RESEARCH ARTICLE

Development and Evaluation of Chitosan Nanoparticle-Loaded Films for Enhanced Bioavailability

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Received: 9th Aug, 2025; Revised: 1st Sep, 2025; Accepted: 9th Sep, 2025; Available Online: 25th Sep, 2025

ABSTRACT

Memantine-loaded chitosan nanoparticles (MNPs) were created utilizing the ionic gelation technique in order to get over these restrictions. MNP4 was chosen as the optimal formulation for additional characterization because it showed the highest entrapment efficiency (%EE) of 84.73±1.214% among the formulations. According to *in vitro* tests utilizing a Franz diffusion cell, this improved formulation had a non-Fickian super case II drug release mechanism, first-order release kinetics (r^2 = 0.913), and an average particle size of 298.6 nm with a zeta potential (ZP) of +24.5 mV. Using single or mixed polymers, the optimized nanoparticles (MNP4) were then added to thin mucoadhesive buccal films (BFs) via the traditional solvent casting method. The mechanical strength, mucoadhesive qualities, swelling behavior, and *in vitro* drug release of the resultant buccal films were assessed. MNBF6 was the most effective buccal film among the formulations; it had the highest mucoadhesive strength (7.5±0.22 N) and the largest drug release at the 12-hour mark. Goat buccal mucosa was used for *ex vivo* permeation tests on this product. The purpose of this study was to compare the improved permeability of memantine from the optimized buccal film loaded with nanoparticles (MNBF6) to a film containing the medication in its plain form (MBF10). The results validate the possibility of using buccal films with Memantine-loaded nanoparticles as a viable substitute delivery method to enhance Memantine bioavailability and therapeutic effectiveness for the management of symptoms associated with Alzheimer's disease.

Keywords: Mucoadhesive drug delivery, Memantine-chitosan nanoparticles, Buccal films, Alzheimer's disease, Ionic gelation and Non-Fickian drug release.

How to cite this article: Venkata Durga Seshu Priya P, Ruby S, Kumar M. Development and Evaluation of Chitosan Nanoparticle-Loaded Films for Enhanced Bioavailability. International Journal of Drug Delivery Technology. 2025;15(3):1318-25. doi: 10.25258/ijddt.15.3.53

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Alzheimer's disease (AD) is the leading type of dementia, impacting millions across the globe. It is a gradually worsening neurological condition marked by memory decline, reduced cognitive abilities, and changes in behavior[1]. The pathophysiology of AD involves multiple mechanisms including beta-amyloid plaque accumulation, tau protein hyperphosphorylation, oxidative stress, and glutamatergic dysfunction. Among the pharmacological agents used in its treatment, memantine, an NMDA (N-methyl-D-aspartate) receptor antagonist, plays a key role in mitigating symptoms, particularly in moderate to severe stages of the disease[2].

Despite its therapeutic benefits, the efficacy of memantine is limited due to its short plasma half-life, poor penetration across the blood-brain barrier (BBB), systemic side effects. Conventional oral administration leads to suboptimal concentrations of the drug in the brain, reducing its potential to effectively block excessive glutamate activity, which contributes to neuronal death in AD. To address these limitations, researchers have explored nanotechnology-based delivery systems, particularly Memantine loaded chitosan nanoparticles, as a strategy to enhance brain-targeted delivery and prolong drug action[3].

Chitosan is a natural biopolymer derived from chitin. It is biodegradable, biocompatible, and possesses mucoadhesive and permeation-enhancing properties. Most importantly, chitosan has a positive surface charge, which enables it to interact favorably with the negatively charged BBB and cellular membranes. These properties make it an ideal carrier for brain-targeted drug delivery[4]. Memantine chitosan nanoparticles are typically prepared using the ionic gelation method**,** which involves the electrostatic interaction between chitosan and a cross-linker such as sodium tripolyphosphate (TPP). This method produces spherical nanoparticles with particle size usually ranging from 100–300 nm, high encapsulation efficiency (often above 85%), positive zeta potential for enhanced stability and interaction with cell membranes and controlled release profile for sustained therapeutic action[5]. These physicochemical characteristics are crucial for enhancing the residence time of Memantine in systemic circulation and promoting its effective passage into the brain[6].

In *in-vitro* studies, Mementine nanoparticles show sustained drug release over extended periods, reducing the

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frequency of dosing. *In-vivo* animal studies using Alzheimer's models have demonstrated that Mementine nanoparticles result in significantly improved cognitive function and memory retention compared to free Memantine[7]. Behavioral tests such as the Morris Water Maze and Y-Maze have shown better performance in animals treated with Mementine nanoparticle. Moreover, Mementine nanoparticle reduce neuroinflammation and oxidative stress markers, two of the critical pathological hallmarks in AD. The improved brain delivery ensures that memantine acts more efficiently on NMDA receptors, helping to reduce excitotoxicity and slow down neuronal damage[8]. Memantine-loaded chitosan nanoparticles represent a promising nanocarrier system to enhance the delivery. By improving brain targeting, sustaining drug release, and minimizing side effects, Mementine nanoparticle can offer improved symptom control and potentially delay disease progression. Ongoing research and clinical translation of this technology may open new frontiers in neurodegenerative disease therapy, particularly for patients suffering from Alzheimer's disease[9].

MATERIALS AND METHODS

Memantine HCl was provided as gift sample by Yerrow Chemicals, Mumbai. chitosan and tripolyphosphate (TPP) were obtained from Sigma Aldrich; acetic acid glacial, methanol were obtained from HiMedia Laboratories. POLYOX and guar gum were purchased from Sigma Aldrich.

Preparation of Nanoparticles

To create NPs with the required particle size, modifications to the ionotropic gelation method were made. To put it briefly, 0.5 %v/v glacial acetic acid was added to water to create a 0.2 % w/v chitosan solution. Dissolving the precisely weighed amount of memantine required by stirring at 900 rpm. The resulting solution's pH is adjusted to the necessary amount using 0.1 M NaOH solution. A syringe pump was used to gradually mix the drug polymer solution with 0.2% w/v TPP solution at a flow rate of 0.5 mL/min. A syringe pump was used to gradually mix the drug polymer solution with 0.2% w/v TPP solution at a flow rate of 0.5 mL/min. Almost immediately after TPP was added, drug-loaded nanoparticles were produced. To improve the formulation, many batches of the medication and chitosan solution were made, each with a different pH. Other formulation parameters were held constant for comparison studies[10]. The formulation table of nanoparticles was shown in (Table 1).

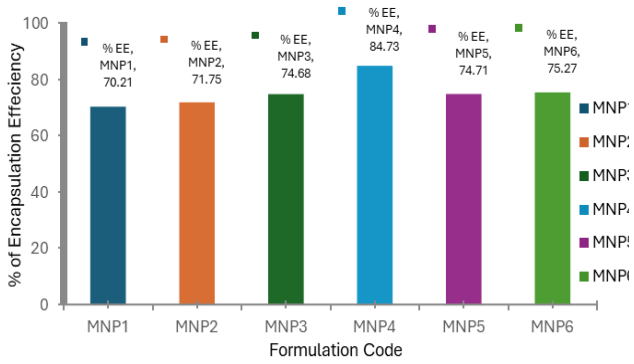

Figure 1: % of Entrapment Efficiency

Evaluation of Nanoparticles

Entrapment Efficiency

The solution was immediately separated in ultracentrifuge operating at 18000 rpm for 60 min at 4°C. With the UV spectrophotometer set to 254 nm, the amount of drug in the obtained clear supernatant sample was calculated. Based on the value of highest %EE (figure 1) the prepared NPs were selected as optimized and further characterization on them will be continued. These optimized NPs will be incorporated into the prepared BFs for the further studies[11].

Particle Size

The Horiba Scientific SZ-100 with dynamic laser light scattering technology was utilised to measure the polydispersity index (PDI) and mean particle size for the optimized NPs based on their highest %EE and showed in figure 2. Before the dispersions were tested at a 90° angle, they were diluted 100 times with deionized water[12].

Zeta Potential

The Horiba scientific SZ-100 was used to calculate the ZP of optimized NPs based on their highest %EE, using the laser light scattering technique[13]. To suitably dilute the mixture, double distilled water was used. A 90° angle was used to take the measurements and showed in figure 3.

In-vitro Drug Release Studies

The release of drug from optimized NPs based on their highest %EE was examined and *in vitro* Franz diffusion cell set at 34±0.5°C. A dialysis bag containing optimized NPs (MNP4) equivalent to 10 mg of drug was tied at both ends in a 100 mL of pH 6.8 PBS and was shaken at 50 rpm[14]. Samples of 1 mL were obtained from the beaker and substituted with an equal volume of pH 6.8 PBS at predetermined intervals (0, 1, 2, 4, 6, 8, 10, 12 hr). Each sample that has been removed is then diluted to 10 mL. The drug concentration was ascertained using a UV-Visible

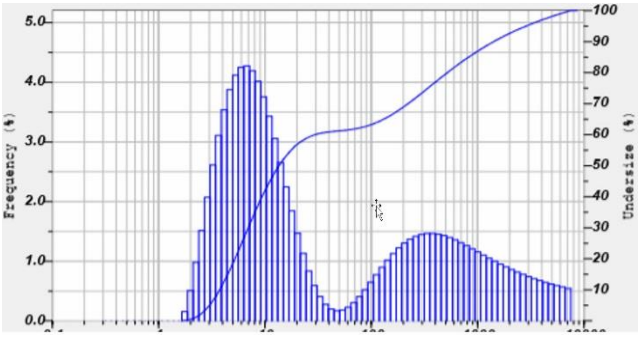

Figure 2: Particle size of optimized nanoparticles (MNP4)

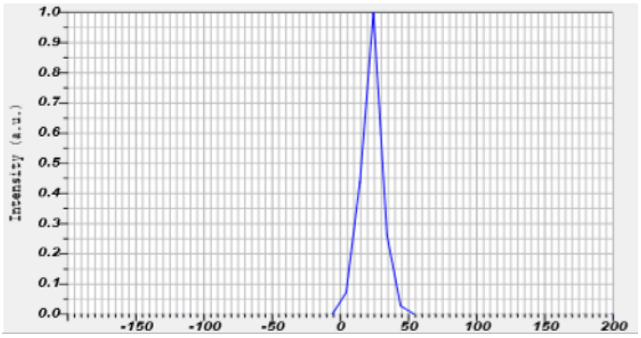

Figure 3: Zeta potential of optimized nanoparticles (MNP4)

spectrophotometer that was adjusted to 254nm and represented their release profile in figure 4.

Preparation of Buccal Films

An inexpensive solvent casting method was used to create the 9 different formulations of mucoadhesive buccal films loaded with optimized Memantine-chitosan nanoparticles (MN4), plain drug and the various concentrations of POLYOX or gellan gum were dissolved in 10 mL of generated optimized NPs dispersion and swirled for 1 h at 600 rpm in 50°C is shown in Table 2. To allow the solvent to evaporate, the solution was placed in a 35 cm^2 petri dish and baked at 40°C for 48 hr. The resultant films were sliced with a cutter into 2x2 cm^2 pieces and kept in a desiccator until used for further research. Table 2[15].

Evaluation of Buccal Films

Examined were physicochemical characteristics includes thickness, surface pH, folding endurance, swelling ratio, drug content, % of mucoadhesion and an *in-vitro* release and reported in table 3. Additionally, the physicochemical characteristics of the optimized BFs were evaluated by SEM analysis. Also the *ex-vivo* permeation studies were performed on the optimized BFs with drug-chitosan NPs and with plain drug.

Thickness

One crucial factor in assessing the homogeneity of the formulation component distribution is the film's thickness. The thickness of each film formulation was measured at five different points using a screw gauge. All six (n=6) of the film's areas should have a maximum difference of less than 5%. To carry out more investigation, the average data were used[16].

pH

To ascertain whether or not each film irritates the buccal mucosa, the surface pH of each formulation was measured. The 1x1 cm films were immersed in 1 mL of distilled water at 370C for an hour. To measure the pH, the electrode of an ELICO pH meter (L1613) was brought into contact with the surface of the film.

Folding Endurance

A narrow (2 x 2 cm2) strip was folded repeatedly until it broke in order to assess the film's ability to fold. The quantity of times a film may be folded in the same location without breaking is known as folding endurance.

Swelling Ratio (%)

Following the weight measurement of a 2x2 cm^2 film (W1), the films' swelling characteristics were assessed by submerging them in pH 6.8 Phosphate buffer solution (PBS) at 34°C. At five-minute intervals, films were removed from the PBS solution, and any remaining PBS was filtered through filter paper until the films started to degrade[17].

Drug Content

Each 2x2 cm2 buccal film was cut from a separate location, submerged in a methanol–water solvent mixture, and

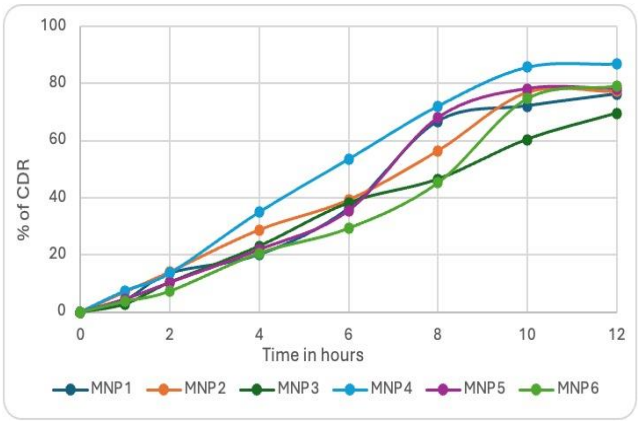

Figure 4: *In-vitro* drug release profile of Memantine Nanoparticle

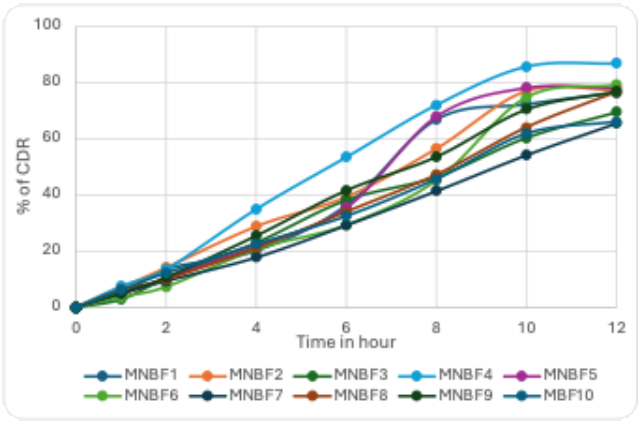

Figure 5: Comparison of *in-vitro* drug release of buccal films

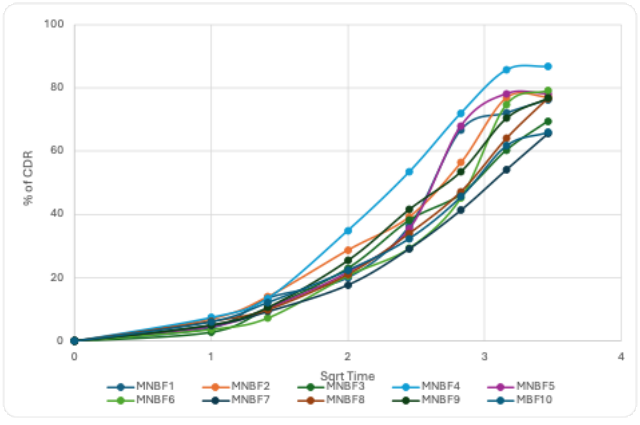

Figure 6: Higuchi kinetic profile of MNBF1-MBF10

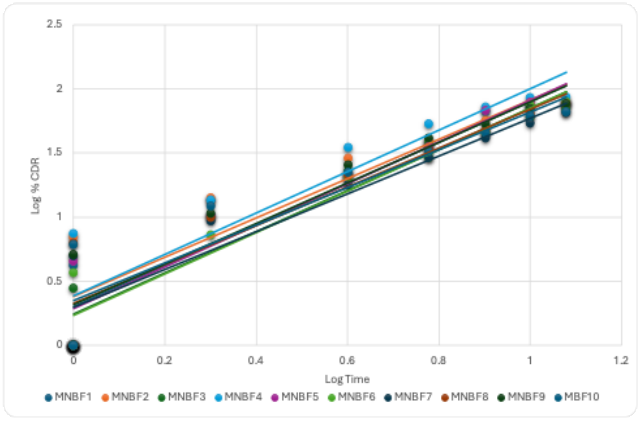

Figure 7: Korsmeyer Peppas kinetic profile of MNBF1-MBF10

swirled for 12 hours in a water bath that was thermostatically controlled at 34±0.5°C. At 254 nm, the API that had been extracted into the solvent was filtered and subjected to spectrophotometric analysis.

Mucoadhesive Strength

The substrate in texture analyzer was goat buccal mucosa of which the mucoadhesive strength of the films was determined.

First, the buccal membrane was attached to the fixed stream of the stage and film, in a sufficient size of 2x2 cm2, to the probe of the analyzer[18]. The wetting at the tissue membrane was done by using the pH 6.8 PBS (simulated saliva). The moveable probe was very slowly brought down until it was in contact with the mucous membrane, at which point it remained in position with one minute. The mucoadhesive strength will be expressed in newtons (N). Table 3.

In-vitro Drug Release

The *in-vitro* release of drugs was done using 0.6 0.6 cm of MNBF with 10 mg of the drug and 34+/-0.5C in a Franz diffusion cell. Each film was immersed in 8 mL of the nonpyrogenic pH 6.8 PBS followed by the placement of a dialysis bag of 2 mL of the nonpyrogenic pH 6.8 PBS and shaken at 100 rpm and at 34 o C in a shaking water bath with sufficient shaking. Samples of each of the dissolution flasks (one milliliter each) were sampled at various intervals (0, 1, 2, 4, 6, 8, 10 and 12 hours) then discarded, and an equal volume of pH 6.8 PBS substituted in their place[19]. Their release kinetics were then detected through UV analysis using 254 nm wavelength which revealed figure 5-7.

SEM Analysis

SEM images of drug, optimized buccal film without drug (Placebo) and with drug were noted in figure 8,9,10. The SEM was used to study the BFs external macroscopic structure.

Ex-vivo Permeation Study

Franz diffusion cell conducted at 34+=0.50 C on goat buccal mucosa was used in conducting the *ex vivo* works. It which was properly washed and attached to an open glass cylinder and submerged in 100 mL beaker which contained 50 mL pH 6.8 PBS. Buccal films containing nanoparticles of drugs and plain drug containing buccal films were left on the mucosa in separate cells. This set up is mounted on magnetic stirrer. A 5mL of the sample was drawn at the pre-planned time point including 0, 1, 2, 4, 6, 8, 10 and 12 hours which were replaced with freshly prepared pH 6.8 PBS to that to allow sink condition[20-34]. It was quantified by domain of UV-Visible spectrophotometer at 254nm and visualized their permeation profile in figure 11.

DISCUSSIONS

% Encapsulation Efficiency

By the determination of %EE of all the prepared MNPs ranges from 70.21 to 84.73% indicating good drug entrapment. Based on these studies, a 4:1 ratio between chitosan and TPP is recommended, due to their higher values than others. The formulation MNP4 is found to have highest value of 84.73%. Hence the further studies: Particle size analysis, ZP, FTIR spectra and *in vitro* drug release were conducted on the optimized NPs (MNP4).

Table 1: Formulation of chitosan loaded nanoparticles

F Code	Ingredients			Chitosan : TPP ratio	pH of the solution
	Meman-tine (mg)	Chitosan (mg/mL)	TPP (mg/mL)		
MNP 1	10	2 (10 mL)	2 (2.5 mL)	4:1	3.5
MNP 2	10	2 (10 mL)	2 (2.5 mL)	4:1	4.5
MNP 3	10	2 (10 mL)	2 (2.5 mL)	4:1	5.5
MNP 4	10	2 (10 mL)	2 (3.3 mL)	3:1	3.5
MNP 5	10	2 (10 mL)	2 (3.3 mL)	3:1	4.5
MNP 6	10	2 (10 mL)	2 (3.3 mL)	3:1	5.5

Table 2: Formulation of buccal films loaded with optimized nanoparticles (MNP4)

F Code	POLYOX (mg)	Gellan gum (mg)	Glycerol (mL)
MNBF1	50	0	1.5
MNBF2	100	0	1.5
MNBF3	150	0	1.5
MNBF4	200	0	1.5
MNBF5	50	50	1.5
MNBF6	100	100	1.5
MNBF7	150	150	1.5
MNBF8	300	100	1.5
MNBF9	400	0	1.5
MBF10	100	100	1.5

Particle Size

Particle size analysis revealed a particle size of 306.6 nm (Fig. 1). The size range of the colloidal NPs was 50-1000 nm. Particle size increases as a result of the RB being loaded into the chitosan matrix.

ZP

Values for ZP typically fall between -30 to+30 mv.The average ZP of optimized MNP4,is determined to be +22.6 mv (Fig. 2), which indicates the successful loading of drug into the chitosan matrix.

In-vitro Drug Release

The data resulting in the *in vitro* release was analyzed using four mathematical models, to elucidate on the release kinetics of the drug released by the improved MNP4: The regression coefficients (r2) of the Hughchi, Korsmeyer-Peppas, zero order and first order models were calculated. The highest value of 0.921 r2 showed that the kinetics of release of drugs out of MNP4 in pH 6.8 PBS fell in the first order model. This implies that the concentration of a drug upon release has a direct correlation. The rate of drug release which is independent or dependent upon the concentration of the drug is explained by the zero order model and first order model respectively.

Characterization of Buccal Films (MNBF)

Thickness

The precision of drug concentration in distinct sections of every film is directly related to the consistency of thickness and drug content. After repeating all measurements, the

Table 3: Characterization of the buccal films loaded with optimized nanoparticles (MNP4)

F Code	Thickness (mm)	Surface pH	Folding Endurance (Number)	Drug Content (%)	Mucoadhesive Strength (N)
MNBF1	0.169 ± 0.03	6.27 ± 0.08	274 ± 1.51	82.3 ± 1.61	6.5 ± 0.14
MNBF2	0.175 ± 0.02	6.45 ± 0.05	250 ± 1.65	80.1 ± 2.98	6.8 ± 0.23
MNBF3	0.182 ± 0.11	6.48 ± 0.08	285 ± 1.69	81.0 ± 1.76	6.7 ± 0.32
MNBF4	0.191 ± 0.05	6.62 ± 0.06	263 ± 1.24	83.1 ± 1.52	7.7 ± 0.13
MNBF5	0.215 ± 0.04	6.57 ± 0.03	252 ± 1.42	85.2 ± 1.56	7.2 ± 0.43
MNBF6	0.244 ± 0.06	6.55 ± 0.02	290 ± 1.64	89.8 ± 1.27	7.5 ± 0.22
MNBF7	0.251 ± 0.03	6.32 ± 0.04	265 ± 1.85	79.1 ± 1.19	6.3 ± 0.92
MNBF8	0.259 ± 0.03	6.41 ± 0.05	259 ± 1.85	81.5 ± 1.89	6.1 ± 0.85
MNBF9	0.262 ± 0.02	6.19 ± 0.09	243 ± 1.72	77.8 ± 2.61	6.7 ± 0.79
MBF10	0.185 ± 0.02	6.48 ± 0.05	240 ± 1.65	76.1 ± 2.98	6.7 ± 0.41

film thickness was found to be between 0.169±0.03 and 0.262±0.02 mm (Table 3).

Surface pH

By measuring the pH of the film's surface, the impact of pH on the buccal mucosa was examined. For every formulation, the surface pH of BFs was determined within the 6.19±0.09 to 6.62±0.06 range (Table 3), which is the pH range of healthy human saliva. Hence they are not supposed to cause the buccal irritation.

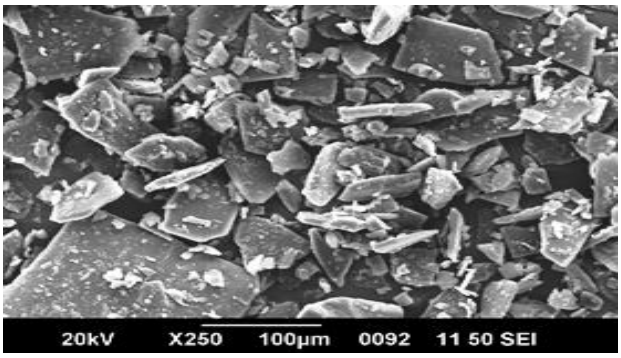

Figure 8: SEM images of Memantine HCl

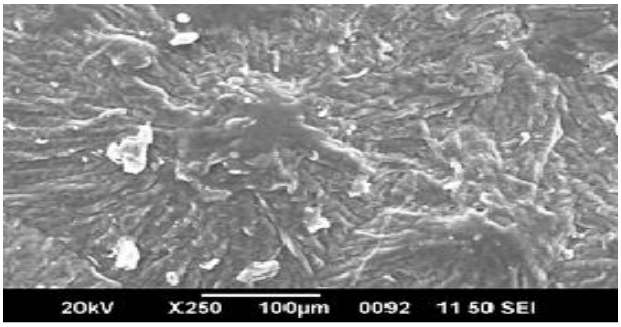

Figure 9: SEM images of Placebo

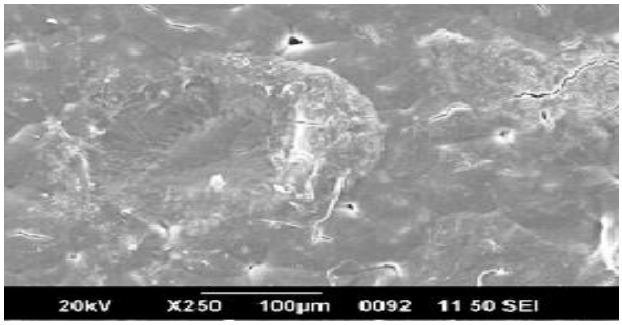

Figure 10: SEM images of MNBF6 with drug

Folding Endurance

The mechanical strength and rupturing resistance of BFs were assessed through folding endurance testing. The values are ranging from 240±1.65 to 290±1.64 (Table 3), which showed good flexibility for all formulas.

Swelling Index

Water-induced swelling causes bioadhesive polymers that were initially stretched, twisted, or entangled to relax. This leads to the quick disentanglement of individual polymer chains and the creation of a macromolecular network of a particular size that raises the film's porosity and starts the drug release process. However, patients may experience discomfort if edema is excessive. Generally, the kind, content, and physicochemical characteristics of the film formers determine the degree of film hydration. It is clear that whilst the hydration values in other films were low, they were somewhat higher and comparable in film MNBF6.

Drug Content

Uniformity of content is one of the crucial pharmaceutical quality control criteria that is normally assessed to ensure there is availability of medication in pharmaceutical products. Values of drug content between 76.1+2.98 and 89.8+1.27 percent (Table 3) are indicative of the content of higher drug content > 89 percent in films MNBF6. The fixed values of multiple formulations revealed that type and composition of polymer did not have an impact on the medication content of the medication.

Mucoadhesive Strength

Since there is a possibility that lack of mucoadhesion can lead to removal of the film at the application site, mucoadhesion is a key ingredient of effective buccal treatment. The values of mucoadhesive strength >7.5 N in films MNBF6 suggest its higher mucoadhesive strength where the mean values of mucoadhesive strength 6.1+/-0.85 to 7.5+/-0.22N (Table 3). The mucoadhesive property of the polymers is POLYOX >> POLYOX + guar gum >> guar gum and may be because of the poly (ethylene oxide) in POLYOX. Increased mucoadhesive strength was also found on films formed by high and low concentrations of both POLYOX and its combination with guar gum.

In-vitro Drug Release

This demonstrated that kinetics profile of MNBF6 drug release at optimized buccal films in the pH 6.8 PBS corresponded to first order model, since the greatest r2 value of 0.921. These imply that the concentration of a drug

and its rate of release have a direct correlation. Depending on the value of exponent of release (n) in the Korsmeyer-Peppas or power law model of the planar/thin films, the drug release mechanism can be classified as Fickian model (Case I), or Non-Fickian models (Case II/Anomalous transport/Super Case II). Model: The model applicable when 0.5 < n < 1.0 and where drug release mechanism is swelling and diffusion is known as non-Fickian (Anomalous transport) model. The non-Fickian (Super Case II) model is used where n is greater than 1.0 and the means of the drug release mechanism is tension and polymer breaking mechanism.

SEM Analysis

The surface morphology of drug, optimized film MNBF6 without drug (Placebo) and with drug were investigated with SEM. SEM of drug alone shows only a normal crystal structure where placebo film shows small holes and homogeneous structure as seen in figure 8-9. The optimized film MNBF6 drug, exhibited amorphous nature of drug, enlarged pore diameters, a smooth surface with suitable surface morphology that could be valuable in buccal application figure 10. According to the results, the images of the movies containing and not containing drug seem surface identical.

Ex-vivo Permeation Studies

The *ex-vivo* permeation tests are usually done so as to understand the drug dynamics of absorption of the drugs through the biological membranes. Broadly, this is because the nature of the drug molecules and physical conditions of the membrane barriers govern drug transport across any given membrane. The amount of drug being transferred across the goat buccal mucosa with optimized buccal films containing drug nanoparticles (MNBF6) and drug-free (MBFs6) was portrayed in Figure 8. In reality, the profiles show that MNBF6 shows a higher drug penetration as compared to MBF10. Comparing the film with nanoparticles to the film with an ordinary medication, an increase in penetration is about 1.7 times higher. The result of increased drug release in the optimized film MNBF6 could be connected to the increased rate of penetration witnessed in the film (Fig. 11).

SUMMARY AND CONCLUSIONS

Ionic gelation is the method used to create MNPs. The MNP4 is chosen as the optimum ones and subsequently analyzed for particle size, ZP, FTIR spectroscopy, and *in vitro* drug release (Franz diffusion cell) based on the greatest value of % EE (84.73±1.214%). With an average particle size of 306.6 nm and a ZP of +22.6 mv, the optimized NPs exhibit first order kinetics (r2 = 0.921) and no discernible interaction between the drug and the excipients utilized in the investigation, according to FTIR. By using a traditional solvent casting technique, the improved MNP4 was integrated into the thin mucoadhesive buccal films (BFs) using either guar gum or POLYOX alone or in combination with other polymers. The mechanical, mucoadhesive (using goat mucosa), swelling, and *in vitro* drug release (using Franz diffusion cells) properties of prepared BFs (MNBF1-9) were investigated. MNBF6 is deemed optimal for SEM analysis, and *ex vivo* permeation (Franz diffusion cell) investigation with goat mucosa. It has the highest mucoadhesive strength (7.5 ± 0.22 N) and the maximum amount of medication released at 12 hours (91.6±1.72). First order kinetics were followed by the optimized BFs (MNBF6) (r^2=0.921). When comparing improved BFs with nanoparticles to the film containing the plain medication, the penetration is approximately 1.7 times greater. This study shows that buccal films containing MNPs have the potential to be a practical and different method of delivering memantine for migraine treatment.

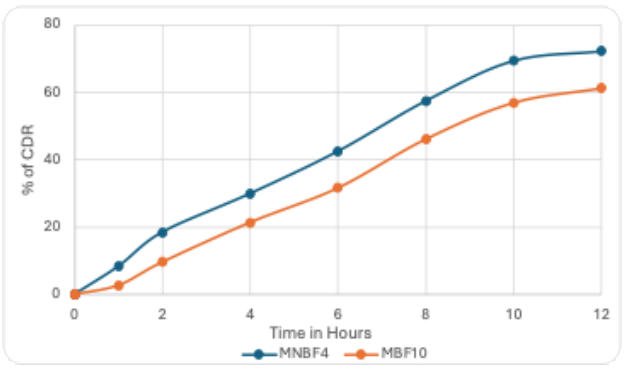

Figure 11: *Ex-vivo* permeation profiles of optimized buccal films with drug nanoparticles (MNBF6) and buccal films with plain drug (MBF10)

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