Formulation And Evaluation Of Chitosan-Based Polyelectrolyte Complex Via Pulmonary Route By Anti-Convulsant Drug Topiramate

Raviraj R. More [1]* ,Gaurav Jain[1], Jyotiram A Sawale[2] ,Rashmi Shrivastava[3],Vinod D. Usnale[1]

[1]IES Institute of Pharmacy, IES University, Bhopal-462044,Madhya Pradesh, India
[2]Department of Pharmacognosy, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth, Karad,(M.S.)
[3]Department of Chemistry, IES College of Technology, IES University, Bhopal- 462044,(M.P.)

***Corresponding Author :** Raviraj R. More
*IES Institute of Pharmacy, IES University, Bhopal-462044,Madhya Pradesh, India

Abstract
To far, no medication has been shown to effectively treat epilepsy. As a result, pharmacological therapy concentrates on symptom management by prescribing anti-epileptic drugs for an extended period. Patients with epilepsy may receive treatment in an urgent situation or while using an acute or long-term medicine.Intranasal delivery may involve the systemic pathway, olfactory and trigeminal nerves, and both. Each of these may have a therapeutic influence since the drug can cross the blood brain barrier (BBB) via the systemic pathway. This method lowers the effective dosage relative to other delivery routes, albeit. The term "chitosan" refers to a group of polymers with varying levels of deacetylation and molecular weights that are deacetylated derivatives of the natural polysaccharide chitin. It is made up of N-acetyl-D-glucosamine (acetylated units) and 1,4-linked glucosamine (deacetylated units), with molecular weights ranging from 10 to 1,000 kDa and typical deacetylation levels between 70 and 95 percent.

Introduction
After migraine, stroke, and Alzheimer's disease, epilepsy is listed as the fourth most common neurological condition worldwide in the World Health Organization's (WHO) publication "Epilepsy." A person is regarded as epileptic when they have two or more unprovoked seizures [1]. Epilepsy's aetiology is commonly identified after diagnosis, yet in other circumstances it might be challenging to pinpoint the causes. The type of seizures, as well as other factors including the patient's age, the co-administration of other medications, and the side effects of the prescription, all affect the course of treatment. A range of comorbidities, including intellectual disability, depression, anxiety, learning disabilities, and attention deficit hyperactivity disorder, are associated with the group of disorders known as epilepsy.
To far, no medication has been shown to effectively treat epilepsy. As a result, pharmacological therapy concentrates on symptom management by prescribing anti-epileptic drugs for an extended period. Patients with epilepsy may receive treatment in an urgent situation or while using an acute or long-term medicine.Intranasal delivery may involve the systemic pathway, olfactory and trigeminal nerves, and both.

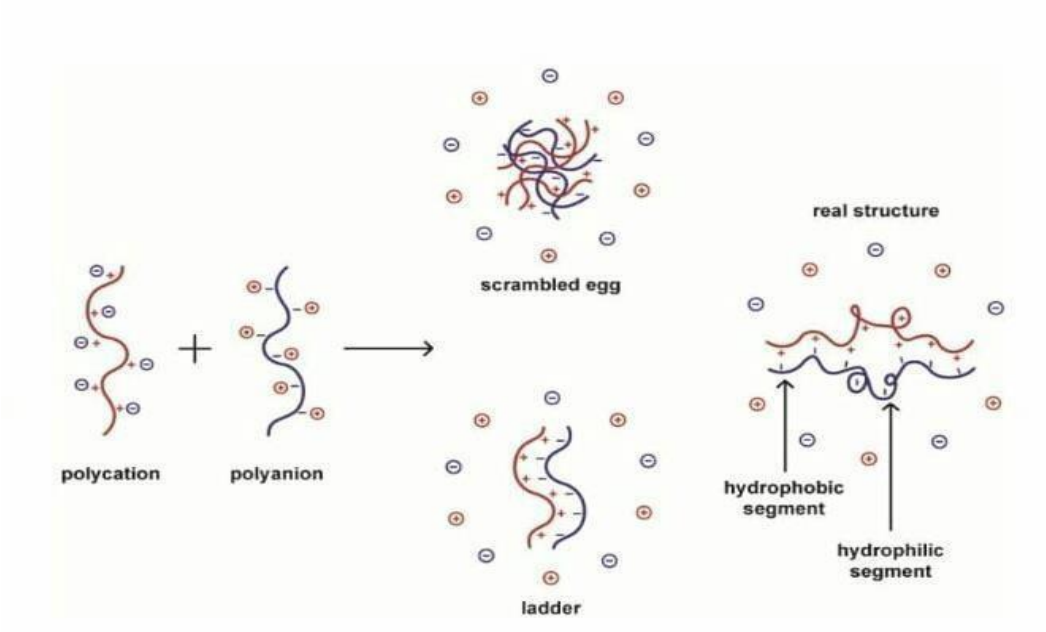


Fig. 1: The structure of polyelectrolyte complex

Formation of Polyelectrolyte Complex

This process involves mainly 3 steps.

- First step is primary complex formation and Coulomb forces are responsible for this step.
- Second step is formation process within intra-complexes. It involves formation of new bonds and/or the correction of the distortion of the polymer chains.
- Third is inter-complex aggregation process, which involves the aggregation of secondary complexes mainly through hydrophobic interactions.

Nasal structure and physiology

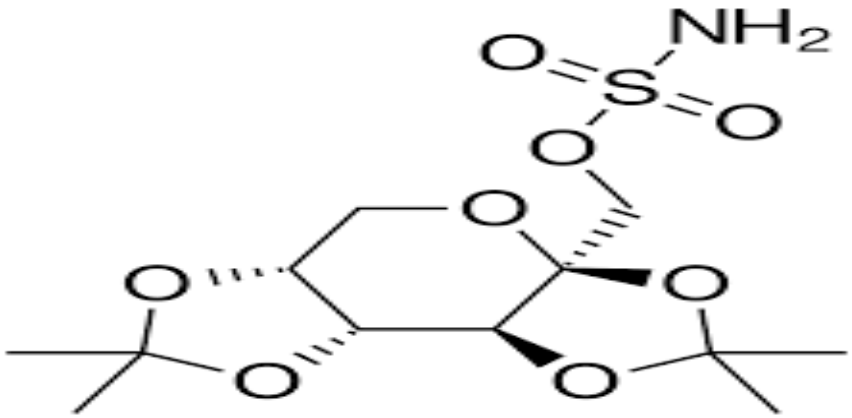
On either side of the nasal septum are two air-filled compartments that make up the nasal cavity. Each side of the cavity is divided by three conchae, or turbinates. The turbinate has a lot of glands and a lot of blood supply. The choanae enter the nasopharynx through the posterior part of the nasal cavity. The nasal cavity supports breathing, olfaction, air cooling, and immunological defense. The nasal cavity is the best place to modify the quality of inhaled air prior to oxygen exchange in the lungs because of its vast, humidified surface area.

DRUG PROFILE

Drug profile

1. Topiramate

2. Structure



Synonym: Topamax, Epitomax, Topamax Sprinkle

IUPAC NAME: [(1*R*,2*S*,6*S*,9*R*)-4,4,11,11-tetramethyl-3,5,7,10,12-pentaoxatricyclo [7.3.0.0^{2,6}] dodecan-6-yl] methyl sulfamate

Molecular formula: $C_{12}H_{21}NO_8S$

Molecular weight: 339.36

Melting point: 123-125 ℃

Description: Topiramate is a monosaccharide with a sulfamate substitution that has anticonvulsant effects. Even though the exact mechanism of action is unclear, topiramate inhibits the kainate/AMPA subtype of glutamate receptors, which are ligand-activated cation channels that mediate the fast component of excitatory postsynaptic currents in central nervous system neurons. This antagonistic activity delays the onset of seizures by stabilising hyperexcited brain membranes, obstructing recurrent neuronal firing, and reducing synaptic impulse propagation.

1. Chitosan

Description: - Chitosan is a sugar that is obtained from the hard outer skeleton of shellfish, including crab, lobster, and shrimp. It is used for medicine. Chitosan is used for High blood pressure, obesity, cancer wound healing, and other conditions.

Experimental

Materials

Table: List of API and excipients

Sr. no	Ingredients	Suppliers
1	Topiramate	Fusion lab Mumbai
2	Chitosan	Loba Chem, Mumbai, India.
3	Pectin	Cipla Ltd, Mumbai
4	Glacial acetic acid	Loba chem, Mumbai, India.

Table 1: Formulation parameters for Topiramate loaded chitosan-based PEC- 3^3 factorial design

Independent Variables	Levels			Dependent Variables	Constraints
	-1	1	+1		
Concentration of Chitosan (% w/v)	0.1	0.2	0.3	Particle Size	Minimum
Concentration of Pectin (% w/v)	0.25	0.5	0.75	EE	Maximum
Concentration of AA (% v/v)	0.5	0.75	1.0	-	-

Characterization of Topiramate loaded CS based PEC

Determination of particle size (PS)

Zetasizer (Malvern Master Sizer 2000, UK) was used to measure the particle size (Z-average mean) of prepared topiramate-loaded chitosan-based PEC.**Entrapment efficacy (EE)**

Preparation of checkpoint batch for validation of experimental design

An optimised batch of PEC (OPEC-1) was created using optimised concentrations of CS, Pectin, and AA and tested for use in EE, PS, PDI, morphological evaluation, and in vitro drug release investigations.

Scanning electron microscopy (SEM)

PEC coated with a thin gold palladium layer by sputter coater unit (VG – Microtech, United Kingdom) and the surface topography was analyzed with a Cambridge stereoscan S120 SEM operated at an acceleration voltage of 10 KV [150].

Result and Discussion

Preformulation study

API characterization

Table: Organoleptic properties of Topiramate

Sr. No.	Properties	Specification
1.	Colour	White
2.	Odour	Unpleasant
3.	Nature	Fine powder

Identification of pure drug

a) Melting Point

Melting point of Topiramate was found to be 124 ℃, which is in range as given in literature (125˚C). Hence the drug can be stated as pure.

a) Determination of λmax: An absorption maximum was found to be at 272 nm. Hence 272 nm was selected as λ max for further studies.

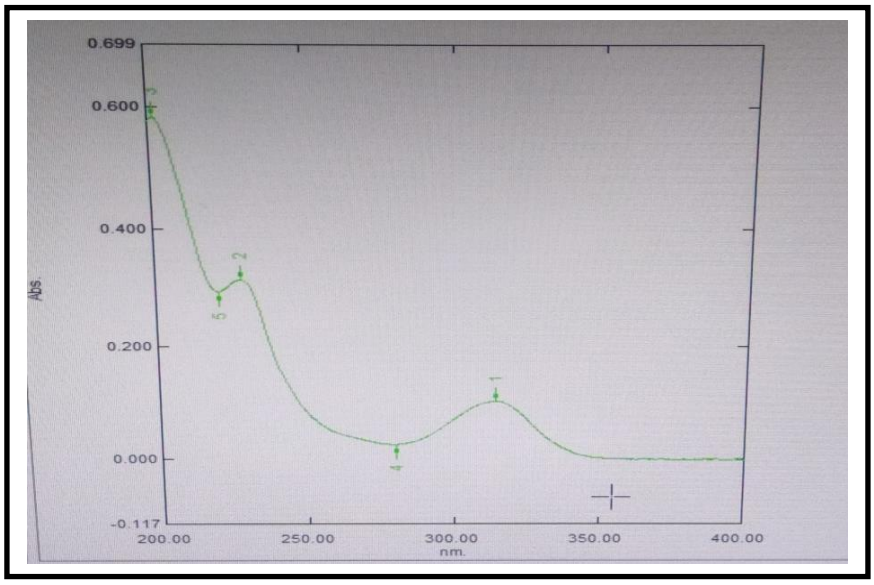


Fig. UV Spectrum of Topiramate

An absorption maximum was found to be at 272 nm. Hence 272 nm was selected as λ max for further studies

b) Calibration curve of Topiramate

The stock solution for the standard drug of 1 mg was prepared using 100 ml of water. The maximum absorbance for the drug solution of 10 mcg/ml was found to be at 272 nm. The linearity was found between the concentration range of 10-35 mcg/ml for UV spectroscopy**.**

Table: 3. Different concentration & absorbance of Topiramate

Sr.No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.125
3	15	0.197
4	20	0.275
5	25	0.344
6	30	0.433
7	35	0.552

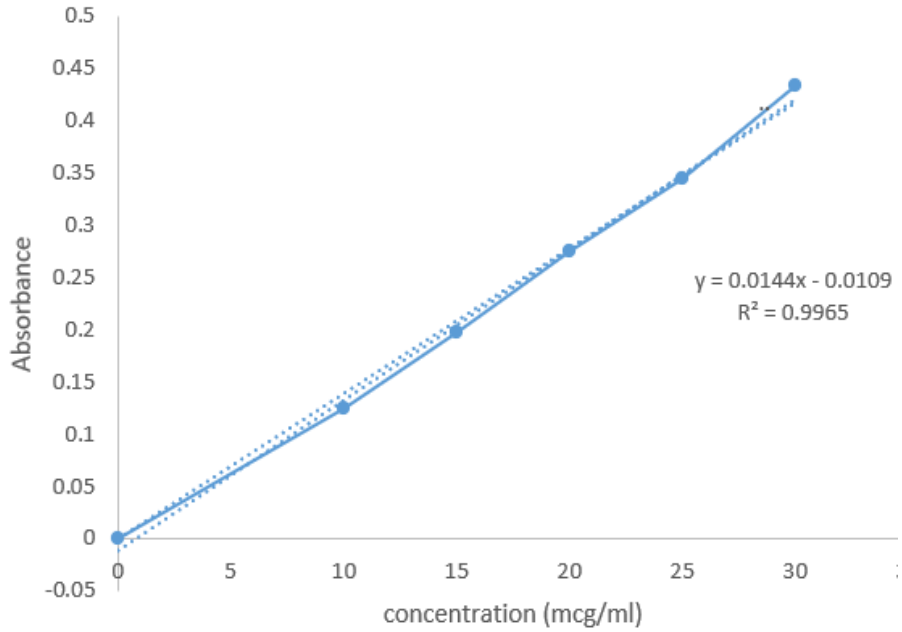


Fig. Calibration curve of Topiramate in water

Drug–excipient interactions study

Fourier-transform infrared spectroscopy (FTIR)

FTIR spectrum of Topiramate was shown in following Fig. revealed characteristic peaks representing the presence of functional groups claim by its chemical structure. From this we can consider that the Topiramate was of pure quality.

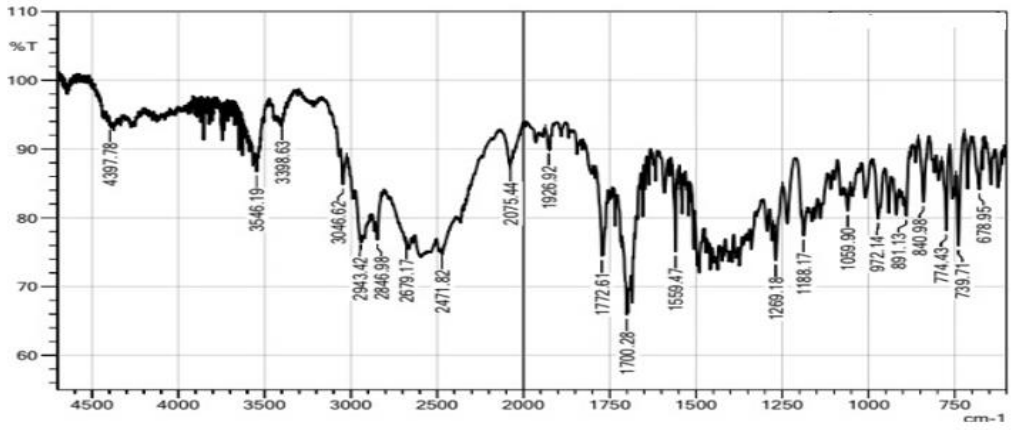


Fig. FTIR spectra of Topiramate

After interpretation of FT-IR Spectrum of drug, it was concluded that all the characteristic peaks corresponding to the functional group present in the molecular structure of Topiramate were found within the reference range and confirming its identity.

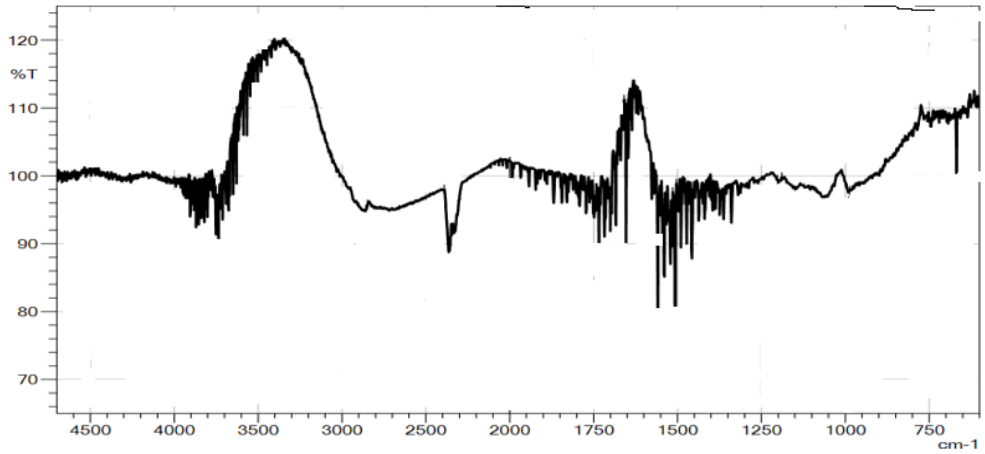


Fig. FTIR Spectra of Chitosan

After interpretation of FT-IR Spectrum of polymer, it was concluded that all the characteristic peaks corresponding to the functional group present in molecular structure of chitosan were found within the reference range, confirming its identity.

Table: Physical mixture Interpretation data of FTIR

Material	**Functional group**	**Standard IR Ranges (cm^{-1})**	**Observed IR Ranges (cm^{-1})**
Physical mixture (Topiramate + Chitosan + Pectin)	C-N Stretching C-H Stretching O-H Stretching	1350 – 1250 2850 – 2970 3650 - 3450	1268.22 2946.32 3558.73

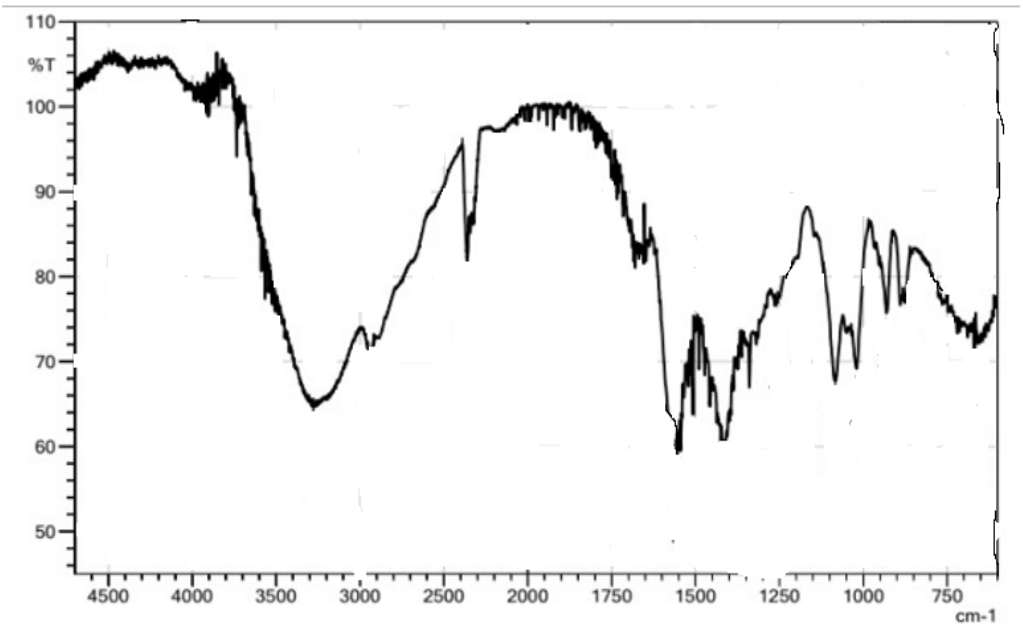


Fig. FTIR Spectra of Formulation OPEC-1

Preparation and optimization of PEC

Design expert software projected 3^2 experimental runs from the three complete level factorial design for the three components of Chitosan (CS) (X_1), Pectin (X_2), and Acetic acid (AA) (X_3), which were adjusted at three distinct levels (coded as 1, 0 and

For 32 batches, the PS and EE values varied from 202 nm to 519 nm and 59% to 90%, respectively. To determine the quantitative effects of the fact factors, an ANOVA was conducted. Multiple regression was used on the data to produce polynomial equations (2FI model for PS and quadratic model for EE).

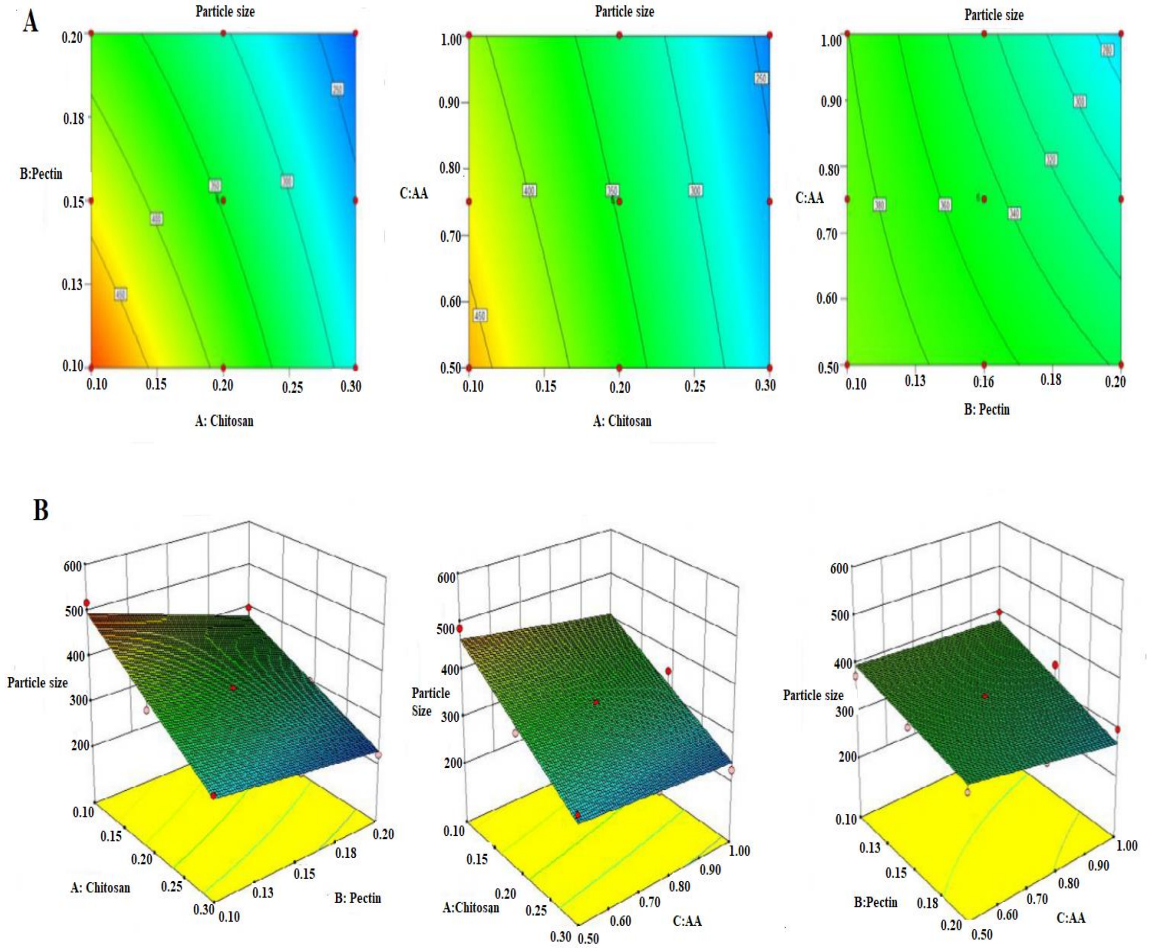


Fig. 1. Contour plots (A) and three-dimensional response surface plots (B) for PS (Y1)

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was done for the surface characterization of OPEC-1 formulation. As shown in fig. the OPEC-1 Formulation was scanned on 5,000x, 15,000x and 3000x.

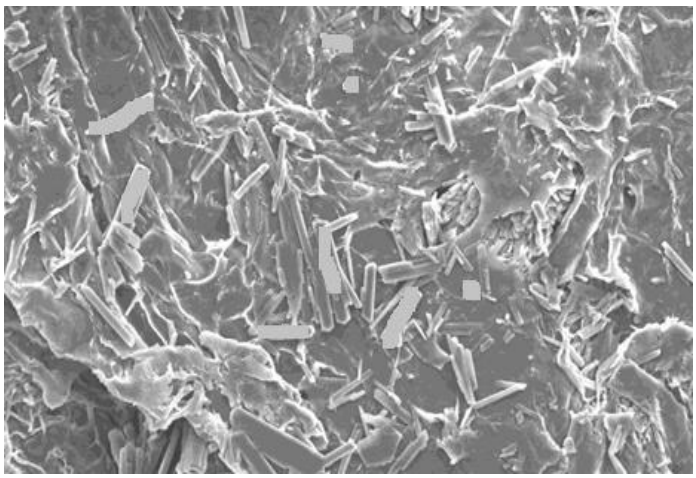


Fig. 3: SEM image of the chitosan based Topiramate OPEC-1

It does not show spherical structure. It shows irregular structure.

Transmission electron microscopy: Size and shape of the optimized batch of PEC were evaluated by transmission electron microscopy (TEM)

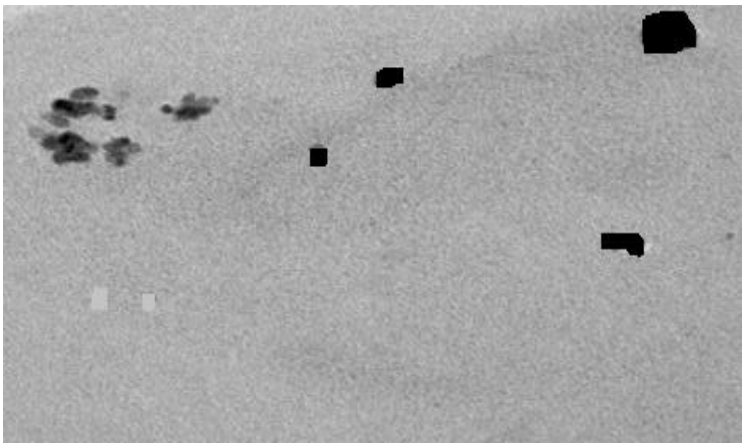


Fig. 4: TEM image of chitosan based Topiramate OPEC-1

Differential scanning colorimetry

The DSC thermogram of Topiramate, Chitosan, Pectin, and OPEC-1 are shown in figure.

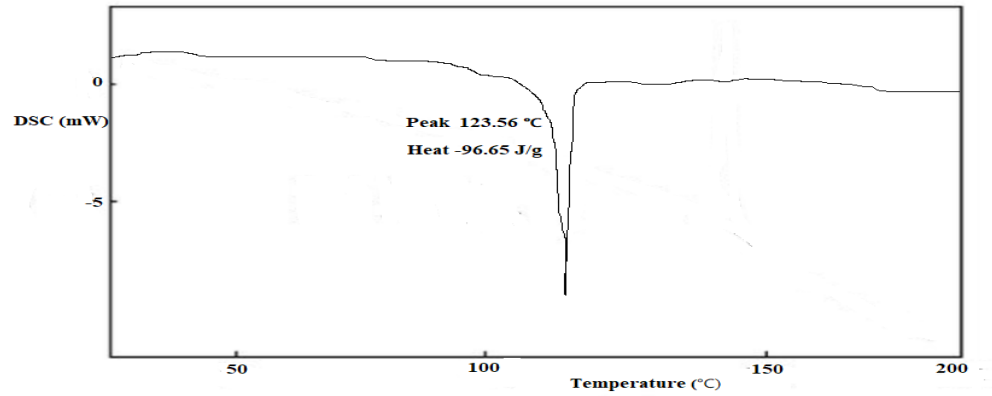


Fig. 5: DSC Thermogram of Topiramate

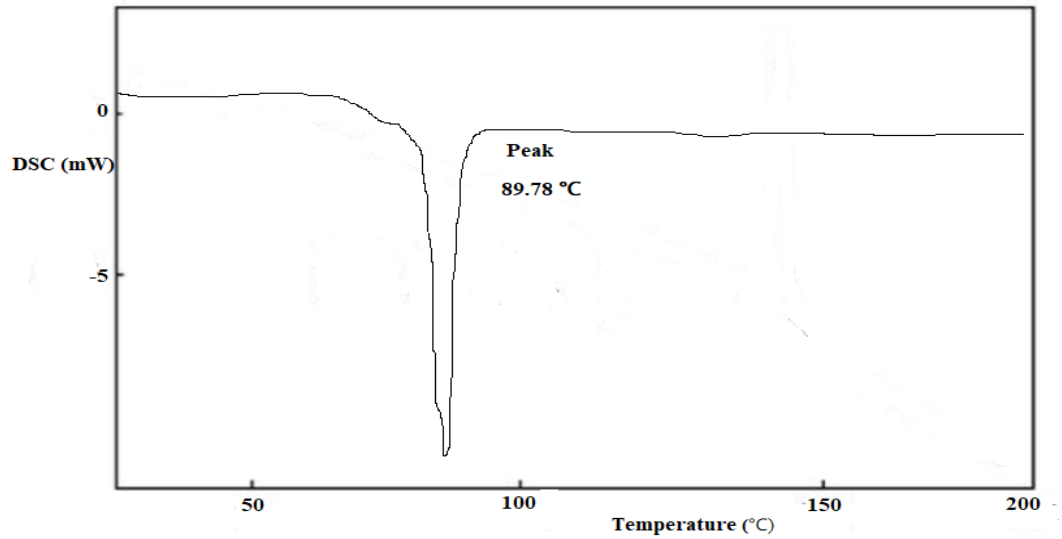


Fig. 6: DSC thermogram of Chitosan

X-ray diffraction study (XRD)

The X-ray diffraction pattern of pure drug Topiramate, chitosan-based OPEC-1, and both polymer i.e., chitosan and Pectin were recorded on an x-ray diffractometer shown in fig. The distinctive sharp peaks of drug were observed at diffraction angles, 11.657 º, 12.852 º, 18.234 º on 2ɵ scale, illustrating the typical crystalline nature of drug.

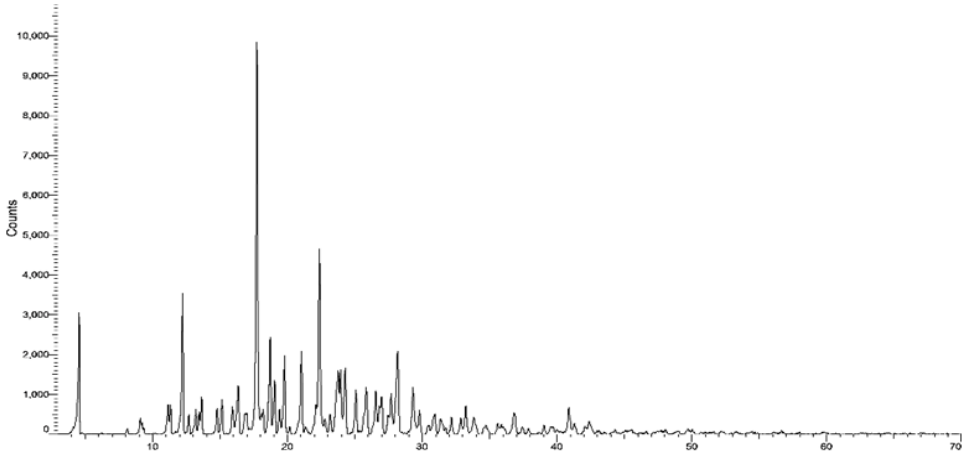


Fig. 9: XRD of pure drug Topiramate

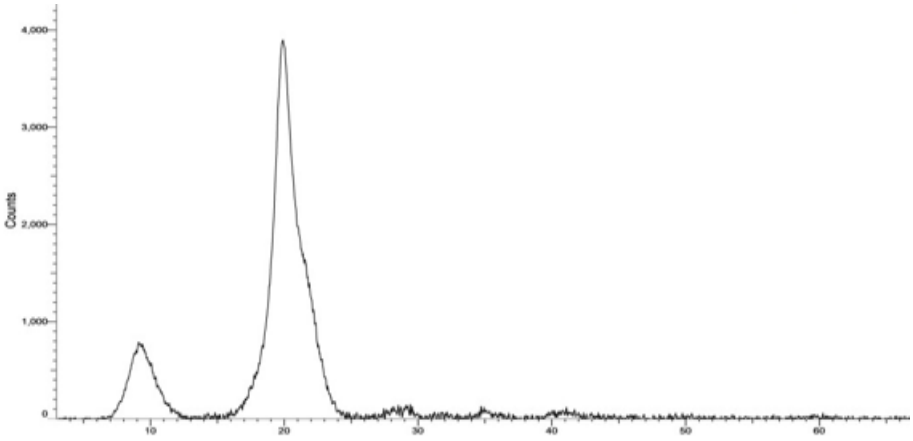


Fig. 10: XRD of Chitosan

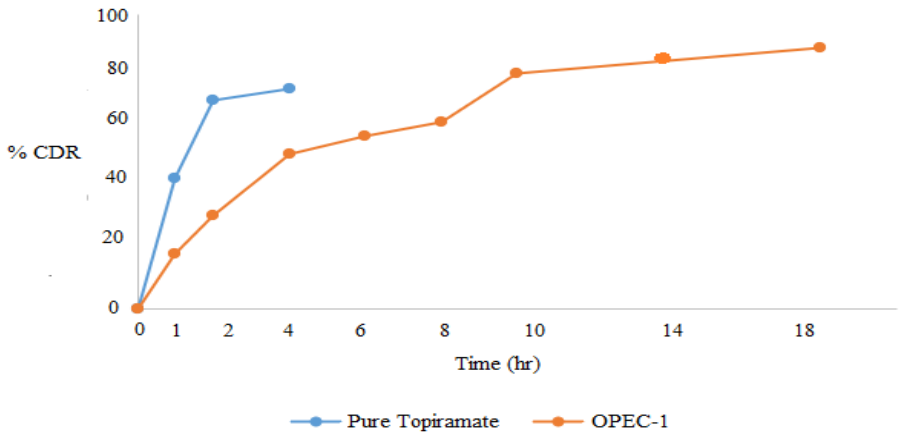


Fig.13: In vitro release pattern of OPEC-1

Ex-vivo permeation studies

The optimised formulation OPEC-1 underwent the ex-vivo permeation investigation. After 180 minutes, it was discovered that 90.04% of the topiramate had permeated from the PEC of batch OPEC-1, as shown in fig. 14.

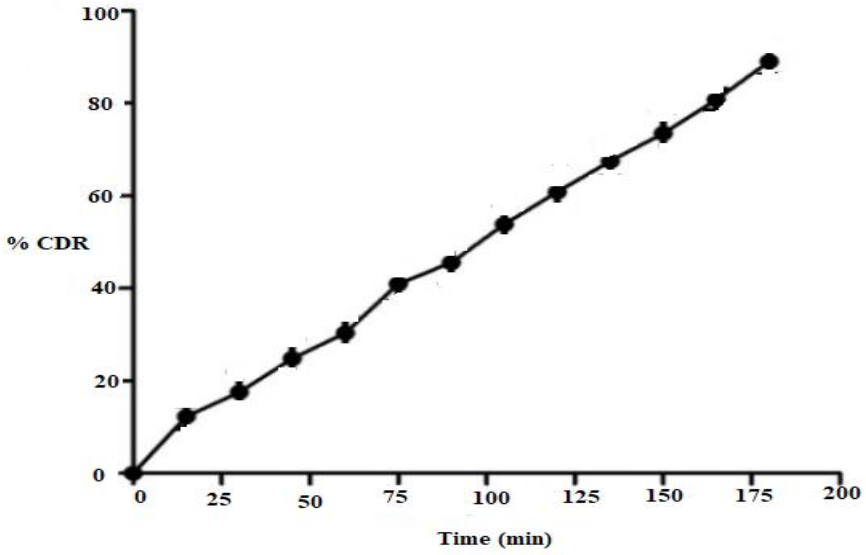


Fig.14: Ex-vivo permeation of topiramate loaded chitosan-based PEC of OPEC-1

Ex-vivo biocompatibility studies: When preparing nasal PEC, it is crucial to protect the integrity of the nasal mucosa because prolonged exposure can compromise the nasal membrane's safety. The nasal mucosa treated with PEC and medication did not exhibit any deformation.

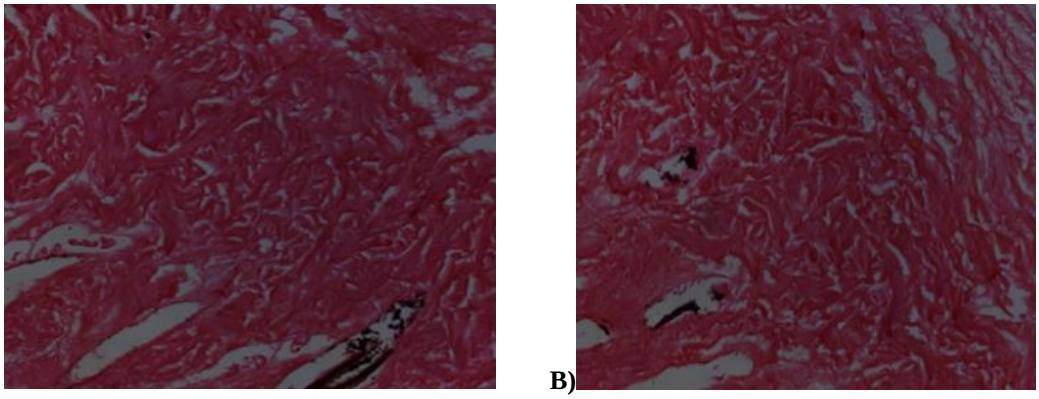


Fig. 15: Histopathological specimen of A) untreated nasal mucosa, B) topiramate loaded chitosan-based PEC treated nasal mucosa.

The aqueous stability of PEC

For three months, OPEC were kept as a nano suspension in deionized water at room temperature. PEC post-storage TEM micrographs demonstrated that, despite the extended storage time, PEC remained spherical in shape and showed no evidence of deformation.

Conclusion

The association complexes created between particles with opposing charges are known as polyelectrolyte complexes. These are created by the electrostatic interaction of polyions with opposing charges. Significant progress has been achieved in the development of innovative medication delivery methods over the past few years. Research on polyelectrolyte complex formation and interpolymer interactions has been heavily concentrated in both basic and applied fields. PECs typically dissolve in water. The electrostatic interaction between water and the charged monomers is what causes their solubility. They can be employed in a range of applications, such as the administration of drugs, coatings, shampoos, or as flocculating agents in water treatment, because they are hydrophilic and typically water soluble due to their charges. These complexes avoid the use of chemical cross-linking agent thereby to reducing the risk of toxicity. These complexes formed is generally applied in different dosage form.

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