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# INTRANASAL TOPIRAMATE POLYMERIC NANOPARTICLES FOR EPILEPSY: *IN VITRO* AND EX- VIVO INVESTIGATION

**PRAVIN KUKUDKAR, SONIYA RAHATE,**

**Affiliation**

Department of Pharmaceutics, Shrimati Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur (M. S.), India 441002

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**ABSTRACT**

**Objective:** Tight connections in the blood-

highly difficult and drastically reduce the amount of therapeutic concentration that can reach the brain. The oral method of administration is the most convenient for treating epilepsy, however it does have a delayed absorption. Furthermore, due to the need for medical intervention, parenteral administration is not an option in emergency situations. For this reason, it is ideal to have a different way of administering the medication if we want it to work.

## INTRODUCTION

Recurrent seizures, periods of abnormal conduct, and, in rare cases, loss of consciousness are symptoms of epilepsy, a chronic neurological illness [1, 2]. Despite being the most convenient method of administering medication for epilepsy, the delayed absorption that occurs when taken orally makes it ineffective in treating acute epileptic attacks. Furthermore, due to the need for medical intervention, parenteral administration is not an option in emergency situations. Thus, for good results, an alternate drug delivery route is particularly desired [3, 4].

The intranasal route offers a larger surface area for drug absorption, thanks to the epithelium layer that is both porous and highly vascularized. Because there is more blood flowing to the nasal region, the medicine may be absorbed more quickly and start working more quickly. Along with this, intranasal delivery helps get centrally active meds to the brain quickly and effectively via the olfactory area and the trigeminal nerves [5]. So, it's a good method for treating epilepsy since it's easy and fitting [6].

However, the amount of medication absorption is limited by mucociliary clearance, which minimises the remaining duration of the drug in the nasal cavity [7]. The use of a mucoadhesive substance in the formulation of a dosage form allows for the circumvention of the mucociliary clearance constraint. The medicine will not be expelled from the nasal cavity as quickly and will have more time to be absorbed to achieve an adequate therapeutic level if the formulation sticks to the mucosal membrane [8, 9]. To manufacture mucoadhesive nanoparticles, chitosan, a naturally occurring polysaccharide with biodegradable, biocompatible, non-toxic, and mucoadhesive properties, has been used as the carrier [10]. By releasing the epithelial cells from their tight connections, it improves paracellular absorption as well [11]. Since chitosan is cationic, it interacts with the mucosal membrane's negatively charged sialic acid moieties electrostatically.

for the mucoadhesive characteristic it has [12]. The formulation, which is based on nanoparticles, allows for targeted medication release to the location, which improves absorption and action. In addition, traditional treatment-related pharmacological adverse effects are mitigated by site-specific administration [13, 14]. Medications like lamotrigine and pregabalin have been shown to be more effective when formulated with chitosan for intranasal administration because it enhances mucoadhesion, release, and absorption [15, 16]. The second-generation antiepileptic medicine topiramate is used for both partial and generalised seizures. As a preventative measure, it is used in the treatment of migraines, mental problems, and obesity. Refractory partial seizures in children, with or without subsequent generalised tonic-clonic seizures, may also be treated with topiramate [17, 18]. Product information: TOPAMAXTM. Topiramate has only been tested in oral dose forms; there is no known intranasal formulation. Publishing year: 2011 by Janssen Pharmaceuticals, Inc., Titusville. Topiramate is oxidised by cytochrome p450 when taken with meals, which slows its absorption rate [19, 20]. As a result, the current study set out to characterise and create topiramate bioadhesive nanoparticles using the ionotropic gelation process with chitosan. Using sheep nasal mucosa, the ex-vivo bioadhesion and penetration of the prepared nanoparticles were assessed.

## MATERIALS AND METHODS

### Materials

Chitosan was purchased from Loba Chemie, Mumbai. Topiramate was procured from Johnson and Johnson Pharmaceutical Ltd., Mumbai. Acetic acid was obtained from Fisher Scientific, Mumbai and sodium tripolyphosphate from Hi-Media Laboratories, Mumbai. All other reagents used were of analytical reagent grade.

### Preparation of bioadhesive nanoparticles by ionotropic gelation method

Mucoadhesive nanoparticles of topiramate were formulated using chitosan and sodium tri-polyphosphate as a crosslinking agent by the ionotropic gelation method. Weighed amount of chitosan and drug was dissolved in 2% aqueous acetic acid. To it weighed quantity of topiramate was dissolved. Subsequently, 50 ml of the polymer solution was added dropwise to the crosslinking solution with magnetic stirring (100 rpm) at room temperature. The prepared nanoparticles were separated after 30 min, washed with deionized water and subsequently dried at 60 °C for 3 h [21]. The composition of different formulations is shown in table 1.

**Table 1: Composition of topiramate loaded chitosan nanoparticles**

| Formulation code | Topiramate (mg) | Chitosan (mg) | STPP (%) |
|---|---|---|---|
| F1 | 100 | 200 | 2 |
| F2 | 100 | 200 | 3 |
| F3 | 100 | 200 | 4 |
| F4 | 100 | 200 | 5 |
| F5 | 100 | 225 | 4 |
| F6 | 100 | 250 | 4 |
| F7 | 100 | 275 | 4 |
| F8 | 100 | 300 | 4 |

**Characterization of nanoparticles Particle size and zeta potential**

The optical microscopy method (Motic BMWB microscope) was used for evaluating the size and shape of the prepared nanoparticles. A small quantity of nanoparticles was dispersed on the slide with the help of a small glass rod. The diameters were determined using a suitable objective (10X, 40X, 100X). The average particle size of nanoparticles can be given by the following formula [22].

$$\text{Average Size} = \frac{\sum nd}{\sum n}$$

Where n is the number of nanoparticles and d is the size NP.

Zeta potential determination (surface electric charge) of the prepared nanoparticles was carried out by photon correlation spectroscopy (PCS) using zeta sizer (Malvern Instruments Ltd, Ver. 6.2) at 25 °C and a scattering angle of 90 °C, maintaining electric field strength of 25 $Vm^{-1}$. Briefly, weighed amount of nanoparticles (5 mg) were dispersed in 10 ml of bidistilled water to get optimum 100-200 kilo-counts $s^{-1}$(kcps) for measurement of zeta potential in the range of+200 mv to-200 mv [23].

**Drug content and entrapment efficiency**

The amount of topiramate incorporated into the nanoparticles was estimated to determine the drug content and entrapment efficiency of the prepared formulations. Nanoparticles equivalent to 10 mg of the topiramate were dissolved in 20 ml of pH 6.8 phosphate buffer solution and kept overnight to extract the drug from the formulation. The solution was then centrifuged (560 rpm) for 10 min to remove the insoluble content. To the obtained solution, 1 ml of ninhydrin solution was added, incubated for 20 min at 70 °C and analyzed spectrophotometrically (Analytical Technologies Ltd., Gujarat, India) for drug content at 260 nm. The data was collected by repeating the procedure in triplicate. Given formula was used for calculating drug content entrapment efficiency [24].

$$\text{Drug content \%} = \frac{Qp}{Q} \times 100$$

Where Qp =quantity of drug encapsulated in nanoparticles Q =weighed quantity of powder of nanoparticles

$$\text{Percent Encapsulation}(E) = \frac{Qp}{Qt} \times 100$$

Where E =percentage of encapsulation of nanoparticles Qp =quantity of drug encapsulated in nanoparticles

Qt =quantity of the drug added for encapsulation

**Scanning electron microscopy (SEM)**

To study the shape and surface morphology

of prepared topiramate nanoparticles, scanning electron microscopy (SEM, JEOL Model JSM- 6390LV) was used. The samples were mounted on a double-adhesive tape stuck to an aluminum stub. The stubs were coated with gold to a thickness of ~300 A ° under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were obtained with SEM [22].

**Ex-vivo bioadhesion studies**

The ex vivo bioadhesion property of nanoparticles was performed on a fresh sheep nasal mucosa. Freshly excised sheep nasal mucosa was procured from the local slaughterhouse, cleaned with isotonic saline solution and cut into a piece of 2 $cm^2$ for the study. The topiramate nanoparticles (100 mg) were applied on the mucosal surface and attached on a polyethylene plate. Simulated nasal electrolyte solution (100 ml) was poured on nanoparticles. Further, it was incubated in desiccators at 90% relative humidity for 15 min so as the polymer interact with the membrane. Further, the plate was kept at an angle of 45 ° relative to the horizontal plane. Phosphate buffer pH 6.8 (37 °C) was peristaltically pumped (5 ml/min) over the tissue and the perfusate was collected. The amount of topiramate in the collected perfusate was estimated after 1 hour spectrophotometrically. The amount of nanoparticles corresponding to the amount of drug in the perfusate was determined. The amount of adhered nanoparticles was calculated as the difference between the amount of nanoparticles applied and the amount of nanoparticles washed off with perfusate. The percent mucoadhesion was determined by the given equation [15],

$$\text{Mucoadhesion potential} = \frac{[\text{Concentration of adhered NP}]}{[\text{Concentration of applied NP}]} \times 100$$

**Fourier-transform infrared spectroscopy (FTIR)**

The compatibility studies between topiramate and chitosan were carried out by FTIR (Thermo Nicolet, Avatar 370) to detect drug-excipient interactions if any. Approximately 2 mg sample was powdered uniformly with 200 mg of KBr for the production of KBr compacts. The samples were triturated first and then mixed thoroughly with KBr in 1:1 (sample: KBr) ratio, KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 4 $cm^{-1}$ from 4000 to 400 $cm^{-1}$. The IR spectra of the physical mixture of the topiramate and chitosan were compared with the spectrum of topiramate and chitosan to determine the compatibility of drug and excipient [24].

**Differential Scanning Calorimetry (DSC)**

The thermal behavior of topiramate, chitosan, physical mixture of topiramate and chitosan and prepared topiramate nanoparticles was studied using differential scanning calorimetry (Mettler Toledo DSC 822e) at a rate of 10 °C $min^{-1}$ from 30° to 300 °C using a nitrogen purge of 50 ml/min [23].

**X-ray diffraction studies (XRD)**

The crystallinities of topiramate, chitosan, physical mixture of topiramate and chitosan and prepared topiramate nanoparticles were analyzed by x-ray diffractometer (Bruker AXS D8 Advance

diffractometer) with a radius of 240 mm. The pattern was collected with 40 kV of tube voltage and 30 mA of tube current and scanned over the 2θ range of 3° to 80°.

### *In vitro* drug diffusion studies

The drug diffusion characteristic was evaluated with the help of Franz diffusion cell with receptor capacity of 12.0 ml and permeation area of 3.14 $cm^2$. A dialysis membrane (0.65 µm and mol. Wt. of 12000-14000) as a diffusion barrier was used in the donor compartment as a diffusion barrier. The membrane was equilibrated overnight before dispersing the formulation. The temperature of the receptor phase (pH 6.6 phosphate buffers) was maintained at 37±1 °C throughout the experiment by continuous stirring. Nanoparticles equivalent to 10 mg topiramate was placed in the donor compartment. 300 µl of the sample was withdrawn at a predetermined time interval from the receiver compartment and the same amount of fresh buffer solution was replaced to maintain the sink conditions. Each experiment was performed in triplicate and the sample was analyzed at a wavelength of 260 nm spectrophotometrically, taking phosphate buffer (pH 6.6) as a blank [23].

### Kinetics and mechanism of drug release

The data obtained from *in vitro* drug diffusion studies were plotted in various kinetic models: Zero-order, first-order, Higuchi's model and Korsmeyer–Peppas model to study the release kinetics of optimized formulation.

### Ex-vivo permeation studies

Ex vivo permeation study was performed for the optimized batch using freshly excised sheep nasal mucosa, as biomembrane obtained from the local slaughterhouse within 1h of sacrificing the animal. Nasal mucosa was carefully cut and mounted on the diffusion chamber with mucosal and serosal surfaces facing towards donor and receptor compartments, respectively. Other experimental procedures of sample collection and analysis were performed in the same way as in for *in vitro* diffusion studies [25].

### Ex-vivo biocompatibility studies

To determine the biocompatibility of prepared nanoparticles with nasal mucosa. histological study was carried out using freshly excised sheep nasal mucosa, thoroughly cleaned with isotonic saline solution. Prepared topiramate nanoparticles (100 mg) were applied properly on the nasal mucosa. After 1 h it was fixed in 10% neutral carbonate buffered formalin solution, routinely processed and embedded in paraffin. The experiment was carried out in a cell culture incubator (Sanyo Incubator, Model MCO-5AC, and Japan) to assure optimal conditions for the viability of the tissue. Further paraffin sections (7.5 µm) were stained with Haematoxylin-Eosin (HE) indicator and observed under the Motic microscope. The untreated mucosa directly fixed after isolation was used as a control [26].

## RESULTS AND DISCUSSION

### Physicochemical characterization

### Particle size and zeta potential

The percentage yield was calculated to determine the yield of nanoparticles obtained by the ionotropic gelation method. The results of percentage yield, drug content and entrapment efficiency are mentioned in table 2. All the batches of topiramate loaded chitosan nanoparticles showed a percentage yield from 72.02 to 83.73%. From the result, it was observed that as the concentration of chitosan was increased, an increase in percentage yield was observed. The particle size of nanoparticles varies with the concentration of chitosan used. At 1% w/v chitosan concentration, the particles of nanoparticles

were irregular with mean size 313.5 nm, which increase for nanoparticles prepared with chitosan, respectively. The topiramate loaded chitosan nanoparticles showed a decrease in particle size. The particle size of all the batches was in the range of 313.5 nm. As the volume of sodium tripolyphosphate was increased, a decrease in the particle size of nanoparticles was observed.

**Table 2: Percentage yield, average drug content and entrapment efficiency of mucoadhesive topiramate loaded chitosan nanoparticles**

| Batch | Percentage yield | Drug content (%) | Entrapment efficiency (%) |
|---|---|---|---|
| F1 | 73.66 | 29.38±2.56 | 75.66±1.54 |
| F2 | 75.48 | 37.15±2.34 | 85.02±2.98 |
| F3 | 82.85 | 35.46±2.46 | 82.42±1.46 |
| F4 | 72.02 | 37.25±2.35 | 88.42±2.8 |
| F5 | 69.85 | 36.87±1.27 | 86.39±1.4 |
| F6 | 68.73 | 34.96±2.13 | 82.28±1.8 |
| F7 | 83.73 | 39.45±2.43 | 90.45±1.49 |
| F8 | 80.33 | 28.24±2.58 | 72.18±2.32 |

Results are shown as mean±SD (n=3)

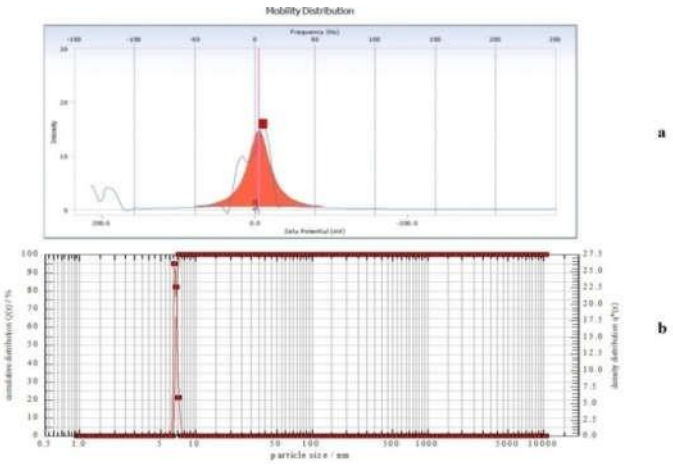


**Fig. 1: a. Zeta potential of topiramate loaded chitosan nanoparticles, b. zeta sizer**

The zeta potential of topiramate and chitosan loaded nanoparticles were observed at -5.21 mv (fig. 1). It showed a negative charge. The formulation displayed negative zeta potential due to the introduction of reduction of droplets size on particles, which increases the anionic property of formulation this permanent negative charge carried by the protonated amino group of the formulation is driving force to the high solubility.

**Drug content and entrapment efficiency**

The resultant topiramate loaded chitosan nanoparticles had high drug content and high entrapment efficiency. As shown in table 2, the drug entrapment in the topiramate loaded chitosan nanoparticles was found to be increased with increased polymer: drug ratio. In general, formulations prepared by ionotropic gelation technique demonstrated considerably higher drug encapsulation

efficiency. This is also evident from previous studies employing chitosan by the ionotropic gelation technique [27]. It is noteworthy that the F7 batch prepared with 275 mg of chitosan and 4% of STPP as a crosslinking agent showed the highest entrapment efficiency as 90.45%. Thus, we have considered this formulation for further characterization and ex vivo evaluation.

**Scanning electron microscopy (SEM)**

The morphology of prepared nanoparticles was determined by SEM and photomicrographs of topiramate loaded chitosan nanoparticles are displayed in fig. 2. The surface morphology observed by the SEM showed the regular shape and smooth surface area of the prepared nanoparticles. The resultant nanoparticles did not show any ruptures on the surface, validating its rapid clearing from the nasal cavity with a good deposition pattern in the nasal cavity.

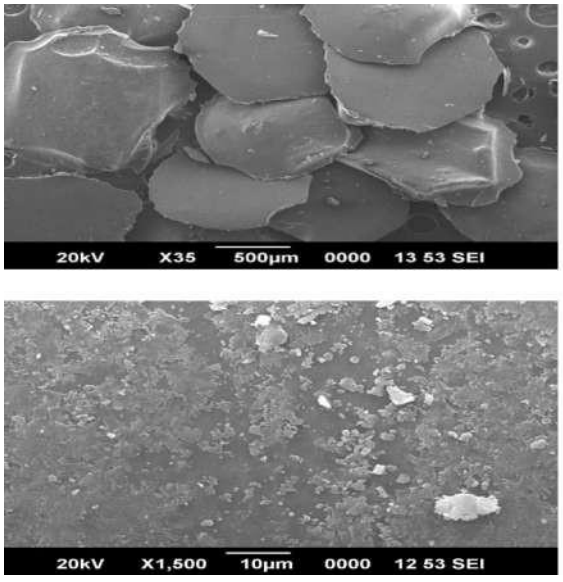


**Fig. 2: Scanning electron microscopy images of topiramate-loaded chitosan nanoparticles**

**Ex-vivo bioadhesion studies**

The ex-vivo bioadhesion study was performed on F7 formulation using freshly excised sheep nasal mucosa. The prepared topiramate loaded chitosan nanoparticles showed high bioadhesion strength i.e. 94.30%. The interaction between cationic groups on chitosan and anionic residues such as sialic acid and sulfonic acid on the nasal mucosa might have facilitated the

strong adhesion of topiramate loaded chitosan nanoparticles on mucosal surfaces. This is speculated by several earlier findings employing chitosan as a polymer for the preparation of microsphere for nasal drug delivery system.

**Fourier-transform infrared spectroscopy (FTIR)**

The FTIR spectra of a mixture of topiramate and chitosan were compared with the spectra of pure chitosan and topiramate for the determination of interaction between drug and excipient**.** The spectrum of chitosan (fig. 3a.) was characterized by the presence of the band at 2890 $cm^{-1}$ of C-H bonds. The band assigned to O-H (3000–3700 $cm^{-1}$) on the chitosan spectrum. The vibration peak at 3443 $cm^{-1}$ was indicative of the O-H group. The characteristic bands at 1307 $cm^{-1}$ and 1091 $cm^{-1}$ on the chitosan spectrum indicated primary and secondary alcohols. The intense band cantered at 1664 $cm^{-1}$ on the chitosan spectrum is assigned to the C-O bonds of the acetamide groups, referred to as amide band. The obtained FTIR spectra also showed the same absorption peaks as mentioned above confirm the polymer was chitosan. The FTIR spectrum of topiramate

(fig. 3b.) showed the characteristics peaks of absorption at 1072.47 $cm^{-1}$(S=0 Stretching), 1552.94 $cm^{-1}$(N-H-stretching) and 1648.25 $cm^{-1}$(C=O stretching). All the absorption peaks are similar as observed in the reference spectra for the drug topiramate (I. P. 2014). The spectrum of topiramate and chitosan physical mixture was characterized by the presence of strong absorption band absorption at 2956.48 $cm^{-1}$(C-H Stretching), 1552.94 $cm^{-1}$(N-H- stretching) and 1648.25 $cm^{-1}$(C=O stretching). The observation of the infrared spectroscopy (IR) spectra of the physical mixture of topiramate and polymer chitosan (fig. 3c.) showed all the major peaks of the topiramate, indicating that there was no interaction between the topiramate and chitosan.

**Differential scanning calorimetry**

Thermograms of pure topiramate, chitosan, physical mixture of chitosan and topiramate and topiramate-loaded chitosan nanoparticles were shown in fig. 4. DSC thermogram of topiramate illustrated sharp endothermic peak 126.24 °C, due to its melting point. Likewise, the DSC thermogram of chitosan exhibited a broad endothermic peak at 85.36 °C. By investigating the thermogram of topiramate loaded chitosan nanoparticles, (fig. 4d.) it was found that the endothermic peak corresponding to the melting point of topiramate was found to be reduced in intensity also seemed to be disappeared. This could be attributed to the incorporation and molecular dispersion of topiramate in chitosan polymer matrices of the prepared nanoparticle formulations.

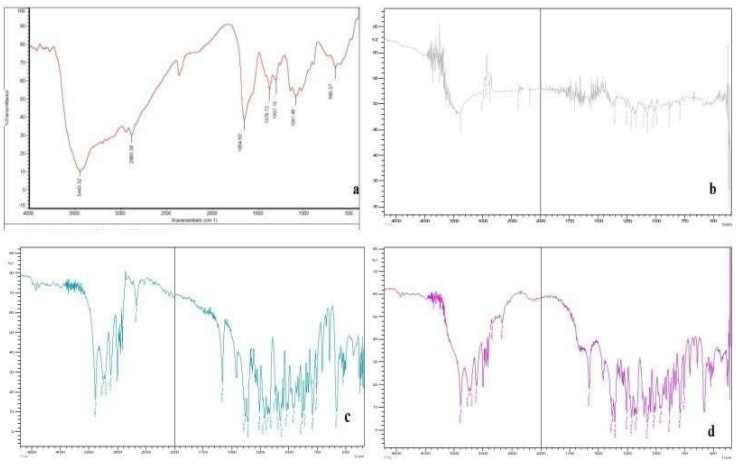

**Fig. 3: FTIR spectrum of a. chitosan, b. topiramate, c. a physical mixture of topiramate and chitosan, d. topiramate loaded chitosan nanoparticles**

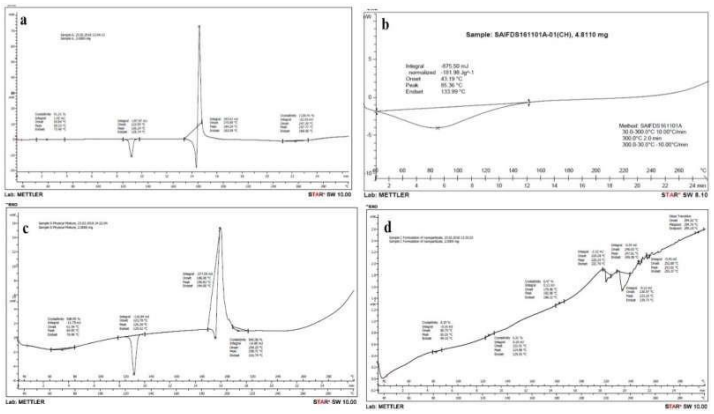

**Fig. 4: DSC thermogram of a. Topiramate, b. Chitosan, c. physical mixture of chitosan and topiramate, d. topiramate loaded chitosan nanoparticles**

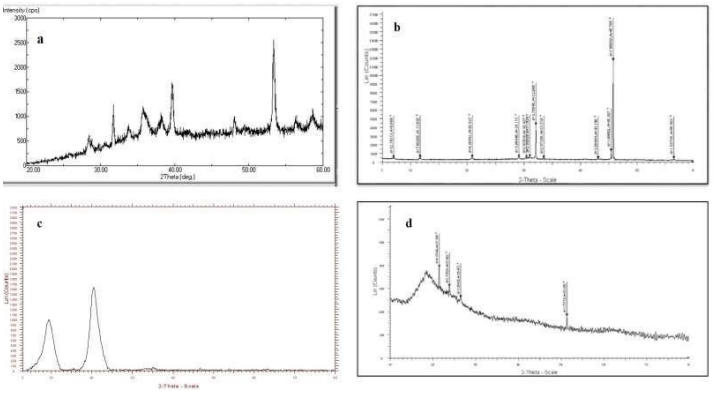

**Fig. 5: X-ray diffractogram of a. topiramate, b. chitosan, c. physical mixture of topiramate and chitosan, d. topiramate loaded chitosan nanoparticles**

**X-ray diffraction studies**

The characteristic XRD spectra of pure topiramate, physical mixture of topiramate and chitosan and topiramate-loaded chitosan–nanoparticles were presented in fig. 5. Characteristic crystalline peaks of topiramate were observed in the pure drug sample reveals the presence of crystalline topiramate. Diffractogram of topiramate loaded chitosan nanoparticles (fig. 5d.) showed the disappearance of crystalline peaks indicating the amorphous form of drugs after its entrapment into chitosan nanoparticles prepared by ionotropic gelation method.

***In vitro* drug diffusion studies**

The drug release profile of batch F1 to F8 was described in fig. 6. From the graph it was observed that an increase in the chitosan concentration significantly increases the the rate and extent of drug release from nanoparticles. A maximum drug release was observed for F7 batch i.e. 94.19 % after 180 min. However, the Release of topiramate from the nanoparticles also changes with the crosslinking of the polymer. An increase in the amount of crosslinking agent reduces the drug release. So the rate of drug release from the nanoparticles prepared by the ionotropic gelation method can be modified by altering the concentration of chitosan and crosslinking agent sodium tripolyphosphate.

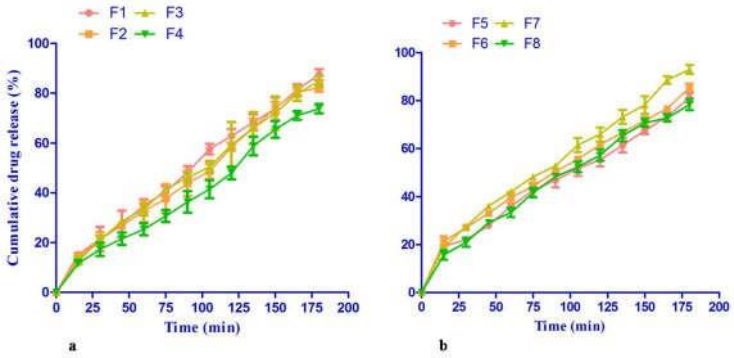


**Fig. 6: *In vitro* drug diffusion study of topiramate loaded chitosan nanoparticles (a: F1 to F4 and b: F5 to F8)**

**Kinetics and mechanism of drug release**

Results of drug diffusion study of the F7 batch were fitted to kinetic models to investigate the kinetics of drug release (table 3). The optimized batch F7 was found to be best fitted in Higuchi kinetic model, as the plot showed highest linearity regression coefficient ($R^2$) of 0.9980 compared to First-order (0.9807) and zero-order model (0.9945). The release data were also found to be best fitted to Peppas exponential model, to investigate the mechanism of drug release from nanoparticles formulation. The corresponding plot of the Korsmeyer-Peppas model indicated good linearity of regression coefficients ($R^2$ =0.9903). The release exponent (n) was found to be 0.9131. The optimized F7 formulation followed the non-Fickian or anomalous diffusion mechanism of drug release when $n>0.5$.

**Table 3: Release kinetics of topiramate loaded chitosan nanoparticles**

| Formulation code | Zero-order (R) | First order (R) | Higuchi (R) | Korsemeyer peppas (R) (n) | |
|---|---|---|---|---|---|
| F7 | 0.9945 | 0.9807 | 0.9980 | 0.9903 | 0.9131 |

**Ex-vivo permeation studies**

The ex–vivo permeation study was carried out for the optimized formulation i.e. F7 based on the results of the *in vitro* drug diffusion. The permeation of topiramate from nanoparticles of batch F7 was found to be 89.03% after 180 min as shown in fig. 7. Cationic bioadhesive polymeric material i.e., chitosan, can be used to enhance the drug dissolution and absorption through nanoparticles formulations of drugs for intranasal administration [28]. The Smaller particle size of nanoparticles provides the larger surface area and thus enhances the drug release from the formulations.

**Ex-vivo biocompatibility studies**

It is important to maintain nasal mucosal integrity while the preparation of nasal nanoparticles as repeated exposure may lead to the safety issue of the nasal membrane. The drug-loaded nanoparticles treated nasal mucosa did not show any deformity. The results of biocompatibility studies demonstrated that the prepared formulation as safe and biocompatible for intranasal administration.

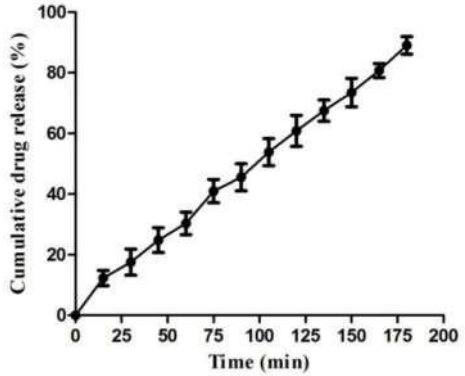


**Fig. 7: Ex-vivo permeation of topiramate loaded chitosan nanoparticles of F7 batch**

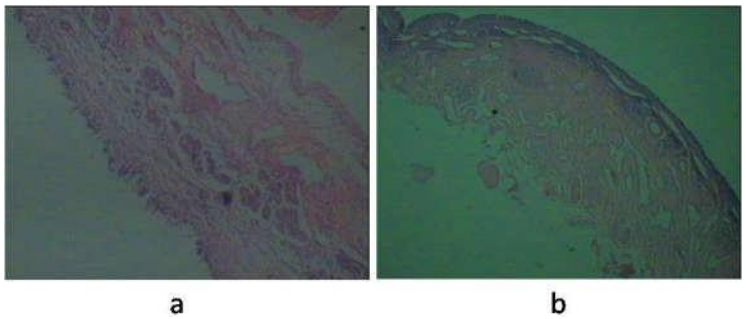


**Fig. 8: Histopathological specimen of A) untreated nasal mucosa, B) topiramate loaded chitosan nanoparticles treated nasal mucosa**

## CONCLUSION

The present study demonstrated the successful formulation of mucoadhesive nanoparticles of topiramate by ionotropic gelation method. The formulation was characterized by percentage yield, entrapment efficiency, bioadhesion potential, ex vivo biocompatibility, *in vitro* drug diffusion profile and ex vivo drug permeation study. Physicochemical investigations demonstrated that the topiramate loaded nanoparticles showed the regular shape and smooth surface for nasal administration, high drug content and encapsulation efficacy and showed strong bioadhesion potential without any morphological toxicity to excised sheep nasal mucosa. Also, permeation across excised sheep nasal mucosa exhibited a good permeability of topiramate loaded chitosan nanoparticles. The results of biocompatibility study of topiramate loaded nanoparticles demonstrated that chitosan as safe and biocompatible polymers and can be applied to the nasal epithelium, which could be able to increase the absorption and bioavailability of the drug. Hence, the intranasal administration of topiramate nanoparticles can be considered as the better alternative for administration as compared to its conventional route of administration and dosage form.

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