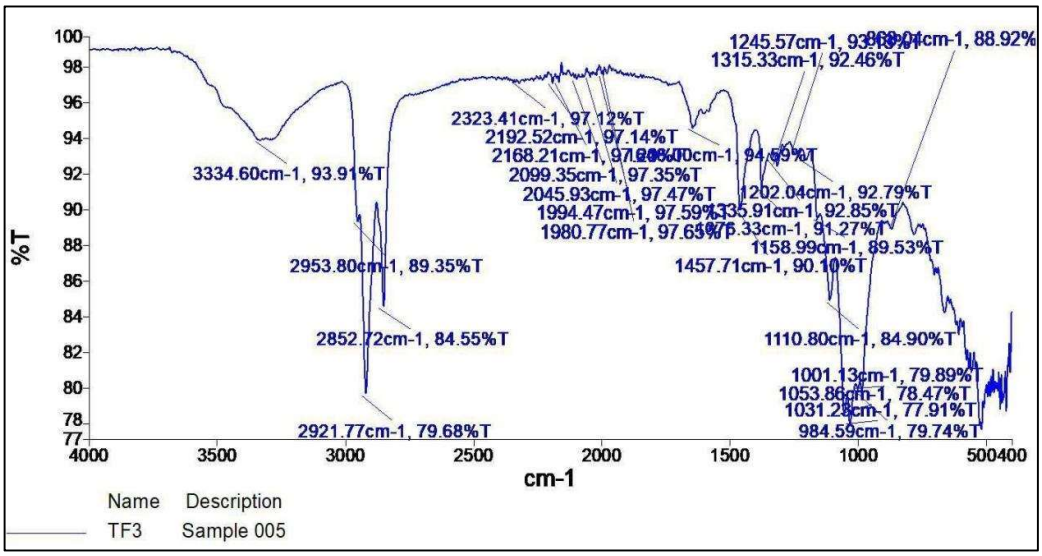

Figure 3: FTIR Spectra of Formulation TRMDL-3

The FTIR spectra of chitosan and formulation TRMDLF3 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 crosslinking 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

iii) 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.

iv) 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 TRMDL3 had the highest percentage yield, followed by TRMDL1, TRMDL2, TRMDL3, TRMDL4, and TRMDL5. It was discovered that the percentage yield ranged from **72.08% to 82.14%**. TRMDL3 formula demonstrated **the highest yield of 82.14%**.

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.

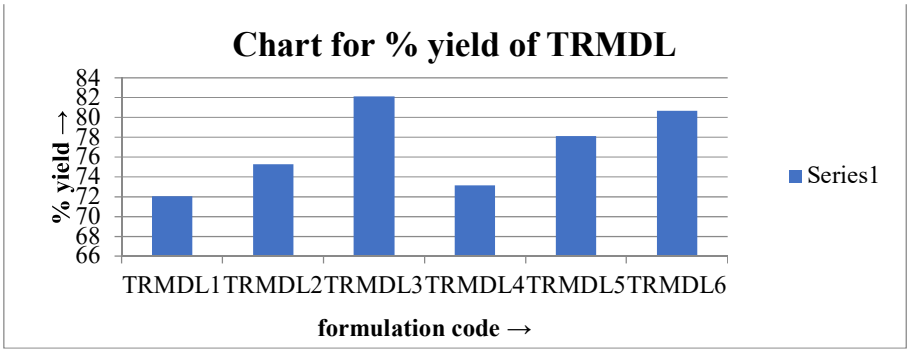

Figure 4. Data for Percentage Yield of Mucoadhesive Microsphere of Tramadol

3.4.2 Drug Content and Entrapment Efficiency: The analysis of the drug content revealed that the technique was very effective in producing microspheres with the maximum possible drug content, even when the polymer composition was altered. The range of the drug content percentage (w/w) was found to be **68.17% to 78.97% w/w.** It was discovered that TRMDL3 has the highest percentage of drug content, followed by TRMDL1, TRMDL2, TRMDL3, TRMDL4, and TRMDLS. The best drug content percentage, 78.97% w/w, was displayed by formulation TRMDL3. Figure 5 displays the microspheres' entrapment efficiency results. For every microsphere, the computed percentage entrapment efficiency varied between **69.9% and 80.76%**. For formulation TRMDL3, the maximum entrapment efficiency is observed. Roughly speaking, the polymer concentration influences the entrapment efficiency. The formulations with 3%w/v of chitosan (TRMDL3 and TRMDL6) had an entrapment efficiency that was higher than the formulations with 1%w/v of chitosan (TRMDL1 and TRMDL2). It was shown that the entrapment efficiency increased as the polymer concentration did.

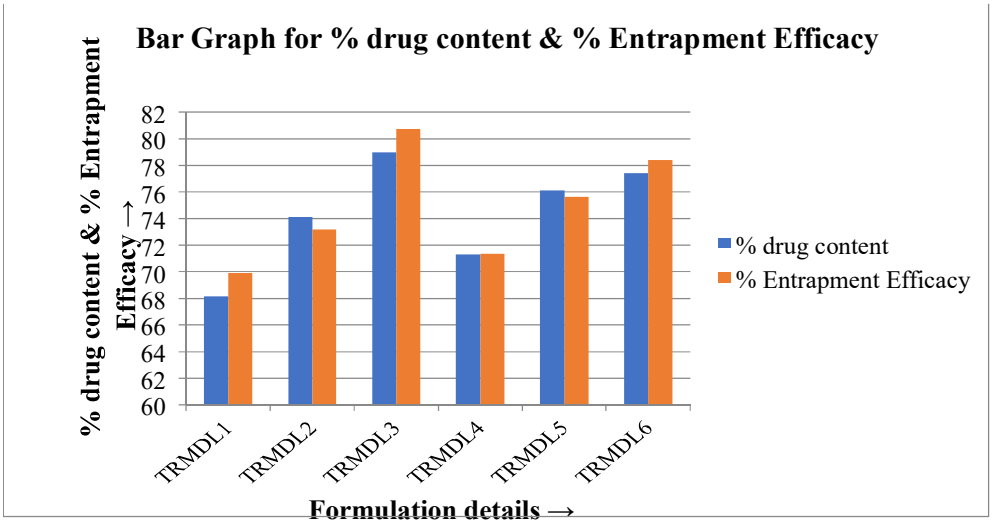

Figure 5: Percentage Drug Content of Prepared Microspheres

3.4.3 Particle Size Analysis of Microspheres: Using OLYMPUS INEA, the particle sizes of all produced microspheres were analysed. Table 2 displays the average particle size of the prepared microspheres. The microspheres measured between 11-39 µm in size. It was discovered that the crosslinking agent concentration had a greater influence on the particle size than the polymer concentration. Up to a certain point, higher chitosan cone causes the development of tiny particles, which may be caused by a high anionic concentration. Out of all the formulations, formulation TRMDL3 had the best suitable particle size of **11 ± 2.11 µm**, making it suitable for nasal administration.

Table 2: Mean Particle Size Analysis of Microspheres

SR. No.	Formulation code	Particle size
1	TRMDL1	35 ± 4.98
2	TRMDL2	29 ± 3.66
3	TRMDL3	11 ± 2.11
4	TRMDL4	32 ± 3.92
5	TRMDL5	30 ± 3.51
6	TRMDL6	25± 4.96

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 TRMDL3 SEM figure. According to the batch TRMDL3 formulation created for SEM investigation, the surface morphology of the microspheres was spherical and smooth.

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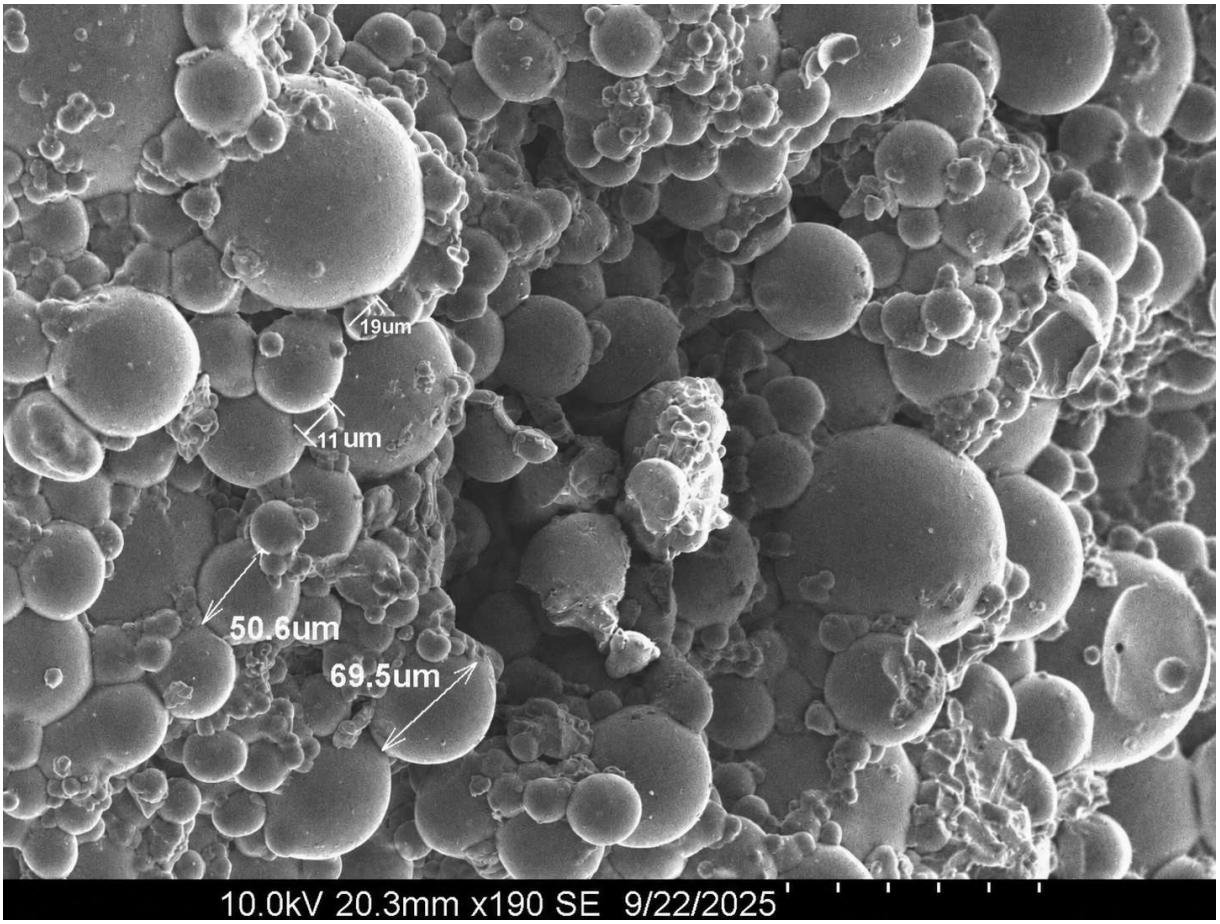

Figure 6: SEM Image of Formulation TRMDL3

3.4.5 Swelling Property: Figure 7 displays the formulas' Swelling Index. In comparison to formulations TRMDLl & TRMDL4 with 1% w/v and TRMDL2 & TRMDL5 with 2% w/v polymer concentration, which lost their integrity after 3 hours, formulations TRMDL3 and TRMDL6 with higher polymer concentration (3 o/ow/v) demonstrated greater swelling and retained their integrity until 4 hours. This could be as a result of the former's higher density, which allowed for a slower rate of solvent penetration over a longer period of time than the latter. 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.

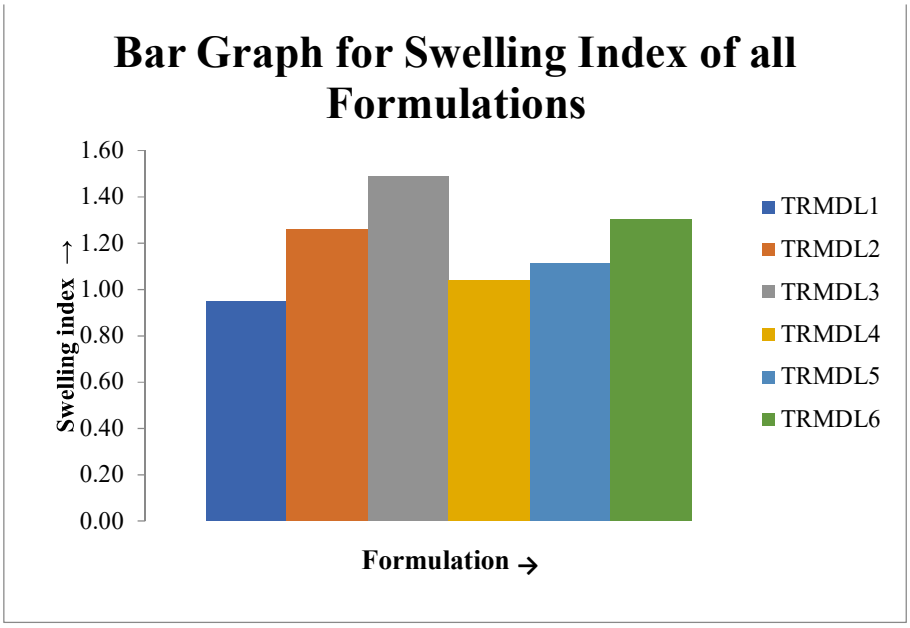

Figure 7: Swelling Index of Microspheres

3.4.6 In-vitro Mucoadhesion Test for Microspheres: Table 3 displays the mucoadhesion test result. The results show that when the concentration of polymer increases, so does the mucoadhesive strength. The formulations with a 3% w/v polymer concentration (TRMDL3 and TRMDL6) exhibited greater mucoadhesive strength than the 1% w/v formulations (TRMDLl and TRMDL2). It was also discovered that the surface area of the particle affected the mucoadhesion. It was discovered that mucoadhesion increased along with particle surface area.

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

SR. No.	Formulation code	Mucoadhesion (%)
1	TRMDL1	62.27 ± 0.306
2	TRMDL2	67.67 ± 0.471
3	TRMDL3	74.65 ± 0.721
4	TRMDL4	63.02 ± 0.335
5	TRMDL5	69.28 ± 0.514
6	TRMDL6	71.67 ± 0.113

In-vitro Release Studies: Figure 8 shows a tabulation of all the formulations' in-vitro release data. After six hours, the total percentage of medication release was supposed to reach 73%. For the formulations TRMDLl through TRMDL6, respectively. Figure 8 depicted the release studies of Tramadol microspheres graphically. It was evident that the drug release was significantly impacted by both the polymer concentration and stirring rate. The medication release was greater than the mucoadhesive polymer concentration as the polymer concentration rose. When the stirring rate was increased from a lower to a higher level, the release of drugs rose sharply. This is most likely caused by the microspheres' lower particle size at greater stirring rates, which results in a significantly bigger surface area that is available for release and a shorter pathlength for the medication to diffuse through. the increased release of the drug from the chitosan, which creates a hydrophilic channel inside the microspheres to aid in drug diffusion. Increased hydrophilic holes created by chitosan made it easier for water to enter microspheres, sped up the erosion of the expanding matrix, and combined the erosion and diffusion mechanisms to release drugs from microspheres.

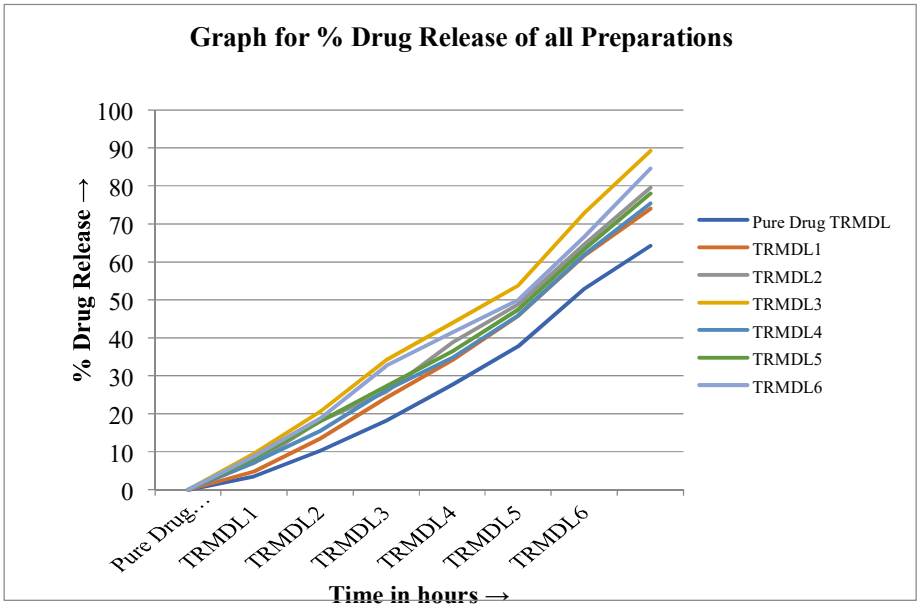

Figure 8: In-vitro Drug Release of Prepared Microspheres Formulations

In-vitro Drug Release Kinetics: Regression analysis revealed that the drug release sequence was zero order. The Korsemeyer Peppas equation's "n" value leads to the conclusion that a nonfickinian diffusion is followed by the drug release. Through the process of diffusion, drugs can be released from microspheres. It was found that drug diffusion predominates as the mechanism controlling the release of Tramadol-loaded chiton microspheres drug delivery system. The outcomes were displayed in Table 4.

Table 4: In-vitro Release Kinetic Data for Tramadol Mucoadhesive Microspheres

Formula code	Zero order	First order	Higuchi's	Korsmeyer-Peppas	
	R	R	R	N	R
TRMDL1	0.9656	0.9492	0.9653	0.6254	0.9744
TRMDL2	0.9678	0.9802	0.9673	0.6575	0.9836
TRMDL3	0.9887	0.9838	0.9844	0.6644	0.9892
TRMDL4	0.9732	0.9738	0.9793	0.6378	0.9797
TRMDL5	0.9757	0.9766	0.9811	0.6456	0.9804
TRMDL6	0.9798	0.9816	0.9834	0.6623	0.9884

K_0= Zero order constant K_1= First order rate constant r= Coefficient correlation n= diffusion exponent

Stability Study: Six-month stability testing of **TRMDL3** at **4±1°C, 25±2°C/60 ±5 RH, and 37±2°C/65±5% RH** showed negligible changes in drug content or entrapment efficiency. This confirms formulation stability, likely aided by minimal polymer matrix erosion during storage.

Table 5: Stability Studies of Formulation TRMDL3

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**	86.90	85.00	86.90	85.05	84.93	83.03
2	**2**	86.80	84.60	86.80	85.03	84.62	83.01
3	**3**	86.70	84.60	86.70	85.00	84.10	82.00
4	**4**	86.00	84.50	86.50	84.90	83.70	81.80
5	**5**	85.70	84.40	86.30	84.80	83.30	81.50
6	**6**	85.72	84.48	86.37	84.86	83.90	81.60

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. Mucoadhesive microspheres of Tramadol 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 TRMDL3 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 controlled release of different medications. Use also lessens drug loss and dosage frequency.

5. REFERENCES

1. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. *J Control Release*. 2004;100(1):5-28.
2. Ahuja A, Kar RK and Ali J. Mucoadhesive drug delivery system-Review. *Drug Dev Ind Pharm.* 1997;23(5):489-515.
3. Alagusundara M. et al; Nasal drug delivery system-an overview. *Int J Res Pharm Sci* 2010; 1(4): 454-465.
4. Amidi M, Mastrobattista E, Jiskoot W, Hennink WE. Chitosan-based delivery systems for protein therapeutics and antigens. *Adv Drug Deliv Rev.* 2010 Jan 31;62(1):59-82.
5. Aranaz I, Alcántara AR, Civera MC, Arias C, Elorza B, Heras Caballero A, et al. Chitosan: An Overview of Its Properties and Applications. *Polymers.* 2021 Sep 27;13(19):3256.
6. Basu SK, Adhiyaman R. Preparation and characterization of nitrendipine-loaded Eudragit RL 100 microspheres by solvent evaporation method. *Trop J Pharm Res*. 2008;7(4):1133-41.
7. 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.
8. Chowdary KPR and Srinivas L. Mucoadhesive drug delivery system-A review of current status. *Indian Drugs.* 2000;37(9):400-406.
9. Chowdary KPR, Rao YS. Mucoadhesive microspheres for controlled drug delivery. *Biol Pharm Bull* 2004; 27(11):1717-1724.
10. Clementino A, Climani G, Bianchera A, Buttini F, Sonvico F. Polysaccharides: New Frontiers for Nasal Administration of Medicines. *Polysaccharides.* 2025;6(1):6.
11. Correa RF, Colucci G, Halla N, Pinto JA, Santamaria-Echart A, Blanco SP, et al. Development of Chitosan Microspheres through a Green Dual Crosslinking Strategy Based on Tripolyphosphate and Vanillin. *Molecules.* 2021 Apr 15;26(8):2325.
12. Dhaliwal S, Jain S, Singh HP, Tiwary AK. Mucoadhesive microspheres for nasal delivery of cyclobenzaprine hydrochloride: in vitro and in vivo forecasting of nasal absorption. *Pharm Dev Technol.* 2008;13(3):209-17.
13. Donato L. Polymeric Membrane-Based Systems in Transdermal Drug Delivery. *PMC.* 2026 Apr 22.
14. Gavini E, Hegge AB, Rassu G, Sanna V, Testti F, Pirisino G, et al. Nasal administration of carbamazepine using chitosan microspheres: in vitro/in vivo studies. *Int J Pharm.* 2006 Feb 3;307(1):9-15.
15. Gavini E., Rassu G., Haukvik T., Lanni C., Racchi M., Giunchedi P. Mucoadhesive microspheres for nasal administration of cyclodextrins. J. *Drug Target* 2008; 17:168179.
16. 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.
17. Harris R, Lecumberri E, Heras A. Chitosan-Genipin Microspheres for the Controlled Release of Drugs: Clarithromycin, Tramadol and Heparin. *Mar Drugs*. 2010;8(6):17501762.
18. He P, Davis SS, Illum L. Chitosan microspheres for nasal drug delivery: I. Characterization and release of amantadine hydrochloride and salmon calcitonin. *Int J Pharm.* 1998 May 10;166(1):75-88.
19. Illum L. Nasal drug delivery--possibilities, problems and solutions. *J Control Release*. 2003 Mar 7;87(1-3):187-98.
20. Indian Pharmacopoeia. Vol. III. Ghaziabad: The Indian Pharmacopoeia Commission; 2022.
21. Juan JT, Alfredo GA, Santiago TS, Luis G. 2001. Spray-dried powders as nasal absorption enhancers of cyanocobalamin. *Biol Pharm Bull* 24:1411–1416.
22. Kataria S, Middha A, Sandhu P, Bilandi A, Kapoor B. Microsphere: A Review. *Int J Res Pharm Chem* 2011; 1(4): 1185-1198.
23. Khan F. Applications of Chitosan Microspheres as Drug Delivery Vehicles. In: Khan F, editor. Chitosan: Properties and Applications. *London: IntechOpen*; 2025. p. 45-62.
24. Kumar, A., Naik, P. K., Pradhan, D., Ghosh, G., & Rath, G. (2020). Mucoadhesive formulations: innovations, merits, drawbacks, and future outlook. *Pharmaceutical Development and Technology*, *25*(7), 797–814.
25. 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.
26. Li B, Shan CL, Zhou Q, Fang Y, Wang YL, Xu F, et al. Synthesis, characterization, and antibacterial activity of cross-linked chitosan-glutaraldehyde. *Mar Drugs*. 2013 May 8;11(5):1534-52.
27. Lisbeth Illum. Nasal drug delivery-Possibilities, Problems and Solutions. *J Control Release*. 2000;87:187-198.

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28. Mahalaxmi R, Kumar S. 2007. Preparation of mucoadhesive microspheres for nasal delivery by spray drying. *Indian J Pharm Sci* 9:651–657.
29. Martin A. Physical Pharmacy and Pharmaceutical Sciences. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
30. 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.
31. Michael IU, Norbert V, Renaat K. 2001. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. *J Pharm Pharmacol* 53:3–22.
32. Mitra A. Chitosan Microspheres in Novel Drug Delivery Systems. *PMC*. [n.d.].
33. 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.
34. Pandey J, Tripathi PK. Formulation and evaluation of levocetirizine loaded mucoadhesive microspheres for nasal delivery. *International Journal of Pharmaceutical Sciences and Research.* 2016 May 1;7(5):2242.
35. Pandey J, Shankar R, Kumar M, Shukla K, Kumari B. Development of nasal mucoadhesive microspheres of granisetron: A potential drug. *Drug research*. 2020 Aug;70(08):367.
36. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of mucoadhesive glipizide microspheres. *AAPS PharmSciTech.* 2005;6(1):E49-55.
37. Patil SB, Sawant KK. Mucoadhesive microspheres: a promising tool in drug delivery. *Curr Drug Deliv.* 2008 Oct;5(4):312-8.
38. Pereswetoff-Morath L. 1998. Microspheres as nasal drug delivery systems. *Adv Drug Del Rev* 29:185–194.
39. Porfiryeva NN. Advances in mucoadhesive and mucus-penetrating materials, nanoformulations, and in situ gelling systems for nasal drug delivery. *Expert Opin Drug Deliv.* 2026 Feb 18;23(2):145-162.
40. Rita JM, Pradip KG, Manish LU, Rayasa SR. 2006. Thermoreversible mucoadhesive gel for nasal delivery of sumatriptan. *AAPS PharmSciTech* 7:E1–7.
41. Saraparn H, Vimolmas L, Narueporn S, Garnpimol CR. 2006. Spraydried mucoadhesive microspheres: Preparation and transport through nasal cell monolayer. *AAPS PharmSciTech* 7: E1–10.
42. Shaji J, Jain V, Lodha S. Design and evaluation of chitosan-based mucoadhesive microspheres of nitroglycerin for nasal delivery. *Indian J Pharm Sci.* 2010 Jul;72(4):454-60.
43. Shaji J, Jain V, Lodha S. Design and evaluation of chitosan-based mucoadhesive microspheres of nitroglycerin for nasal delivery. *Indian J Pharm Sci*. 2010;72(4):454460.
44. Singh R, Pant K, Saini S, Pant S, Sharma P. Formulation and evaluation of mucoadhesive microspheres of nitroglycerin. *J Pharm Res*. 2012;5(8):4152-5.
45. Sinha RV. Chitosan microspheres as a potential carrier for drugs. *Ovid*. [n.d.].
46. Sinha VR, Singla AK, Wadhawan S, Kaushik R, Kumria R, Bansal K, et al. Chitosan microspheres as a potential carrier for drug delivery. *Int J Pharm.* 2004;274(1-2):1-33.
47. Thakkar H, Patel B, Thakkar S. Development and evaluation of chitosan microspheres for nasal delivery of sumatriptan. *Curr Drug Deliv*. 2009;6(4):359-67.
48. Thanoo, B. Chithambara, M. C. Sunny, and A. Jayakrishnan. "Cross-linked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals." *Journal of pharmacy and pharmacology* 44.4 (1992): 283-286.
49. Thanoo BC, Sunny MC and Jayakrishnan A.; Cross-linked Chitosan Microspheres:
50. Preparation and Evaluation as a Matrix for the Controlled Release of Pharmaceuticals." *Journal of Pharmacy and Pharmacology* 44 (1992): 283–286
51. 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.
52. 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.
53. Ugwoke MI, Verberke N and Kigent R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. *J Pharm Pharmacol*. 2001;53:3-22.
54. Venkatesan P, Puvvada R, Babu S. Evaluation of ionotropic cross-linked chitosan/gelatin B microspheres of tramadol hydrochloride: drug-polymer compatibility by FTIR. *J Pharm Bioallied Sci.* 2011;3(1):154-159.