

FORMULATION AND OPTIMIZATION OF FROVATRIPTAN-LOADED CHITOSAN NANOPARTICLES FOR INTRANASAL DELIVERY IN MIGRAINE MANAGEMENT

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Running Title: Frovatriptan-Loaded Chitosan Nanoparticles for Migraine management

ABSTRACT

This study addresses the challenge of delivering frovatriptan, a commonly used antimigraine medication, more effectively to the brain. Despite its therapeutic benefits, frovatriptan suffers from a slow onset of action and low bioavailability, limiting its effectiveness. The goal of the study was to develop chitosan-based nanoparticles that could effectively deliver frovatriptan from the nasal to brain. Nanoparticles were prepared through ionic gelation, varying the concentrations of chitosan and sodium tripolyphosphate, as well as homogenization speed, to optimize particle size and entrapment efficiency. The optimized nanoparticles had desirable properties: particle size suitable for nasal delivery, high entrapment efficiency (91%), and a high zeta potential (54.7 ± 4.77 mV), indicating good stability. Drug release studies demonstrated that the nanoparticles provided a sustained, controlled release of frovatriptan over 24 hours, release exhibited Fickian diffusion mechanism with diffusion and polymer relaxation. Importantly, *ex vivo* studies revealed that the nanoparticle formulation significantly improved nasal permeation compared to a standard drug solution, with a 2.73-fold increase in both flux and permeability. This enhanced delivery was ascribed to the mucoadhesive properties of chitosan, increased surface area, and the ability to temporarily open epithelial tight junctions. Overall, results indicate that chitosan nanoparticles are safe and efficient vehicle for the intranasal administration of frovatriptan, facilitating regulated drug release and enhanced cerebral targeting. This innovative approach has the potential to enhance the therapeutic efficacy of frovatriptan in migraine treatment while minimizing side effects and improving patient convenience.

Keywords: Migraine, Frovatriptan, Chitosan nanoparticles, Ionic gelation, Intranasal delivery

How to cite this article: Litha Thomas^{1*} Ramya A¹ K Chethana¹ Keerthana S¹. FORMULATION AND OPTIMIZATION OF FROVATRIPTAN-LOADED CHITOSAN NANOPARTICLES FOR INTRANASAL DELIVERY IN MIGRAINE MANAGEMENT. Int J Drug Deliv Technol. 2026;16(81s):1479-1486. DOI: 10.25258/ijddt.16.81s.181.

INTRODUCTION

The World Health Organization defines headache disorders as conditions involving recurrent headache episodes that impose substantial personal and societal burdens, including pain, disability, diminished quality of life, and financial costs¹. In 2021, approximately 40% of the global population (3.1 billion people) affected by headache¹. Migraine is characterized by a pulsatile, unilateral headache of disabling intensity. Although the precise pathophysiology of migraine remains unclear, the World Health Organization suggests that it involves the activation of brain mechanisms that release pain-producing inflammatory substances, such as neuropeptides, around cranial nerves and blood vessels, resulting in vasoconstriction^{2,3}.

Triptans are the first-line pharmacological treatment for migraine and act specifically on 5-HT₁ receptors. Their mechanism involves 5-HT_{1B/1D} receptor-mediated vasoconstriction of dilated cerebral blood vessels, inhibition of vasoactive neuropeptide release from trigeminal nerves, and suppression of nociceptive neurotransmission^{4,5}. Frovatriptan, the seventh triptan introduced to the market, primarily targets the 5-HT_{1B/1D} receptor but is limited by a slow onset of action and low bioavailability⁶. Consequently, there is a need to

develop an efficient drug delivery system for frovatriptan that can traverse the blood-brain barrier and provide controlled drug release for optimal therapeutic effect. Nose-to-brain delivery offers a non-invasive approach for transporting drugs across the blood-brain barrier via the olfactory and trigeminal nerves in the nasal cavity⁷.

Chitosan, a natural biopolymer, facilitates drug transport by opening tight junctions between epithelial cells⁸. The objective of this study was to evaluate the possibility of formulating chitosan nanoparticles loaded with frovatriptan for the management of migraine.

MATERIALS AND METHODS

Materials

Frovatriptan was used as the model drug. Chitosan (medium molecular weight) was used as the mucoadhesive, cationic polymeric carrier, and sodium tripolyphosphate (TPP) was used as the crosslinking polyanion. Glacial acetic acid was used to dissolve chitosan, and a phosphate buffer of pH 6.4 was used as the dissolution and dilution medium throughout the study.

Formulation of Frovatriptan-Loaded Chitosan Nanoparticles

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Chitosan solution in acetic acid was prepared, and then pH of the solution was adjusted to 4.6 using 1 M sodium hydroxide (NaOH). Sodium tripolyphosphate (TPP) solution was prepared separately using deionized water. Both the chitosan and TPP solutions were stirred individually at 600 rpm for 1 hour using a magnetic stirrer to ensure complete dissolution. The TPP solution was then added dropwise to the chitosan solution at a controlled rate of 0.1 mL/min while maintaining continuous stirring at 800 rpm. Following the complete addition of TPP, the resulting dispersion was stirred for an additional 1 hour to facilitate ionic gelation and nanoparticle formation. The dispersion was subsequently homogenized in an ice-water bath to prevent heat generation and then allowed to stand overnight in the same ice-water bath to ensure stabilization of the nanoparticles. The nanoparticle was filtered using filter paper to eliminate any aggregates, diluted as necessary, and subjected to sonication in a bath sonicator for 2 minutes prior to characterisation. The prepared nanoparticles were further characterized for particle size, polydispersity index (size distribution) and zeta potential⁹. Chitosan nanoparticles were formulated using a three-factor, three-level Box–Behnken design (BBD) was generated with Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, MN, USA) to optimize the formulation process. Based on preliminary formulation studies, three independent variables were selected: TPP concentration (A), chitosan concentration (B), and homogenization speed (C). These variables were assessed at three different levels: TPP concentration (1.0, 1.75, and 2.5% w/v), chitosan concentration (0.5, 0.75, and 1.0% w/v), and homogenization speed (5000, 7500, and 10000 rpm). The design resulted in a total of 17 experimental runs, which included five center-point replicates indicated in Table 1^{10,11}.

Characterization of Nanoparticles

The prepared nanoparticles are evaluated for particle size, entrapment efficiency, zeta potential, *in vitro* release studies, and *ex vivo* permeation studies.

Particle Size, Size Distribution and Zeta Potential: Malvern zeta sizer Nano ZS-90 was used to evaluate particle size, and zeta potential¹⁰.

Entrapment Efficiency: The nanoparticles were centrifuged for 30 minutes at 50,000 rpm. The supernatant was collected, diluted, and 1 mL of this solution was further diluted to 10 mL using phosphate buffer¹². The percentage of drug entrapped within the nanoparticles was calculated using the following formula:

Entrapment Efficiency (%) = $[(C_t - C_f) / C_t] \times 100$
where C_t = total concentration of drug and C_f = concentration of free (unentrapped) drug.

Surface Morphology: The optimized formulation was intended to be characterized for surface

morphology by Scanning Electron Microscopy (SEM)¹³.

In Vitro Drug Release: The release of Frovatriptan from chitosan nanoparticles was investigated using the dialysis method. The dialysis bag (molecular weight cut off 350 Da, Sigma-Aldrich Co.) was soaked overnight in the diffusion medium (PBS pH 7.4). The frovatriptan chitosan nanoparticle suspension was filled into the dialysis bag ($n=3$), which was subsequently sealed at both ends and suspended in 20 ml of PBS pH 7.4 at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. The aliquots samples were withdrawn at a predetermined time (0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 24 hours) and subsequently re-added with the same volume of fresh release medium. The samples were filtered and analysed^{14,15}.

Kinetic Modeling of In vitro Drug Diffusion Profile: The *in vitro* release data was fitted into various kinetic model to study drug release mechanism¹⁵.

Ex vivo Permeation study: The Franz cells having the area of 3.14 cm^2 were used and the receptor compartment with a volume of about 50 ml. The tissue was isolated and mounted in Franz diffusion cells, with receptor chamber was filled with phosphate buffer pH 7.4 at $37 \pm 0.5^\circ\text{C}$ at 50 rpm^{15,16}. 4 ml of drug solution (1mg/ml) was filled into the donor compartment of prepared Franz diffusion cell. At a predetermined time, the sample was withdrawn and same amount of fresh sample was replaced. The withdrawn samples were analysed at 244 nm.

RESULTS AND DISCUSSION

Frovatriptan nanoparticles were formulated using an ionic gelation method in which the chitosan was dissolved in acetic acid and then mixed with tripolyphosphate (a polyanionic solution). The electrostatic interaction between the negatively charged tripolyphosphate groups and the positive charged amine groups of chitosan leads to the formation of the nanoparticles. The method was evaluated for measuring particle size, and entrapment efficiency, by varying the concentrations of chitosan and tripolyphosphate solution represented in Table 2 and evaluated by Box–Behnken design. The model showed generated a polynomial equation (Eq. 1 and Eq 2) to predict the influence of independent variables on encapsulation efficiency and particle size.

$$\begin{aligned} \text{EE} = & +422.19044 + 177.55098 \text{ TPP-} \\ & 1248.43222 \text{ Chitosan concentration (\%)-} \\ & 0.015740 \text{ Homogenization speed-} \\ & 120.71111 \text{ TPP * Chitosan concentration} \\ & (\%)+0.000176 \text{ TPP * Homogenization} \\ & \text{speed}+0.005920 \text{ Chitosan concentration (\%)*} \\ & \text{Homogenization speed-9.81195 TPP} \\ & ^2+862.03200 \text{ Chitosan concentration} \\ & (\%)^2+6.48270\text{E-07 Homogenization speed}^2 \\ & \text{-----Eq 1} \end{aligned}$$

$$\begin{aligned} \text{Particle size} = & +3131.49915-101.76000 \text{ TPP -} \\ & 3458.31378 \text{ Chitosan concentration (\%)-} \end{aligned}$$

$$\frac{0.225185 \text{ Homogenization speed} + 221.51111 \text{ TPP} * \text{Chitosan concentration} (\%) - 0.008674 \text{ TPP} * \text{Homogenization speed} + 0.273462 \text{ Chitosan concentration} (\%) * \text{Homogenization speed}}{\text{-----Eq 2}}$$

Effect of chitosan concentration on entrapment efficiency and particle size

Increasing the chitosan concentration from 0.5% to 1.0% generally increases the entrapment efficiency of the nanoparticles. Chitosan provides a larger polymeric matrix to encapsulate the drug. A higher polymer concentration results in increased viscosity, which reduces drug diffusion into the external phase during ionic gelation. More amino groups of chitosan interact with TPP, forming a denser cross-linked network capable of retaining a greater amount of drug^{18,19}, indicated in Figure 1.

An increase in chitosan concentration also increases the particle size. Higher chitosan concentration increases the viscosity of the polymer solution. Increased viscosity reduces the efficiency of droplet breakup during homogenization. More polymer chains participate in ionic cross-linking with TPP, producing thicker nanoparticle shells and larger particles^{18,19}, indicated in Figure 2.

Effect of TPP Concentration on Entrapment Efficiency and Particle Size

The entrapment efficiency and particle size of the chitosan nanoparticles was significantly influenced by the effect of TPP. Increasing the TPP concentration from 1.0% to 1.75% increased the mean entrapment efficiency from approximately 76.75% to 84.11%. This accounts for the increased availability of negatively charged phosphate groups in TPP, which interact ionically with the positively charged amino groups of chitosan. The resulting increase in cross-linking density produces a stronger polymeric network and improves drug retention within the nanoparticles¹⁹, indicated in Figure 1.

However, a further increase in TPP concentration to 2.5% did not produce a proportional improvement in entrapment efficiency, with the mean value decreasing slightly to approximately 83.05%. This may be due to excessive cross-linking, rapid particle formation, or expulsion of a portion of the drug from the tightly cross-linked polymeric matrix. Therefore, an intermediate TPP concentration of approximately 1.75% appeared to be more favourable for achieving higher entrapment efficiency^{18,19}, indicated in Figure 2.

The mean particle size was approximately 254.53 nm at 1.0% TPP, decreased to 199.19 nm at 1.75% TPP, and subsequently increased to 231.88 nm at 2.5% TPP. At the intermediate concentration, sufficient ionic cross-linking may have promoted the formation of compact nanoparticles. In contrast, excessive TPP may have caused interparticle bridging, aggregation, or formation of a highly cross-linked network, resulting in an increase in

particle size. Thus, the effect of TPP concentration on particle size appeared to be nonlinear, with the intermediate level producing comparatively smaller particles^{18,19}.

Effect of Homogenization Speed on Entrapment Efficiency and Particle Size

Homogenization speed showed a pronounced effect on particle size. Increasing the homogenization speed from 5,000 to 10,000 rpm progressively reduced the mean particle size from approximately 253.38 nm to 179.93 nm. The reduction in particle size may be attributed to the greater shear force generated at higher homogenization speeds, which breaks larger droplets and particle aggregates into smaller and more uniformly dispersed particles, indicated in Figure 2.

The mean entrapment efficiency also increased from approximately 80.30% at 5,000 rpm to 83.93% at 10,000 rpm. Improved dispersion of the polymer and cross-linking agent at higher speed may promote rapid and uniform nanoparticle formation, thereby reducing drug loss during preparation. However, excessively high homogenization speeds beyond the investigated range may potentially reduce entrapment efficiency because of polymer-chain disruption, temperature generation, or leakage of the entrapped drug, indicated in Figure 1.

Overall, increasing homogenization speed within the selected range was beneficial for reducing particle size and moderately improving entrapment efficiency. Among the investigated levels, 10,000 rpm produced the smallest particles, whereas an intermediate TPP concentration of approximately 1.75% provided a favourable balance between high entrapment efficiency and reduced particle size^{20,21}. After establishing the relationship between the main effects (Concentration of TPP, homogenization speed and Concentration of chitosan), on entrapment efficiency and particle size, were optimized by using Design-Expert software. The desirability plot displays that the desirability value of 0.883 was identified at the optimum concentrations of the independent variables (Figure 3). The optimized formulation particle size is represented in Figure 4.

Zeta Potential

The magnitude of the zeta potential is an important indicator of the physical stability of colloidal nanoparticle systems. The optimized chitosan nanoparticle formulation exhibited a zeta potential of $+34.7 \pm 4.77$ mV represented in Figure 5. This high positive surface charge is attributed to the protonated amino groups of chitosan. Zeta potential values greater than ± 30 mV are generally considered indicative of good colloidal stability due to sufficient electrostatic repulsion between particles, thereby minimizing aggregation. Therefore, the optimized formulation is expected to possess excellent physical stability.

Scanning Electron Microscopy

Figure 6 shows that the optimized formulation exhibited a particle size in the range of 210–230 nm. The observed particle size is consistent with values reported in the literature for chitosan nanoparticles prepared using similar fabrication methods, indicating the successful formation of nanoparticles within the expected nanoscale range²².

***In vitro* Drug release**

The optimized chitosan nanoparticle exhibited a controlled and prolonged drug-release profile compared with the Frovatriptan solution, with approximately 83% drug release at 24 h, indicating the potential of the nanoparticle system to sustain drug release (Figure 7). The release profile demonstrated an initial relatively slow release, followed by an increased release phase and a subsequent gradual release, suggesting diffusion of the drug through the hydrated chitosan polymeric matrix²³.

The optimized nanoparticle followed first-order release kinetics, as evidenced by the highest regression coefficient (R^2), indicating that the drug-release rate was dependent on the concentration of drug remaining within the nanoparticles. Accordingly, the release rate was relatively higher during the initial phase and gradually decreased as the drug concentration within the polymeric matrix diminished. Furthermore, the Korsmeyer-Peppas model showed a release exponent ($n = 0.0524$), indicating a Fickian diffusion mechanism. This suggests that drug release occurred predominantly through diffusion across the chitosan matrix, with minimal contribution from polymer relaxation or erosion²³. Overall, the findings confirm that the optimized chitosan nanoparticles provided concentration-dependent, diffusion-controlled and sustained release of Frovatriptan over 24 h.

***Ex vivo* Permeation Studies**

The *ex vivo* nasal permeation study demonstrated enhanced permeations of frovatriptan nanoparticle formulation compared with the drug solution. The nanoparticle formulation also exhibited a higher flux (4.449 vs. 1.63) and permeability coefficient (44.49 vs. 16.3), corresponding to approximately 2.73-fold increases represented in Figure 8. The enhanced permeation may be attributed to the nanoparticles increased surface area and increased mucoadhesion as result of electrostatic interaction between chitosan and mucin protein coating of the nasal epithelium. This creates strong adhesion and close contact with the epithelium; chitosan nanoparticles shrink the unstirred water layer and thus reduce the resistance between the drug and absorptive cells. Also loses the close fit junction between the epithelial cells and opens paracellular routes and gaps between the cells, and hence increases the permeability. This is supported by the literature; closely fitted junctions in the cells are opened by chitosan, which facilitates permeability through the cell layer. This mechanism

however usually supports of water-soluble drugs permeation. Recently, it has been shown that the biodegradation of nanocapsules by enzymes in the mucus barrier or intracellularly could be a critical factor in the increase of the transcellular transport of lipophilic drugs²⁴. These results from the *ex vivo* permeation studies on porcine nasal mucosa confirmed and added further evidence for the efficient delivery of frovatriptan and enhanced the anti-migraine effect.

CONCLUSION

The study successfully developed frovatriptan-loaded chitosan nanoparticles using the ionic gelation technique for potential intranasal delivery. Chitosan, TPP concentration, and homogenization speed influenced particle size and entrapment efficiency. Design-Expert optimization yielded a desirability of 0.883, with an experimental entrapment efficiency of 92.60% and size of 220.7 nm. The optimized formulation exhibited a high positive zeta potential ($+54.7 \pm 4.77$ mV), indicating good colloidal stability, while SEM confirmed nanosized particles (210–230 nm). The formulation demonstrated controlled drug release (~83% over 24 h), following first-order kinetics with predominantly Fickian diffusion. *Ex vivo* nasal permeation showed approximately 2.73-fold higher flux and permeability coefficient compared with frovatriptan solution. Overall, the findings indicate that chitosan nanoparticles are a promising platform for enhancing nasal delivery of frovatriptan, with potential benefits of improved permeation and sustained drug release.

ACKNOWLEDGEMENT: The authors thank Krupanidhi College of Pharmacy, Bengaluru for providing all the facilities to carry out this research.

CONFLICT OF INTEREST: The authors declare no conflict of interest

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TABLES AND FIGURES

Table 1: Factors and levels used optimization

	Levels used, actual (coded)

FORMULATION AND OPTIMIZATION OF FROVATRIPTAN-LOADED CHITOSAN NANOPARTICLES FOR INTRANASAL DELIVERY IN MIGRAINE MANAGEMENT

	Low (-1)	High (+1)
INDEPENDENT VARIABLE		
A: Concentration of TPP(%)	0.5	1
B: Chitosan Concentration(%)	1	1.75
C: Homogenization Speed(rpm)	5000	10000
DEPENDENT VARIABLE		
R1: Particle size	Minimum	
R2: Entrapment Efficiency	Maximum	

Table 2: Results of variables on response

N o of T r a i l s	Conce ntrati on of Chitos an	Conce ntrati on of TPP	Homog enizati on speed	Entr apme nt Effici ency	Par tiel e Siz e
1	1	0	1	82.4	281.1
2	-1	-1	0	68.9	247.8
3	-1	0	-1	77.3	209.7
4	1	-1	0	82.1	293.55
5	0	-1	1	85	221.56
6	0	0	0	78.8	240.09
7	0	0	0	79.6	240.09
8	1	0	-1	84.7	254.69
9	0	1	-1	85.3	191.226
10	0	0	0	75.6	273.2
11	0	1	1	90.6625	232.1
12	0	0	0	79.64	241.8
13	-1	1	0	84.225	184.9
14	0	0	0	79.64	271.6
15	1	1	0	80.45	241.8
16	-1	0	1	74.0125	284.9

17	0	-1	-1	83.3375	341.6
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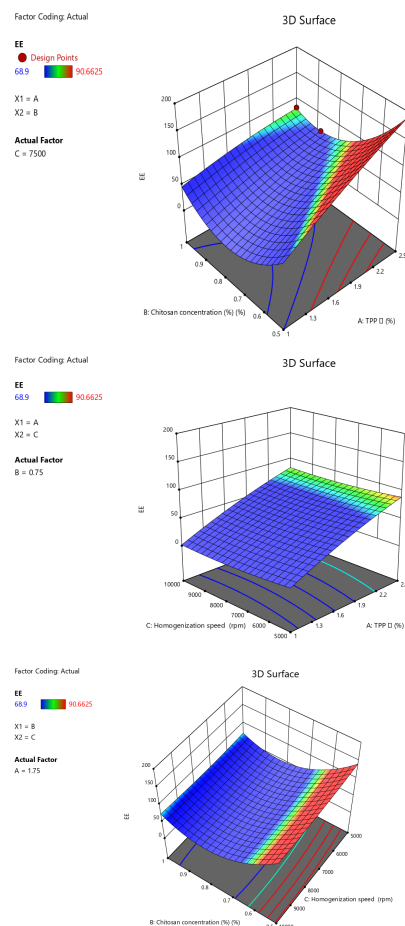


Figure 1: 3D surface plot for the effect of chitosan concentration, TPP concentration and homogenization speed on encapsulation efficiency

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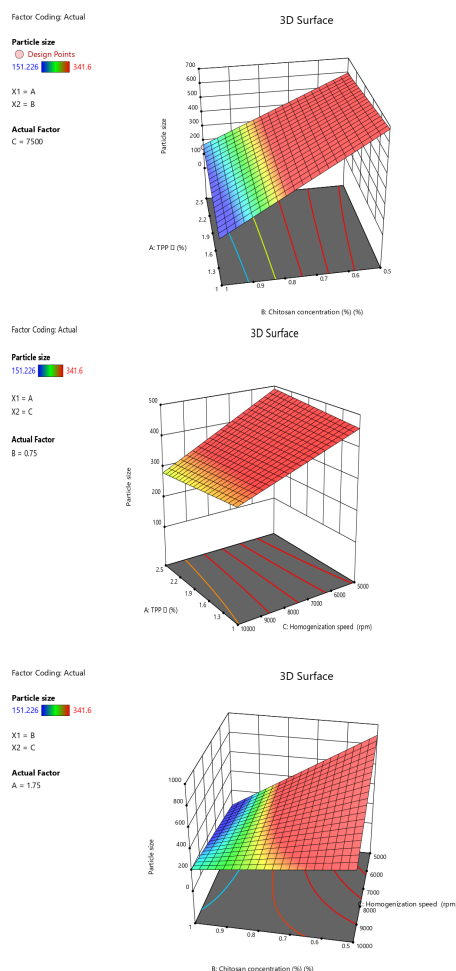


Figure 2: 3D surface plot for the effect of homogenization speed, TPP concentration and Chitosan concentration on particle size

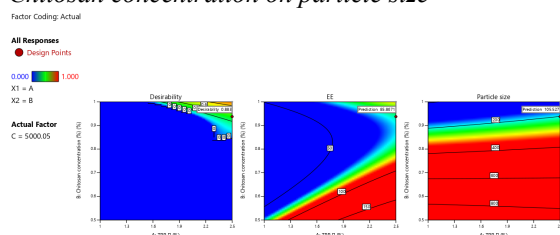


Figure 3: Desirability plot of optimized formulation

Factors	Desirability	Model	Experiment
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Cone of chitosan(%)	Concentration of TPP(%)	Homogenization speed(rpm)	Entrapment Efficiency(%)	Particle Size(nm)	Entrapment Efficiency(%)	Particle Size(nm)
1	1.5	5000	0.883	85.86	205.67	92.7

Z-Average (d.nm): 220.7
PdI: 0.287
Intercept: 0.598
Result quality: Refer to quality ref

Size (d.nm): 204.6
Peak 1: 19.62
Peak 2: 0.000
Peak 3: 0.000

% Intensity: 93.4
6.6
0.0
0.000

St Dev (d.nm): 59.87
3.717
0.000
0.000

Di(0.1): 114
Di(0.5): 191
Di(0.9): 289

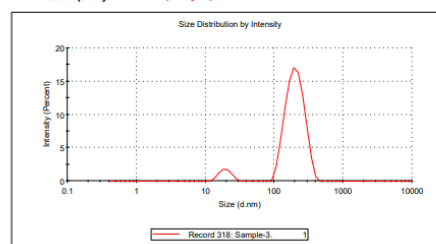


Figure 4: Optimized formulation particle size

Mean (mV): 34.7
Area (%): 100.0
St Dev (mV): 4.37

Zeta Potential (mV): 34.7
Zeta Deviation (mV): 4.37
Conductivity (mS/cm): 0.293

Peak 1: 34.7
Peak 2: 0.00
Peak 3: 0.00

Result quality: Good

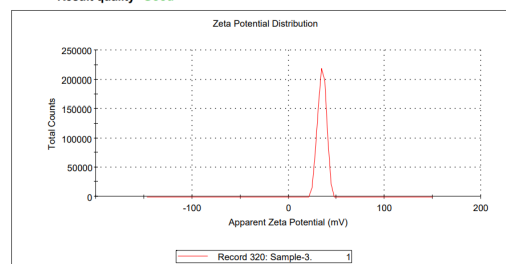


Figure 5: Zeta potential of optimized formulation

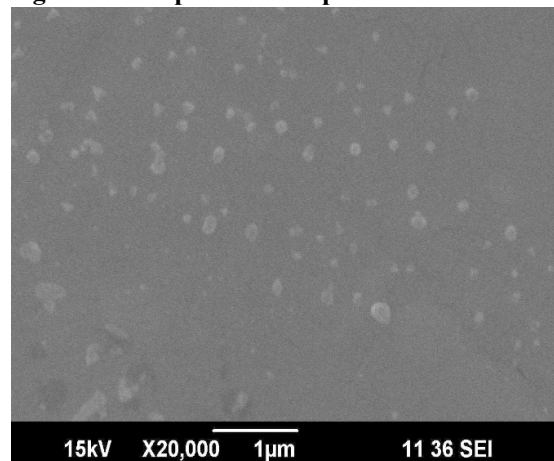


Figure 6: SEM image of optimized formulation

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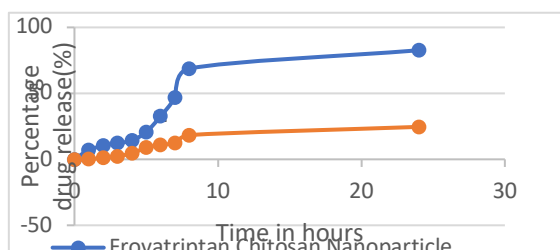


Figure 7: *In vitro* release study of Chitosan nanoparticle

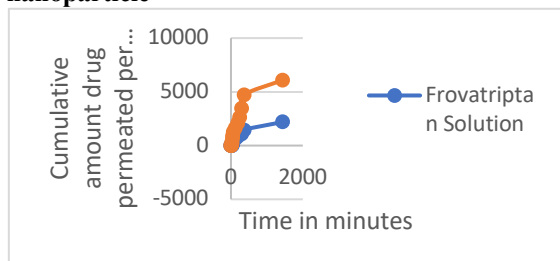


Figure 8: *Ex vivo* permeation study of Chitosan nanoparticle