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FORMULATION, OPTIMIZATION AND EVALUATION OF CHITOSAN COATED OPTIMIZED NANOLIPOSOMES OF LAMOTRIGINE FOR MANAGEMENT OF EPILEPSY

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Abstract
Creating lamotrigine nanoliposomes (LTG-NLs) coated with chitosan for use in seizure treatment was the goal of this research. Using the thin film hydration and rehydration technique, the formulation was primarily composed of phospholipon 90 G, cholesterol, and tween 80. Using optimization approaches such as response surface methodology (RSM) and plucket burman design (PBD), the nanoliposomes were fine-tuned. Surface morphology, in-vitro release, stability, confocal laser scanning microscopy (CLSM) analysis, and toxicity were among the areas studied to better understand the enhanced chitosan coated LTGNLopt.. The findings demonstrated that LTGNLopt exhibited nano size performance in terms of drug release and trapping. Both the confocal laser imaging and ex-vivo permeation studies in goats verified the improved penetration over the nasal mucosa. Researchers found that optimizing the NLs with respect to the independent factors had a notable impact on the dependent variables, suggesting that this approach could be useful for developing an efficient intranasal delivery method based on lipids...

Keywords: plucket burman design, CLSM, lamotrigine nanoliposomes, response surface methodology, ect.

1. Introduction

There are around 70 million people around the world who are affected with epilepsy, which is a neurological illness that is chronic and affects the brain. Epilepsy is a burden that lasts a lifetime. In spite of the fact that epilepsy is still seen as either a punishment from God or a consequence of witchcraft, there is no awareness of the condition in India. Around the year 600 BCE, medical practitioners in Greece and India began to consider epilepsy to be a condition of the brain. The International League Against Epilepsy (ILAE), which is the largest epileptic community, is also in the forefront of this movement. A brief start of undesirable symptoms that are triggered by aberrant or excessive neural activity in a particular region of the brain is what is referred to as an epileptic seizure, according to the new definition of epilepsy [2]. The diagnosis of this illness, which is defined by an excessive amount of neuronal discharge or rhythmic firing of brain cells, can be confirmed through a clinical examination as well as an electroencephalographic (EEG) recording. There is a wide range of possible symptoms that might accompany a seizure episode, ranging from a quick twitch of the muscles to a full loss of consciousness or even ongoing convulsions [3]. Seizures can occur anywhere from one to many times every day, at any given time of the year.

2. Signs and symptoms of Epilepsy[4]

Symptoms of seizures vary depends upon the region of brain from where seizure started first and how far to spread. Temporary symptoms of seizure include:

Jerking in one part of the body

Movement disruptions,

Perceptional disruption (smell, sight, and hearing)

Mood or psychological disorder.

Seizures are associated with an increased risk of a wide range of medical complications, including a greater prevalence of bruises and fractures, and a greater prevalence of mental health disorders like anxiety and sadness.

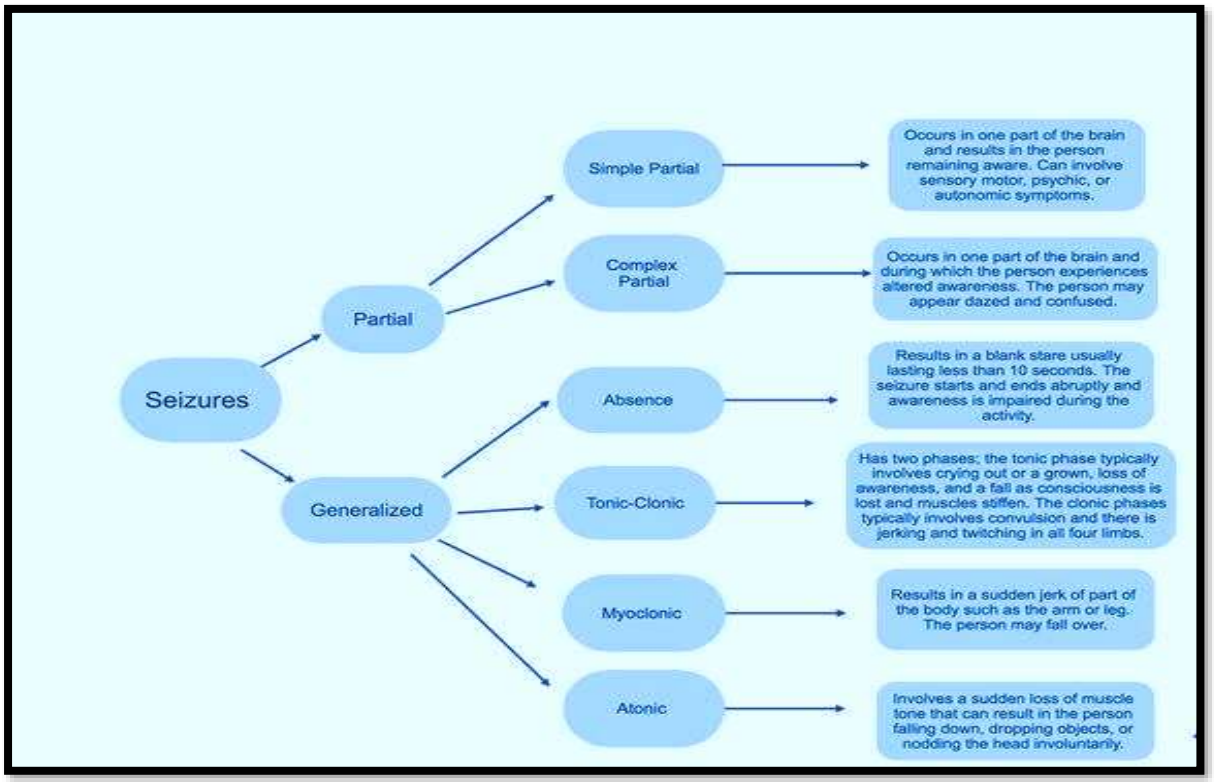


Fig.1 A schematic depicting the many kinds of seizures and their symptoms

International Classification of epilepsy[5]

Partial (focal, local) seizures

Generalized seizures (convulsive or nonconvulsive)

Unclassified epileptic seizures (caused by incomplete data)

I. Focal seizure (Partial seizure)

Seizures can be either simple or complicated, with the former affecting only one section of the brain and the latter affecting both hemispheres of the cortex. Seizure symptoms are related to the normal functioning of the brain region where the seizure is occurring. For instance, clonic jerking of the body can be caused by a seizure that emerges in the motor cortical region. Consciousness maintenance is associated with simple partial seizures, whereas impairment of consciousness is associated with complex partial seizures.

II. Generalized seizures:

While generalized epileptic seizures start in one spot, they swiftly spread across the central nervous system's lattice, which is located on both sides of the body. Although it is not required to do so, the pretentious bilateral area can take into account subcortical and cortical

components. Seizures that affect the entire body can be broadly classified as either tonic-clonic, absence, or myoclonic. A few seconds of abnormal, continuous activity, including a blank stare, followed by an abrupt return to normal activity, characterize an absence seizure.

3. Classification of Antiepileptic drugs[6,7]

Antiepileptic drugs are classified according to mechanism of action.

(i) Na-K inhibitor

(ii) GABA analogue

(iii) Ca^{2+} inhibitor

4. Intranasal route of delivery[8]

The biological and metabolic barriers to active pharmacological molecules are provided by the BBB, which mainly consists of endothelial cells that form a tight connection with the extracellular base membrane, perivascular astrocytes, microglia, and adjacent pericytes. When administering medication using droplet method, it is essential to arrange the patient's head correctly. The intranasal route of administration has been shown to be effective for a variety of medical purposes, including the management of anxiety, pain, hypoglycemia, and seizures, according to numerous studies [9]. It is possible to employ injectional medications for intranasal delivery because there are limited formulations for this route of administration. However, intranasal administration is not typically considered while developing parenteral formulations due to potential issues with drug concentration and dosage amount. It is possible to administer the most concentrated parenteral formulations by intranasal injection with the smallest possible amount. The nasal route is quickly replacing the parenteral route as a preferred option. It eliminates the need for needles and increases the rate of drug uptake in the brain area due to direct transit and reduced presystemic metabolization with the blood-brain barrier.

Advantages of Intranasal Delivery system[10]

- It provides rapid, non- invasive andi comfortable routeof delivery.
- It bypasses the BBB andi directly targets the CNS (Central nervous system) to reduce the systemic exposure of drug and also reduces the systemic side effects
- It successfully delivers a wide range of bothi micro-molecules and macro-molecules from nasal mucosa toi brain.

- This route of deliveryreduces the dose frequencyandi dosesi of drugs.
- Richi ini blood epithelial andi highlypermeable structure of nasal mucosa greatly enhance drug absorption.
- Avoidsi hepatic firsti pass metabolismi andi bypass the BBB.

Shortcoming:

- Restricted surface area of nasal mucosa reduces formulation volume to 50-250 µl
- It shows fast drug clearance because of the nasal mucosaciliary system.
- Nasal congestion and allergy after drug administration.

Nanocarrier for intranasal delivery[11,12]

The advent of nanotechnology has resulted in the development of new research strategies in the field of pharmaceutics. These strategies aim to develop drug delivery systems that are more practical and safe. These systems can range from nano particles to nanovesicles, including polymeric nanoparticles, metal nanoparticles, nanoliposomes, nanoemulsions, and lipid nanocapsules. On the other hand, pharmaceutical researchers are taking into consideration a variety of nano formulations, such as nanoemulsions, nanoliposomes, nanolipid carriers (NLC), solid lipid nanoparticles, and others that facilitate rapid transport from the nasal mucosa to the brain. In respecti of permeability boosting agents, lipidi nanocarriers systems also seemi as a promisingi method to improve the therapeutic bioavailability. In addition to enhancing the permeability via the mucus epithelium, it also protects the medication from quick mucociliary clearance, which allows it to remain in the body for a longer period of time and, as a result, improves epithelial absorption. Through the concurrent administration of surfactants, it is possible that additional permeability qualities will be improved.[13].

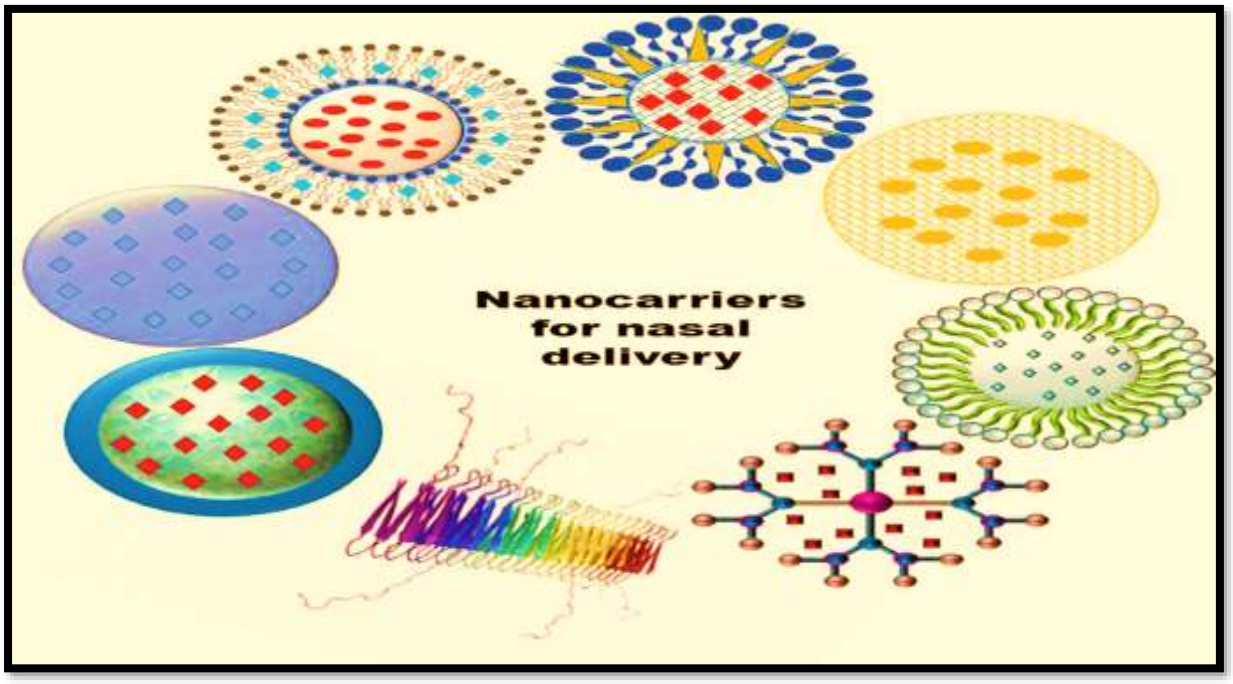


Fig.2 systematic diagram present the types of Nanocarriers for nasal delivery

Chitosan coating of nano lipid carrier[14]

Mucoadhesive agents are able to keep drug entity in local region of nasal mucosa to improve absorption and enhance the concentration gradient of drug over the epithelial membrane. Moreover, because of the mucoadhesive properties, they managed to extend the amount of time that the formulation remained on the nasal mucosa, allowing for a more gradual release of the medicine. Different Mucoadhesive agents work by different ways depending on their functional groups attached to polymer backbone. Ionizable and non-ionizable groups in the polymeric structure of many mucoadhesive agents interact with the mucosal glycoproteins on the surface of the mucosa through the formation of hydrogen bonds and the development of electrostatic interactions [15]. One of the important examples of cationic polymer including chitosan that revealed high positive charges density with beneficial approach for powerful interactions with negative charged mucosal glycoproteins of naso-mucosa tissue.

5. Method of preparation of lamotrigine loaded Nanoliposomes[16,17]

The modified thin film dehydration-rehydration process was used to prepare lamotrigine loaded nanoliposomes. To summarize, a round-bottom flask was used to dissolve the necessary amounts of Phospholipon 90 G, cholesterol, and antiepileptic medication lamotrigine in a chloroform and methanol mixture (2:1 V/V). A thin coating of lipid was created on the inner wall of the flask after the solvents were evaporated under the vacuum in a rotary evaporator.

To further eliminate any organic solvent residue, the film was vacuum-sealed for the night. The lipid film was treated with tween 80, then hydrated with NSB (pH 6.5), and stirred for one hour at the lipid's transition temperature (Tm). Under pressure, the resulting liposome large multilamellar vesicles were extruded through polycarbonate membrane filters with pore sizes of 0.4 µm (5 cycles), 0.2 µm (5 cycles), and 0.1µ (3 cycles) (supplied by Axiva sichem Pvt. Ltd.). To remove any free drug, the resultant unilamellar vesicles were subjected to sonication on a medium of ice-cold water using an HD100 ultrasonic probe sonicator from Heilcher in Germany. After that, they were centrifuged at 25,000 × g for 1 hour at 4°C with the assistance of an ultracentrifuge from Thermo Fisher Scientific in the US. For subsequent analysis, the produced nanoliposomes were kept at 2-8°C (Fig.3).

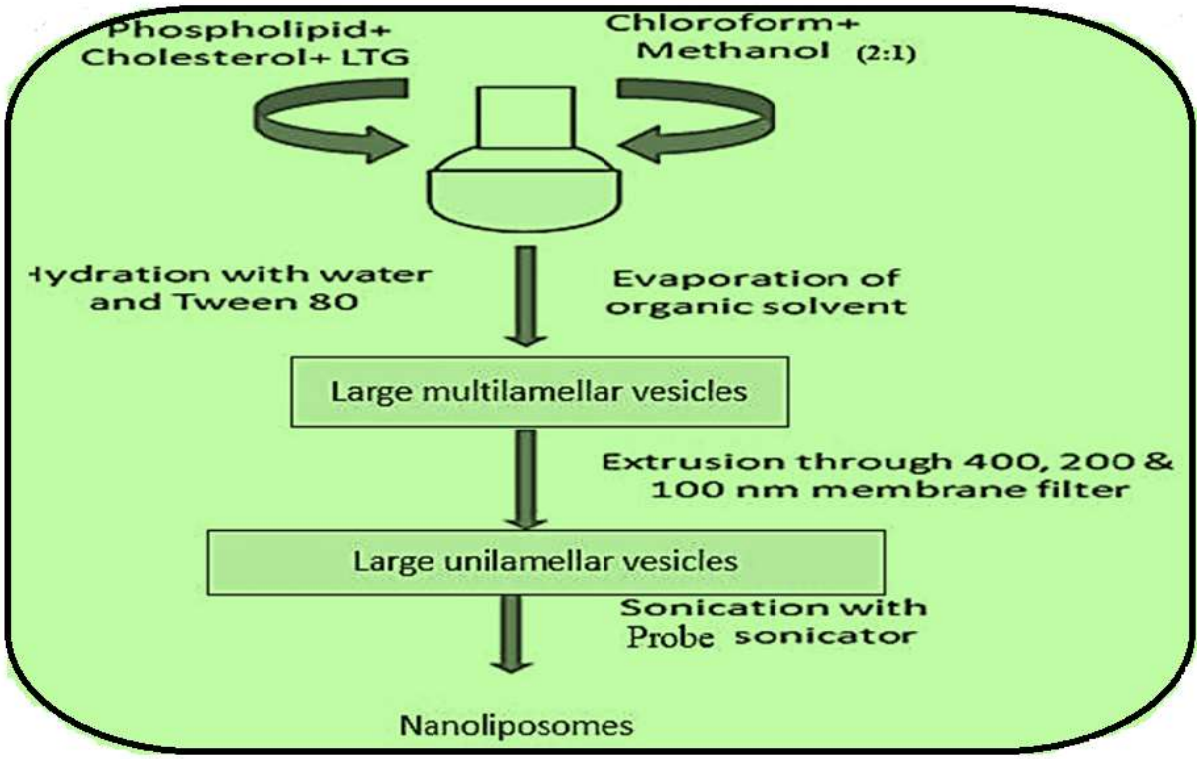


Fig.3 Diagrammatic representation of preparation of nanoliposomes

6. Optimization of lamotrigine loaded nanoliposomes bydesign of experiment[18]

Different methods have been applied in the designing of these nano formulations and each method involves many process and excipient variables influencing the characteristic of formulation. Screenings of these variables are very critical through conventional method.An optimal pharmaceutical formulation with the right particle size, maximum drug entrapment efficiency, and an effective release profile was designed during the creation of nanoliposomes by studying numerous aspects. This can be achieved with the help of many statistical methods,

such as the Plackett-Burmani design, the Response surface approach, and the central composite design, all of which simplify the process of optimizing and understanding the mechanism of the many variables involved in formulation.

Chitosan coating of optimized lamotrigine loaded nanoliposomes[19]

The objective of this study was to improve the muco adhesivness on nasal mucosa by coating the Opt-LTG-NLs with chitosan. This was done in order to increase the nasal residence period and decrease the naso clearance. 0.1 and 0.3% (w/v) of chitosan solution were used to cover Opt-LTG-NLs in order to prepare the nanoliposomes that were coated with chitosan. The chitosan solution was prepared by dissolving a weighed quantity of chitosan in an aqueous solution of acetic acid with a volume-to-volume ratio of 0.1% while stirring the mixture. The mixture was then allowed to sit at room temperature for an entire night. To prevent any contamination, the chitosan solution that had been created was filtered using a membrane filter with a pore size of 2 micrometers. In order to obtain the final coated vesicles, lamotrigine-loaded nanoliposomes were added drop by drop to an equal volume of chitosan solution (five milliliters) while stirring for one hour at a temperature of twenty-five degrees Celsius without interruption. After being rinsed three times with NSB, the coated vesicle medium was ultra-centrifuged at 15,000 rpm for thirty minutes at a temperature of four degrees Celsius in order to eliminate any excess chitosan.

7. Evaluation of chitosan coated optimized lamotrigine loaded nanoliposomes [20,21]

The optimized lamotrigine loaded nanoliposomes after coating with 0.1 % and 0.3 % chitosan was subjected to various evaluation parameters to confirm its coating over the nanoliposomes surface.

I. Size of Vesicle

The vesicles size of Opt-LTG-NLs was 88.90± 1.56 nm and after coating with 0.1 %i and 0.3 % chitosan, the vesicles size was increased up to 131.72 ± 1.37 and 308.12 ± 1.62 nm respectively (Table 1). Following the chitosan coating, the size range of the chitosan coated nanoliposomes increased which confirm the coating process. 0.1 % Chit-NLs was still under the desirable size range for efficient nasal uptake. But 0.3 % Chit- NLs showed particle size above 300 nm which are not suitable for intranasal delivery (Fig.4). Many reports revealed that intranasal routei of delivery for brain targeting require vesicle size below 200nm. So, 0.1 %i Chit-NLs come under this range and suitable for intranasal delivery.

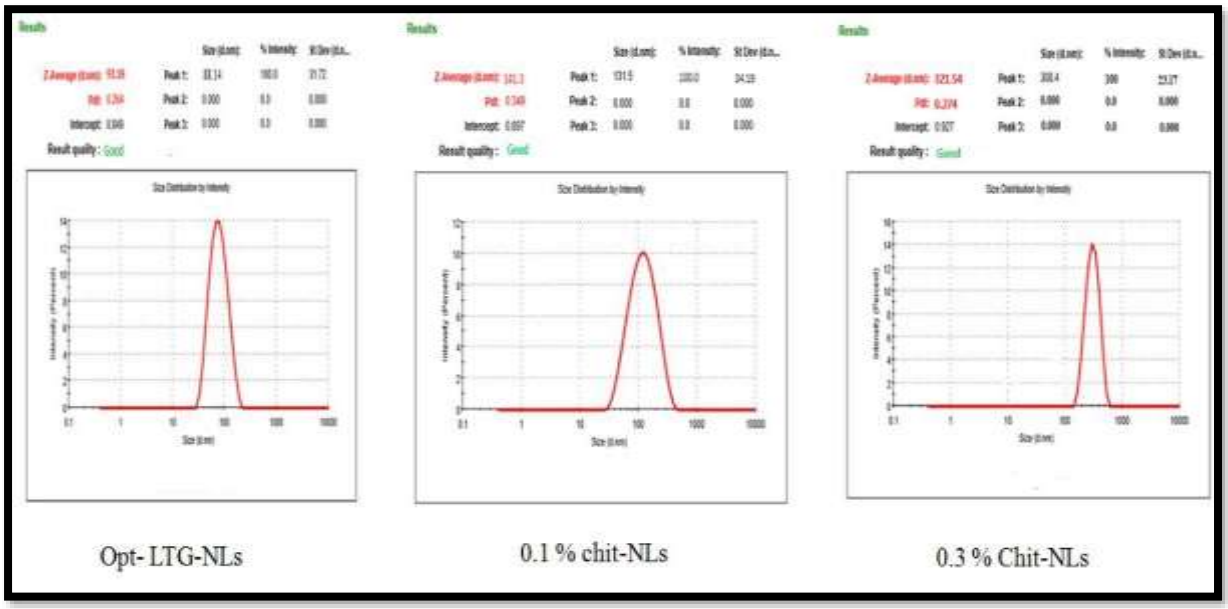


Fig.4: Vesicle size distribution of optimized nanoliposomes before and after coating

II. Entrapment efficiency (% EE) of Opt-LTG-NLs

The percentage of drug entrapment was going to reduce to 64.56±1.03% and 61.92±2.72% correspondingly after coating with 0.1% and 0.3% chitosan, from 68.75±2.11% before (Table 1). As the amount of chitosan in nanoliposomes grew, there was a little drop in their EE. Tani et al. (2013) found that the coating and insertion of chitosan chains into phospholipid

bilayers had a little detrimental effect on drug entrapment due to drug leakage. Entrapment was significantly lower in our investigation using 0.3% Chit-NLs compared to 0.1% Chit-NLs.

III. In-vitro release study of Opt-LTG-NLs

Table 1 shows that the prepared Opt-LTG-NLs and Chit-NLs released a lower percentage of drug (58.26 ± 2.15% from 0.3% Chit-NLs) in the presence of NSB (P 6.5) at 37 ± 5°C when tested using the cellophane dialysis bag method, also known as the membrane diffusion technique. The release rate was satisfactory and effective (73.43±1.13) in 0.1% Chit-NLs. The results are displayed in Table 1 and Figure 5 after the chitosan coating increases the size of the vesicles and decreases their release.

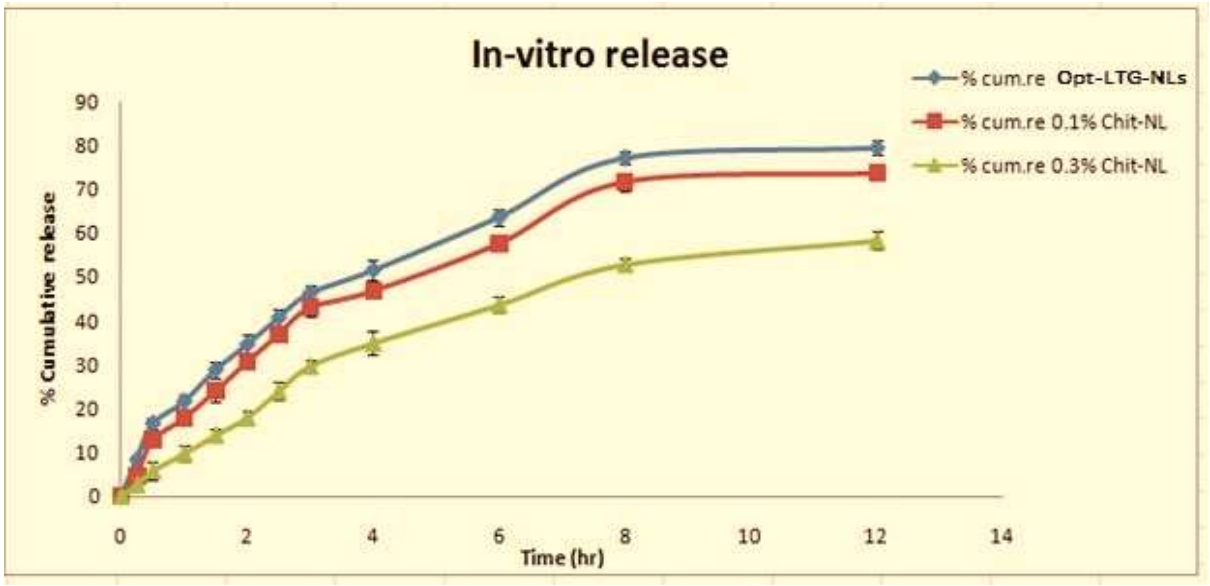


Fig 5. In vitro drug release profile of Opt-LTG-NLs, 0.1% Chit-NLs and 0.3% Chit NLs.

Table No.1: Optimization of nanoliposomesi before and after chitosan coating by characterization.

Formulation	Chitosan %	Particle size (nm± SD)	Entrapment efficiency (% ± SD)	In vitro Release (% ±i SD)
Opt-LTG-NLs	0 (Uncoated)	88.90± 1.56	68.75±2.11	**79.41±1.15**
Chit-NLs -1	0.1 % (Coated)	131.72± 1.37	64.56± 1.03	**73.43±1.13**
Chit-NLs-2	**0.3 % (Coated)**	**308.12±1.62**	**61.92± 2.72**	**58.26± 2.15**

IV. PH determination of Opt-LTG-NLs

The PH of the all formulations was shown in Table No. 2. This PH valuei is in desirable range for intranasal delivery andi does not cause anyirritationi onnasal mucosa.

Table No. 2: **PH value of the optimized prepared formulations**

Formulation code	PH ±SD
Opt-LTG-NLs	**6.5± 0.17**
0.1 % Chit-NLs	**6.4±0.32**
0.3% Chit-NLs	**6.2±0.24**

V. Zeta potential study of Opt-LTG-NLs

Optimal nanoliposomes coated with 0.19% and 0.3% chitosan solutions showed zeta potentials of 20.19 ± 0.23 mV and 27.53 ± 0.12 mV, respectively, compared to the -10.54±0.15 mV reported in the control group (Fig. 6). According to the data presented, the vesicles' zeta potential shifted from negative to positive charge. The vesicles surfaced with a positive charge after being coated with chitosan, in contrast to the optimized nanoliposomes constructed of phospholipid bilayer, which had a negative charge initially. Chitosan coating of nanoliposomes is confirmed by the change from negative to positive zeta potential of vesicles. Nanoliposomes covered with chitosan had better mucoadhesion than those without due to the electrostatic interactions that were already present between the mucus and the chitosan. The evaluation of chitosan coated nanoliposomes revealed that 0.1% Chit-NLs were more efficient than 0.3% Chit-NLs in terms of particle size, trapping, and in vitro release. Not suited for intranasal distribution were the extremely large particle size and extremely low release rate of 0.3% Chit-NLs. Looking at it from a selection standpoint, 0.1% Chit-NLs was deemed an optimal formulation (Chit-Opt-NLs) for conducting more investigations.

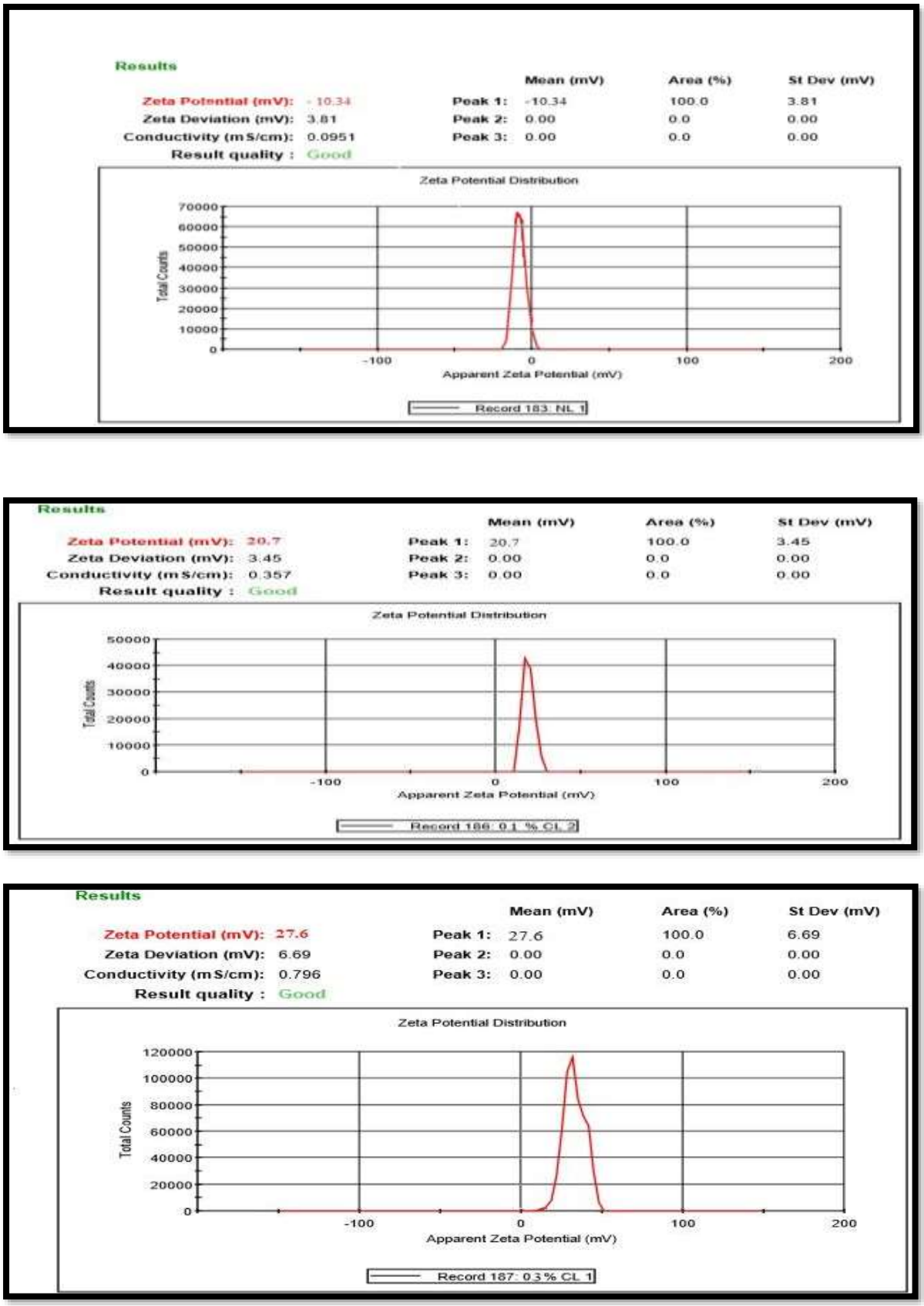
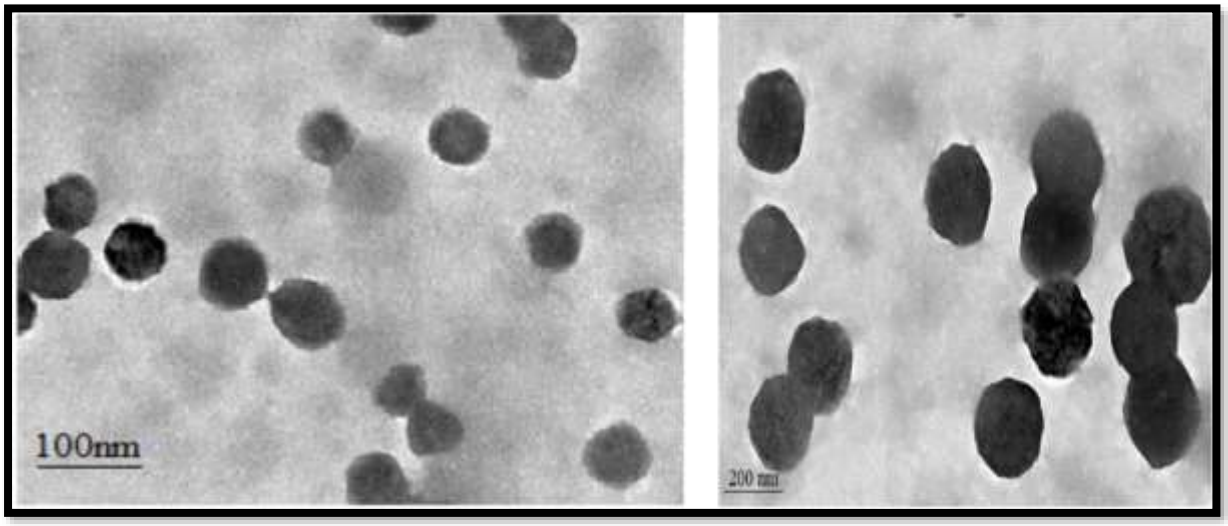


Fig.6: Zeta potential of (A) Opt-LTG-NLs (B) 0.1% Chit-NLs (C) 0.3% Chit-NLs

VI. Surface morphology study of Chit-Opt-NLs

Transmission electron microscopy (TEM) analysis of Opt-LTG-NLs and Chit-Opt-NLs was performed to investigate its visual information, surface morphology, and size uniformity of liposomal vesicles. The image of Opt-LTG-NLs and Chit-Opt-NLs showed that the vesicleswere uniform in size near to 100 nm and above with homogenous size distribution (Fig.7) TEM images of vesicles confirms the formation of liposomes in nano range and increase in its size confirm the chitosan coating process.



(A) **(B)**

Fig. 7: TEM image of (A) Opt-LTG-NLs (B) 0.1 %Chit-NLs

VII. Confocal laser scanning microscopy (CLSM) visualization

Instead of lamotrigine, rhodamine B dye was encapsulated into the lipid bilayer of liposomes to visualize the penetration of Opt-LTG-NLs and Chit-Opt-NLs through goat nasal mucosa. Using confocal microscopy, we examined rhodamine-loaded nanoliposomes coated with chitosan and pure rhodamine solution after 12 hours of treatment with tissue. The confocal photos of the nasal mucosa in Fig. 21 indicate that both the rhodamine-loaded and chitosan-coated nanoliposomes showed intense fluorescence in the deepest layer of the mucosa, whereas the neat rhodamine solution barely reached the surface layer. The photos clearly showed that Opt-LTG-NLs and Chit-Opt-NLs were very effective for intranasal administration. According to numerous theories, the vesicle carrier penetrates the mucosa by way of an intracellular, intercellular channel that opens the tight junctional proteins. Nanoliposomes may have an intercellular pathway in the mucosal layer, as shown in CLSM images of nasal mucosa. With their incredibly small particle size and vesicle flexibility, nanoliposomes are able to penetrate

deeper layers of mucosa than pure rhodamine solutions. Nanoliposomes laden with rhodamine were found to have the ability to rapidly penetrate mucosa, according to this study. Tween 80, when added to nanoliposomes, reversibly opens the epithelial cell tight junction, making them more permeable.

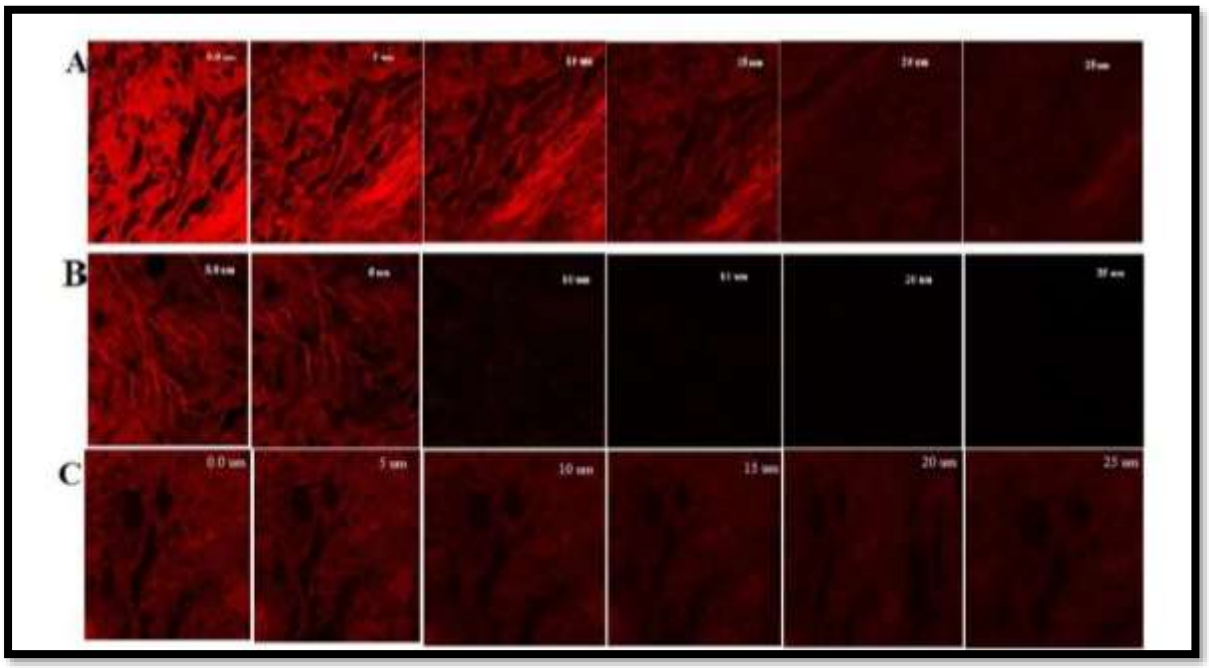


Fig.8 : CLSM image of goat nasal mucosa treated with (A) Rhodamine loaded nanoliposomes (B) Rhodamine pure suspension (C) Rhodamine loaded chitosan coated nanoliposomes showing depth of penetration.

VIII. Toxicity study of nasal mucosa

In order to assess the optimized formulation's safety parameter, investigations of nasal toxicity were carried out. The optical microscope images of the nasal mucosae treated with the formulation are shown in Figure 9. Typical histological features, such as the lining of the epithelial layer beneath the connective tissue, blood vessels, and glandular structure, were observed in the nasal mucosai that were treated with NSB (negative control) (Fig.9; a). In contrast, the positive control group's nasal mucosa treated with isopropyl alcohol had extensive damage to the epithelial layer and connective tissue (Fig. 9 ; b). Both these were considering as a standard to compare with Chit-Opt-NLs and Opt-LTG-NLs and simple drug suspension. The histological structure of nasal mucosa treated with Opt-LTG-NLs showed no significant change in epithelial lining, similar result was found with Chit-Opt- NLs (Fig.9; d and e). Whenever, pure suspension of lamotrigine showed partly denuded nasal mucosa with focal sloughing of epithelial cells (Fig.9 ; c). Overall results suggest that encapsulation of lamotrigine inside the lipid bilayer increases the safety parameter of lamotrigine for intranasal route and deliveryinto brain.

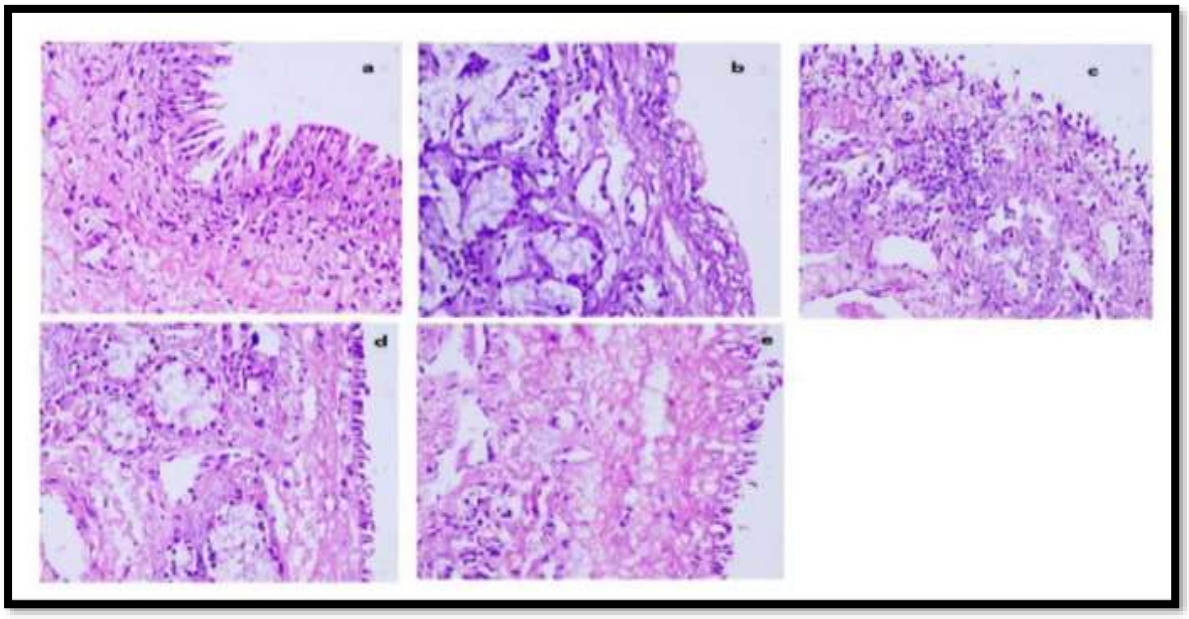


Fig.9: Optical micrographic image of histopathological structure of goat nasal mucosa treated with (a) Nasal saline buffer pH 6.5 (b) Isopropyl alcohol (c) Drug suspension (d) Opt-LTG-NLs (e) Chit-Opt-NLs.

8. Result and Discussion

Epilepsy is a well-known brain illness; around one percent of the global population will have it at some point in their lives. There are a lot of individuals in underdeveloped nations who suffer from epilepsy, and a lot of them don't get the medication they need to control their symptoms. The modified thin film dehydration-rehydration process was used to generate lamotrigine loaded nanoliposomes. Phospholipon 90 G, cholesterol, and tween 80 were used as excipients. Using design-of-experiment (DOE) techniques like Plackett-Burman designs (PBD) and response surface methodology, we were able to optimize the lamotrigine-loaded nanoliposomes and gain a better understanding of the formulation's complex variables and their mechanisms. Nanoliposome preparation parameters that significantly impact results, such as particle size, % EE, and in-vitro release, can be initially screened with PBD. The most effective formulation of lamotrigine-loaded nanoliposomes was chosen using an optimization strategy based on numerical point predictions generated by design expert software. The improved formulation of lamotrigine nanoliposomes (Opt-LTG-NLs) demonstrated an in-vitro release rate of 79.51%, an entrapment efficiency of 68.55%, and a PDI of 0.247±0.04, according to the experimental results. The untreated Opt-LTG-NLs had vesicles that were 88.90± 1.56 nm in size. However, after being coated with 0.1% and 0.3% chitosan, respectively, the size of the vesicles rose to 131.72 ± 1.37 and 308.12 ± 1.62 nm. Prior to coating with a 0.1% chitosan

solution, the Opt-LTG-NLs had a Zeta potential of -10.54±0.15 mV. After coating, their zeta potential values increased to 20.19 ± 0.23 mV and 27.53 ± 0.12 mV, respectively. The surface morphology of liposomal vesicles was investigated using transmission electron microscopy (TEM) study of Opt-LTG-NLs and Chit-Opt-NLs. The vesicles exhibited a homogeneous size distribution and were consistently around 100 nm in size, as revealed by the Opt-LTG-NLs and Chit-Opt-NLs images. Investigation of Opt-LTG-NLs and Chit-Opt-NLs' ex-vivo penetration via goati nasal mucosa. At first, the release of Chit-Opt-NLs (0.1%) was lower than that of Opt-LTG-NLs (72.45% ± 2.06%), but after a certain amount of time had passed, its release grew to 78.32% ± 2.12%, which was noticeably higher. The safety parameter of the improved formulation was evaluated using the nasali toxicity tests. Histological analysis of nasal mucosae treated with Opt-LTG-NLs or Chit-Opt-NLs revealed a significant alteration in the epithelial lining. The experimental data and results show that Opt-LTG-NLs is a good formulation for intranasal delivery; adding chitosan to it improves its therapeutic efficacy and brain targeting, making it more effective at protecting against PTZ-induced seizures. The next step is to test it in humans to see how it works and whether it poses any safety risks.

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