RESEARCH PAPER

Design And Development of Mucoadhesive Microspheres of Telmisartan For Nasal Delivery

Ada Pandey[1] and Prof. Jai Deo Pandey[*2]

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

***Correspondence to Author :** Prof. Jai Deo Pandey
Head, Department of Pharmaceutics, Rajarshi Rananjay Sinh College of Pharmacy, Amethi, Sultanpur, U.P., 227405, 9450169055, jaideo.p@gmail.com , adapandey026@gmail.com

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ABSTRACT
Mucoadhesive drug delivery devices allow for prolonged, close contact between the drug and the lining of the mouth. In order to boost therapeutic efficacy, extend residence period, and reduce systemic first-pass metabolism, the current study aimed to develop mucoadhesive microspheres for nasal administration.. In this study, we used the Emulsification cross linking approach to generate Telmisartan mucoadhesive microspheres developed by using chitosan polymer. The microspheres' analysed for particle size, percentage yield, in vitro drug release, in vitro mucoadhesion, entrapment efficiency, swelling index and stability studies characteristics were assessed. SEM and FTIR were used to characterize microspheres. Each batch was guaranteed to have the proper handling characteristics the prepared microspheres showed the particle size in the range of 10 and 40 µm, to make sure the appropriate handling characteristics had been applied to every batch. When tested for drug release analysed in 6.8 pH phosphate buffer, all the formulations given regulated release for up to 6 hours. According to information obtained in analysis the mucoadhesive microsphere formulation techniques are a highly promising nasal application approach that can improve adherence for patients and offer medication for a longer period of time.

Keywords: Telmisartan, Mucoadhesive's Microspheres, Nasal Administration, Anti-Allergic Agent, Chitosan, Emulsification Cross-linking Method.

1. INTRODUCTION

One of the greatest risk factors for cardiovascular morbidity and death in the globe is still hypertension. Reducing the risk of consequences including heart failure, stroke, myocardial infarction, and renal impairment requires effective blood pressure control. Because it may specifically prevent angiotensin II from binding to AT1 receptors, telmisartan, a strong angiotensin II receptor blocker (ARB), is widely used to treat hypertension. Even though telmisartan has good pharmacological action, poor water solubility and inconsistent gastrointestinal absorption frequently restrict its therapeutic efficacy after oral treatment, which can negatively impact its systemic availability. Alternative medication delivery methods have been investigated recently to get around the drawbacks of traditional oral dosing forms. Nasal medication administration has garnered significant attention among these methods due to its distinct anatomical and physiological features. Drugs can be quickly absorbed into the systemic circulation thanks to the nasal cavity's highly vascularized mucosal layer. Additionally, the nasal route avoids gastrointestinal breakdown and hepatic first-pass metabolism, potentially improving bioavailability and accelerating therapeutic response. Because of these benefits, nasal administration is a viable method for medications that need a quick beginning of action or have poor oral absorption. Despite its benefits, nasal drug delivery faces certain challenges, particularly the rapid clearance of formulations from the nasal cavity by the mucociliary mechanism. This natural defense process limits the contact time between the drug and the nasal mucosa, reducing the extent of drug absorption. Therefore, strategies that can prolong the residence time of drug formulations within the nasal cavity are essential for achieving effective drug delivery. Mucoadhesive microspheres have emerged as an effective carrier system for enhancing nasal drug absorption. These multiparticulate systems are designed to adhere to the mucus layer covering the nasal epithelium, thereby increasing the retention time of the formulation at the site of administration. Prolonged residence within the nasal cavity can facilitate greater drug permeation and improve therapeutic outcomes. In addition, microspheres offer several advantages, including protection of the incorporated drug, controlled drug release, uniform distribution over the mucosal surface, and reduced dosing frequency.

Mucoadhesion is primarily achieved through the use of polymers capable of interacting with mucin present in the mucus layer. Chitosan is one of the most widely investigated mucoadhesive polymers owing to its excellent biocompatibility, biodegradability, and safety profile. Its cationic nature promotes strong interactions with negatively charged mucosal surfaces, resulting in

*Author for Correspondence: : jaideo.p@gmail.com

enhanced adhesion and prolonged retention. Moreover, chitosan has been reported to improve epithelial permeability, which may further facilitate drug absorption across the nasal membrane. Considering the therapeutic importance of Telmisartan and the advantages offered by mucoadhesive nasal delivery systems, the development of Telmisartan-loaded mucoadhesive microspheres represents a promising strategy for improving drug delivery efficiency. Such a formulation may enhance drug residence time within the nasal cavity, improve absorption, and potentially increase systemic bioavailability while minimizing the limitations associated with oral administration. Therefore, the present investigation was focused on the design and development of mucoadhesive microspheres of telmisartan for nasal delivery. The formulated microspheres were evaluated for their physicochemical properties, drug loading efficiency, mucoadhesive behavior, and in vitro drug release characteristics to assess their suitability as a nasal drug delivery system.

2. MATERIALS AND METHODS

2.1 Materials:

Telmisartan was obtained as a gift sample from a reputed pharmaceutical company. Chitosan, sodium tripolyphosphate (TPP), and other excipients used in the formulation were of analytical grade and procured from authorized suppliers.

All chemicals and reagents employed during the study were used without further purification. Double-distilled water was utilized throughout the experimental work.

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

1. In 1st step internal phase prepared by using ten ml of 2% acetic acid(aqueous) solution in which required quantity chitosan (0.1/0.2/0.3gm) and API (0.1 gm Telmisartan) dispersed in 2% aqueous acetic solution in 50ml beaker that produces internal phase(Disperse Phase).
2. To produce a dispersed phase, add the medication (0.1 gm) gradually while stirring the produced chitosan solution.
3. The External Phase Prepared by using 50ml of heavy liquid paraffin & 50ml light liquid paraffin (1:1 ratio) in 500ml PVC beaker that produces external phase.
4. Stabilizing agent prepared by using DOSS (50 mg) was dissolved in 25 ml glycerine with continuous stirring by using glass rod to produce 0.2% DOSS solution.
5. After that, 50 ml of liquid paraffin(heavy) and 50 ml of liquid paraffin(light) were put together in a 500 ml beaker and placed under electronic stirring for 15 minutes at 1255 rpm, the external phase was prepared.
6. Added DOSS (stabilizing solution) as per the given quantity (2 ml or 3 ml) constant stirring at 1250-1350 rpm for 15 minutes.
7. The dispersed phase added slowly into the external phase under constant stirring at 1200-1300 rpm for 15 minutes.
8. Glutaraldehyde(Cross linking agent) was added in given quantity (2ml/3ml/4ml) to above solution using continuously stirring after 1 hour and continue for next two hours at 1510-1605 rpm.
9. Prepared microspheres subjected for filtration by vacuum flirtation.
10. Prepared microspheres were washed with the n-hexane and then washed with the purified water to remove the unreacted glutaraldehyde & keep it for air drying about 26 hours and as well as stored in desiccator for further evaluation.

Table 1: Formulation Variables and Process Optimization:

Formulation Code	Ratio of Drug to Polymer	Dioctyl Sodium Sulfosuccinate (mL)	Glutaraldehyde (mL)	Aqueous : Oil Phase proportion	Mixing Speed (rpm)	Cross-linking Time (hrs)
TF1	1 : 1	2	2	10 : 100	1640 ± 10	2
TF2	1 : 2	2	2	10 : 100	1640 ± 10	2
TF3	1 : 3	2	2	10 : 100	1640 ± 10	2
TF4	1 : 1	3	4	10 : 100	1640 ± 10	2
TF5	1 : 2	3	4	10 : 100	1640 ± 10	2
TF6	1 : 3	3	4	10 : 100	1640 ± 10	2

2.2 Characterization & Evaluation

2.2.1 Determination of Percentage Yield of Microspheres: The production yield of the microspheres was evaluated by measuring the weight of the dried product obtained after formulation and comparing it with the theoretical weight of the starting materials. The dried microspheres were carefully collected, weighed, and the percentage yield was calculated using the following formula:

$$\% \text{ yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer}} \times 10$$

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

2.2.3 Particle Size Analysis: The particle size of the prepared telmisartan-loaded mucoadhesive microspheres was determined using an optical

microscope equipped with a digital imaging system. A small quantity of dried microspheres was dispersed in glycerine to obtain a uniform suspension and placed on a glass slide. The sample was observed under the microscope, and images were captured using an Olympus digital camera. The particle diameter of a representative number of microspheres was measured using Magnus Pro 3.0 image analysis software. The average particle size was calculated from the measured values and expressed as mean particle diameter. The shape and surface appearance of the microspheres were also evaluated during microscopic examination.

2.2.4 Shape and Surface Characterisation: The surface morphology and shape of the prepared telmisartan-loaded mucoadhesive microspheres were examined using Scanning Electron Microscopy (SEM). A small quantity of microspheres was mounted onto an aluminum sample stub using double-sided adhesive tape. The samples were then sputter-coated with a thin layer of gold under vacuum conditions to enhance their electrical conductivity. The coated microspheres were observed using a scanning electron microscope at suitable magnifications, and micrographs were recorded to evaluate the surface characteristics, shape, and structural integrity of the microspheres.

2.2.5 Degree of Swelling: The swelling index of the prepared telmisartan-loaded mucoadhesive microspheres was determined by immersing 50 mg of microspheres in phosphate buffer (pH 6.8) for 24 h. The swollen microspheres were separated, blotted to remove excess surface moisture, and weighed (Wt).

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

Mucoadhesion = No. of microspheres adhered / No. of microspheres applied x 100

2.2.7 In-Vitro Drug Release or Dissolution Studies: The in vitro drug release of the prepared telmisartan-loaded mucoadhesive microspheres was evaluated using a USP dissolution apparatus (basket method). The study was carried out in 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C and stirred at 50 rpm. Microspheres equivalent to the required dose of telmisartan were placed in the dissolution medium. Samples were withdrawn at predetermined time intervals and replaced with an equal volume of fresh medium to maintain sink conditions. The collected samples were analyzed using a UV–Visible spectrophotometer at 296 nm, and the cumulative percentage drug release was calculated.

2.2.8 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.

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

3. RESULTS AND DISCUSSION

3.1 **FTIR Spectra:** FTIR spectroscopy was performed to evaluate the compatibility between telmisartan and the excipients used in the formulation. The infrared spectrum of pure telmisartan was recorded using the KBr pellet method. The characteristic peaks of the drug were analyzed and compared with those of the optimized formulation to identify any possible drug–excipient interactions.

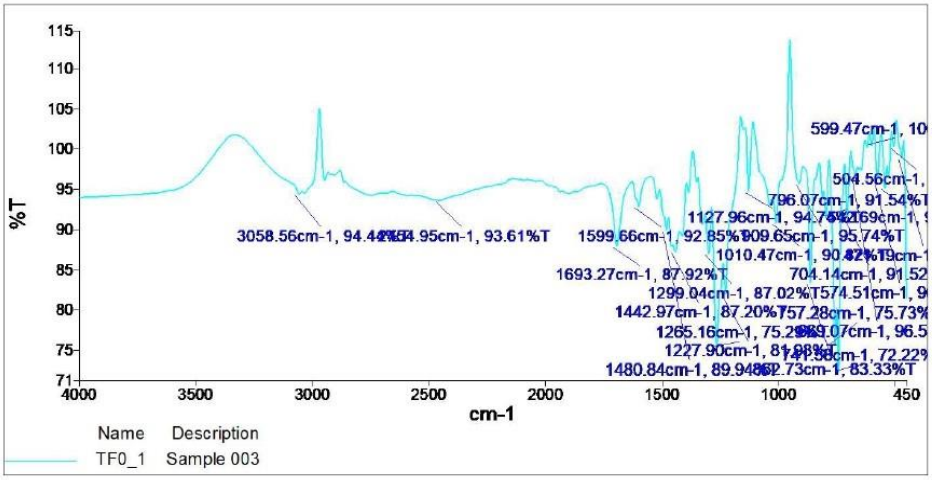


Figure 1 FTIR Spectra of Telmisartan

3.2 Compatibility Study: Drug–polymer compatibility was assessed using FTIR spectroscopy. The infrared spectra of pure telmisartan, chitosan, and the optimized formulation (CP0) were recorded and compared. The characteristic peaks of telmisartan were retained in the formulation spectrum without any significant shifts or disappearance, indicating the absence of chemical interaction between the drug and polymer.

The FTIR spectra of chitosan and the optimized formulation (CP0) are presented in Figures 2 and 3, respectively.

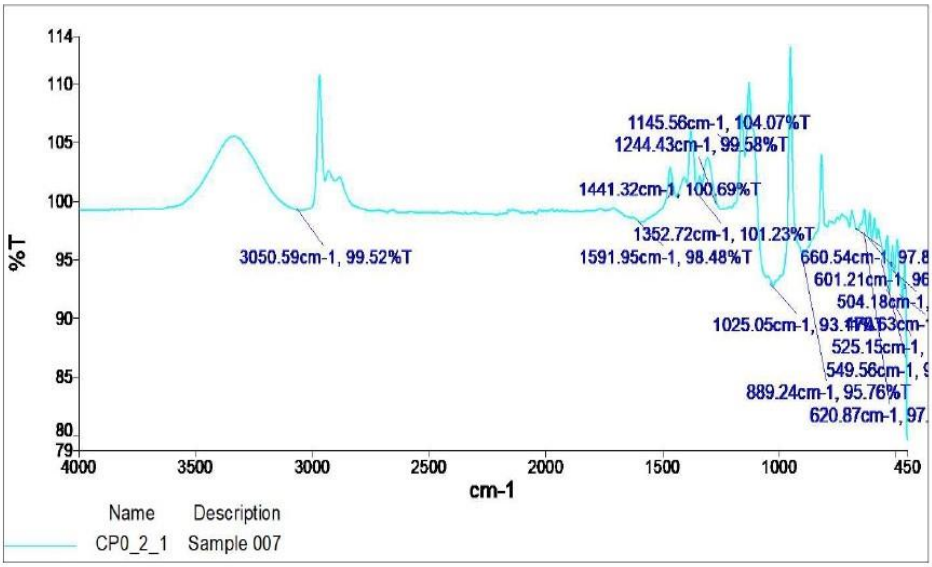


Figure 2: FTIR Spectra of Chitosan

*Author for Correspondence: : jaideo.p@gmail.com

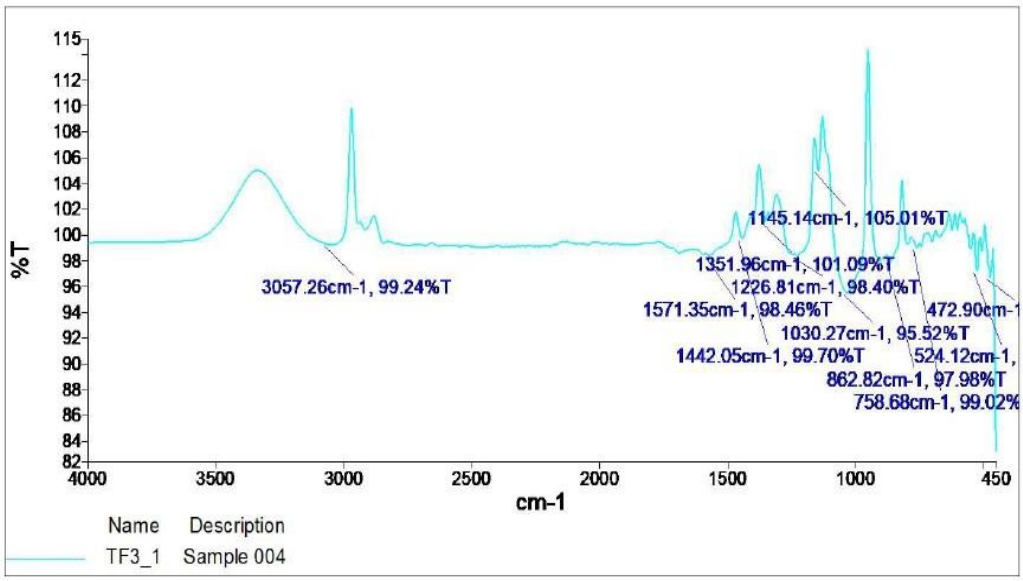


Figure 3: FTIR Spectra of Formulation TF-3

The FTIR spectra of chitosan and the optimized formulation (TF3) were compared to assess drug–polymer compatibility. The characteristic absorption peaks of telmisartan and chitosan were retained in the formulation spectrum without any significant shift, disappearance, or appearance of new peaks. These findings indicate the absence of any chemical interaction between the drug and polymer, confirming the compatibility of telmisartan with chitosan and the stability of the formulation.

Optimization of Process and Formulation Variables

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

ii) Selection of Internal phase

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

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

3.3 Characterization and Evaluation

Production Yield: After the microspheres were prepared, the practical yield and percentage yield were calculated. The yield percentage of various formulations is shown in Figur.

The formulation with the highest yield was TF3, which was followed by TF1, TF2, TF4, TF5, and TF6. The yield percentage was determined to be between 86.58% and 92.68%. For the TF3 formulation, the highest yield was 92.68%.

It was observed that microspheres do not form properly when the concentration of polymer and cross-linking agent is too low or too high. Some loss of material also occurred during the preparation process due to handling and processing conditions.

Additionally, aggregation of microspheres and sticking of polymer to the walls of the beaker and stirrer may also contribute to the loss in yield during preparation.

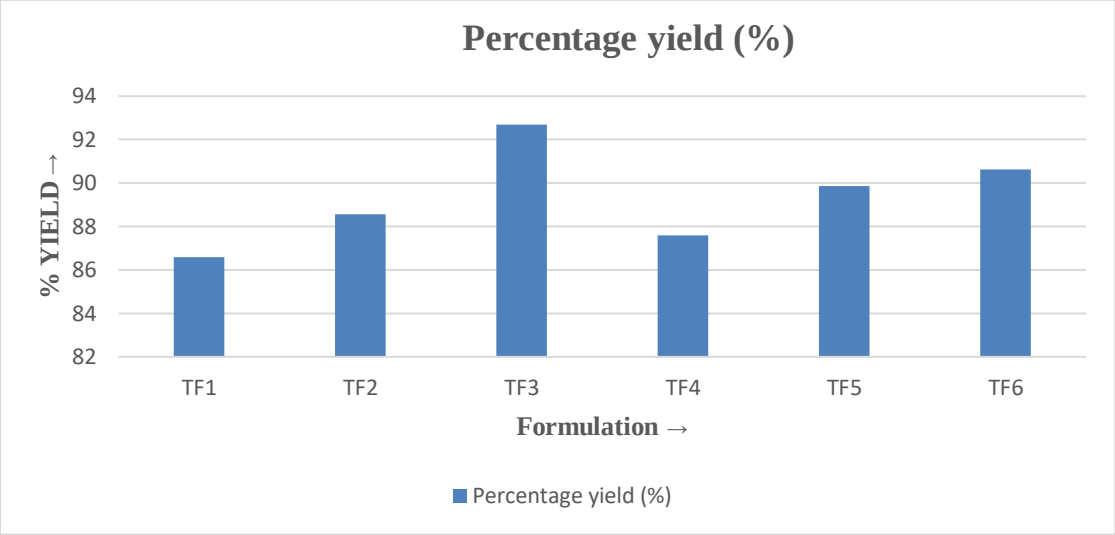


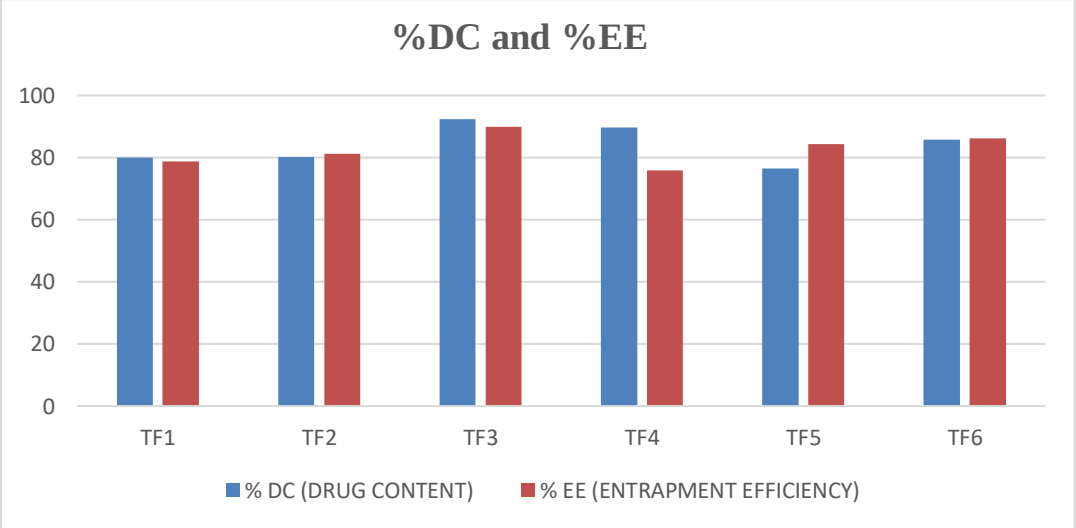
Table 4. Data For Percentage Yield of Mucoadhesive Microsphere Telmisartan

Drug Content and Entrapment Efficiency: Even when the polymer concentration was changed, the drug content research demonstrated that the preparation technique was successful in creating microspheres with excellent drug loading. The range of the percentage drug content (w/w) was 76.48% to 92.42%.

Among all formulations, TF3 showed the highest drug content (92.42% w/w), followed by TF1, TF2, TF4, TF5, and TF6. This indicates that the formulation process was efficient in incorporating the drug into the microspheres.

Figure displays the microspheres' entrapment efficiency data. It was shown that the percentage entrapment effectiveness ranged from 75.86% to 89.89%. The TF3 formulation had the highest entrapment efficiency.

It was revealed that entrapment efficiency is greatly impacted by polymer concentration. Formulations containing 3% w/v chitosan (TF3 and TF6) had a higher entrapment efficiency than formulations containing 1% w/v chitosan (TF1 and TF2).



Percentage drug content of prepared microspheres

Particle Size Analysis of Microspheres: Using an optical microscope (OLYMPUS INEA), the produced microspheres' particle size was measured; the average results are shown in Table. Microspheres ranged in size from 10.29 ± 1.13 µm to 50.96 ± 1.93 µm. It was shown that the cross-linking agent concentration had a greater impact on particle size than the polymer concentration.

Smaller particles were formed when the concentration of chitosan was increased up to a particular point. This might be because there are more ionic groups available, which promotes improved cross-linking and the creation of compact microspheres.

Among all the formulations, TF3 showed an optimum particle size of 10.29 ± 1.13 µm, which is suitable for nasal drug delivery.

Table : Mean Particle Size Analysis of TF

S. No.	Formulatison	Averagse particsle size inµm
1	TF1	18.09±1.12
2	TF2	20.09±1.72

3	TF3	10.29±1.13
4	TF4	29.03±2.62
5	TF5	50.96±1.93
6	TF6	19.05±1.81

Surface Morphology by Scanning Electron Microscopy (SEM): Scanning electron microscopy (SEM) was used to examine the produced microspheres' surface morphology. The dried microspheres were set on a brass stub for SEM inspection, and an ion sputtering technique was used to apply a thin coating of gold. Figure 6 displays the SEM image of formulation TF3. The results showed that the microspheres had a smooth surface and a spherical form.This demonstrates that the produced microspheres are appropriate for drug administration applications due to their consistent shape and appropriate structure.

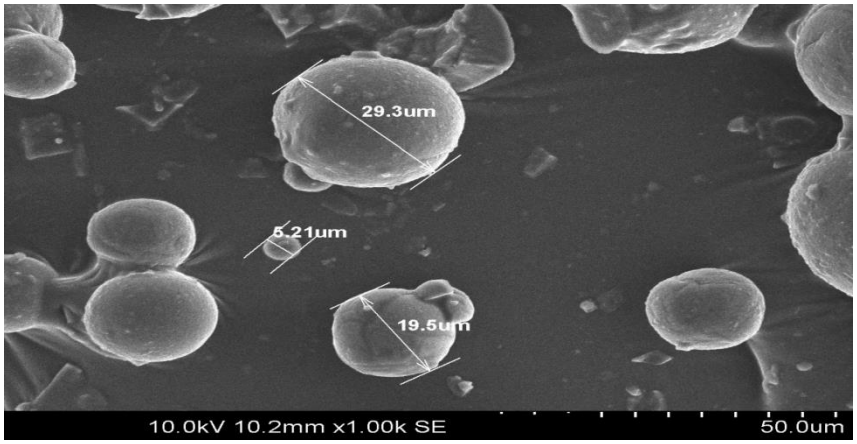


Figure 6: SEM image of Formulation TF3

Swelling Property: Figure displays the swelling index of several formulations. Formulations TF3 and TF6, which have a higher polymer content (3% w/v), were found to exhibit more swelling and to be able to hold their structure for up to four hours. However, after around three hours, formulations TF1 and TF4 (1% w/v) and TF2 and TF5 (2% w/v) lost their structural integrity. The increased polymer content in TF3 and TF6, this might be explained by the development of a denser structure that permits longer-term, slower solvent penetration. Additionally, it was noted that swelling behavior is significantly influenced by particle surface area. As the surface area of the particles increased, so did the swelling index.

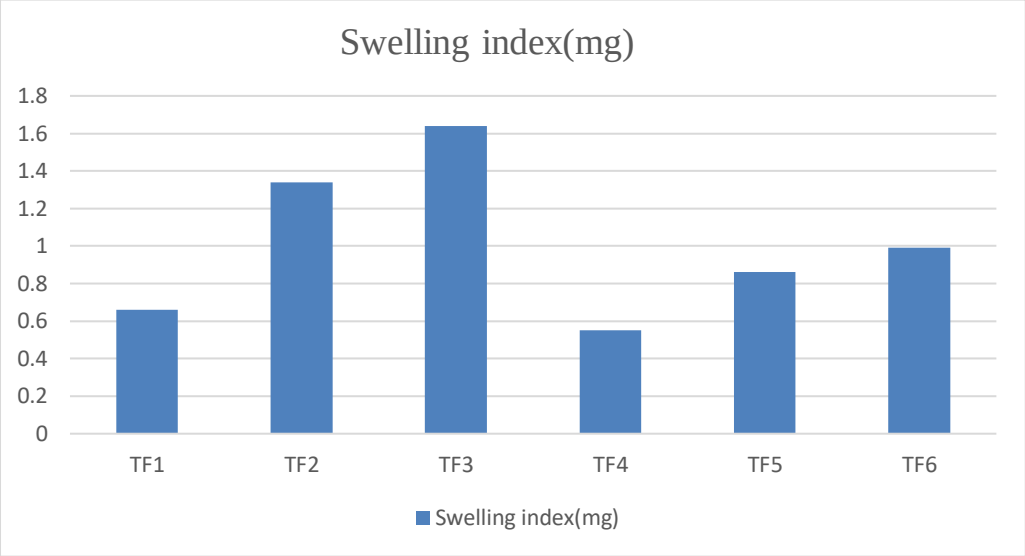


Figure 7: Swelling index of Microspheres

In-vitro mucoadhesion Test for Microspheres: The results of the mucoadhesion test are presented in Table. It was shown that when polymer content increased, mucoadhesive strength increased as well.
Formulations with higher polymer content, such as TF3 and TF6 (3% w/v), showed better mucoadhesive strength compared to formulations with lower polymer concentration like TF1 and TF2 (1% w/v).
Mucoadhesion was shown to be influenced by particle surface area, with greater surface area improving microspheres' mucoadhesive qualities.

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

SR. No.	Formulation code	Mucoadhesion (%)
1	TF1	63.16 ± 0.326
2	TF2	65.17 ± 0.931
3	TF3	74.45 ± 0.121
4	TF4	64.72 ± 0.225
5	TF5	67.38 ± 0.184
6	TF6	69.59 ± 0.723

In-vitro Release Studies: Figure 3.12 displays the in-vitro drug release statistics for each formulation. For formulations TF1 through TF6, it was found that approximately 75% of the medication was released within 6 hours.
The results clearly show that both polymer concentration and stirring speed have a major influence on drug release. The drug release rate increased as the polymer concentration increased because the formulation contained more mucoadhesive polymer.
It was also found that increasing the stirring speed resulted in higher drug release. This may be because higher stirring speed produces smaller sized microspheres, it shortens the diffusion channel length and expands the surface area accessible for drug release. Additionally, chitosan was crucial in improving medication release. It forms hydrophilic network inside the microspheres, which helps in easy penetration of water. This increases drug diffusion by causing the matrix to expand and erode more quickly.
The medicine is released from the microspheres under regulated conditions according to the overall drug release mechanism, which combines erosion and diffusion processes.

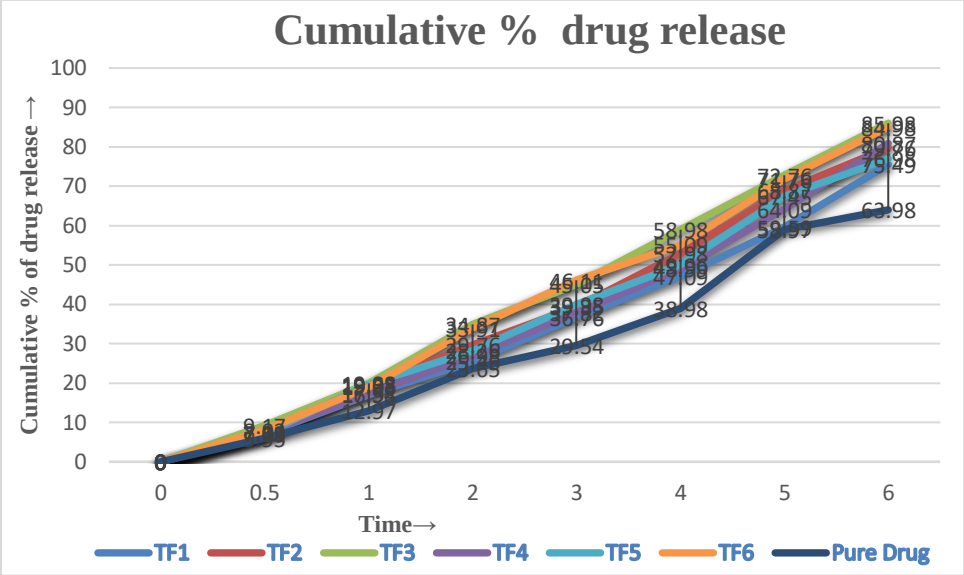


Figure 8: In-vitro drug release of prepared microspheres formulations

In-vitro drug release kinetics: The drug release data was analyzed using a number of kinetic models. The drug release follows zero-order kinetics, as shown by the regression coefficient values that fell between 0.9734 and 0.9949.
The value of the diffusion exponent (n) obtained from the Korsmeyer–Peppas model was 0.9887.. This result indicates that non-Fickian diffusion is the mechanism of drug release.
This indicates that diffusion and polymer relaxation mechanisms work together to release drugs from microspheres. Among them, it was discovered that the primary mechanism for drug release from the drug-loaded chitosan microspheres was drug diffusion.

Table 3.11 displays the kinetic analysis's complete findings.

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

Formula code	Zero-order		First-order		Higuchi's diffusion model	Korsmeyer-Peppas model	
	K_0	R	K_1	R	R	N	R
TF1	3.0216	0.9741	0.0347	0.9868	0.9865	0.6266	0.9666
TF2	3.0313	0.9736	0.0321	0.9881	0.9878	0.6681	0.9686
TF3	2.9998	0.9949	0.0321	0.9867	0.9908	0.6358	0.9887
TF4	2.9897	0.9828	0.0288	0.9766	0.9916	0.6775	0.9761
TF5	2.9578	0.9878	0.0277	0.9906	0.9955	0.6623	0.9813
TF6	2.9765	0.9894	0.0197	0.9861	0.9901	0.6636	0.9731

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

Stability Study: For six month, stability tests were conducted on the TF3 formulation at various temperatures and humidity levels, including 4 ± 1°C, 25 ± 2°C/60 ± 5% RH, and 37 ± 2°C/65 ± 5% RH.
The samples were examined for drug content and entrapment efficiency percentage following the research period. The findings demonstrated that the medication content of the TF3 formulation had not changed significantly.
This indicates that the formulation remained stable under the given conditions of storage. The polymer matrix, which aids in safeguarding the medication and preserving its integrity over time, may be the cause of the formulation's stability.

Table 3.12: TF3' Stability studies

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
6	**6**	83.6	83.0	84.2	84.6	84.1	82.0

CONCLUSION

Using chitosan as the mucoadhesive polymer and the W/O emulsion cross-linking process, the current work effectively created mucoadhesive microspheres of telmisartan for nasal administration. Particle size, drug entrapment efficiency, mucoadhesion, swelling behavior, and in vitro drug release were among the physicochemical and performance parameters of the prepared microspheres that were assessed. TF3 was determined to be the optimal formulation since it demonstrated the best outcomes of all the created formulations. The results imply that mucoadhesive microspheres based on chitosan can successfully increase nasal residence duration and offer prolonged medication release. With the potential to improve therapeutic effectiveness, decrease dose frequency, and boost patient compliance, the proposed microsphere system therefore provides a viable strategy for improving the nasal administration of telmisartan.

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