RESEARCH PAPER

Intranasal delivery of Fosphenytoin loaded Nano lipid carriers (NLC) - Synthesis, Characterization, Drug release an in vitro study.

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Abstract

Background: one of the major neurological disorder is epilepsy needs rapid and effective drug delivery to the brain. Conventional parenteral administration of antiepileptic drugs has some issues like systemic adverse effects and limited brain targeting. Now the promising strategy using nanocarrier system gives an extraordinary results to enhance brain bioavailability while minimizing systemic exposure.

Objective: This present study aims to prepare a fosphenytoin-loaded nanostructured lipid carriers (NLCs) and to evaluate their physicochemical properties and in vitro drug release behavior.

Methods: Fosphenytoin-loaded NLCs were prepared using the solvent injection method and characterized by UV-visible spectrophotometer, particle size analyzer, zeta potential, and FTIR analysis. Entrapment efficiency and in vitro drug release study was assessed using the dialysis bag diffusion method.

Results: UV-Visible analysis confirmed formation of NLC and average size observed around 153 nm and zeta potential at -19 mV. FTIR confirms the formulation of NLC loaded fosphenytoin and entrapment efficiency of formulated NLCs was obtained 80% which confirms the drug loaded on NLC. In vitro drug release study showed an initial mild burst followed by sustained drug release over 24 hours, suggesting diffusion-controlled release from the lipid matrix.

Conclusion: The study results shows the preparation of NLC loaded fosphenytoin, characteriztion, entrapment efficiency and better drug release behaviour of fosphenytoin-loaded NLCs

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1. Introduction

In worldwide, one of the most common chronic neurological disorder is epilepsy, contributing to both morbidity and mortality [1]. Approximately, 50 million individuals are distressed globally, while almost 5% of the population expose at least one non-febrile seizure during their lifetime [2]. The prevalence rate of 0.5 - 1 % has disorder with annual incidence rates reported at 50–70 per 100,000 people in industrialized nations and as high as 190 per 100,000 in developing regions [3]. Extremely, almost four out of five individuals with epilepsy live in growing countries [4]. The exalted load in these areas is often linked to inadequate obstetric care, central nervous system infection rate is higher and traumatic brain injuries are increased [5]. In low resource settings 80 - 90 % of patients encounter barriers to effective treatment. This consequential treatment gap has been attributed to low structured healthcare systems, high costs of therapy, limited drug availability, and sociocultural factors [6]. The maintenance of epilepsy remains challenging due to the versatile nature of the disorder. Side effects of antiepileptic drugs (AEDs), potential drug–drug interactions, and the presence of medical or psychiatric comorbidities often complicate treatment. Some patient groups, including pregnant women, the elderly, and individuals with HIV/AIDS or psychiatric conditions, present additional complexities that require managed therapeutic approaches [7]. Phenytoin, valproate, phenobarbital, and MK801 are the known AEDs drugs, and it has been shown to induce significant region-specific apoptotic neuronal death in the immature brain. Interaction between seizures and AED-induced programmed cell death (PCD), neonatal rats were exposed to electroshock seizures (ECS) for three consecutive days (postnatal days 5–7). The long-term association of these findings remain unclear. While seizure-induced neuroprotection may be beneficial, it could also interfere with normal developmental processes by preventing natural PCD. Conversely, excessive AED-induced neuronal loss raises concerns about potential harm from treatment [8]. Fosphenytoin, a prodrug of phenytoin, provides the same pharmacological effects as phenytoin but avoids the injection site reactions and cardiac rhythm disturbances commonly associated with intravenous phenytoin. Although fosphenytoin is more expensive, the costs of managing complications from both status epilepticus itself and intravenous phenytoin therapy may offset this difference. Overall, fosphenytoin is better tolerated and allows for faster administration compared to intravenous

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phenytoin [9]. Intranasal drug delivery offers a promising alternative to parenteral administration for brain-targeted therapy. Beyond improving patient comfort, this route can limit systemic drug exposure, thereby enhancing safety, while also enabling direct transport to the brain, which may improve therapeutic efficacy [10]. Nanostructured lipid carriers (NLCs) are advanced drug-delivery systems consisting of a solid–liquid lipid matrix. Compared to conventional carriers, NLCs offer several advantages, including enhanced solubility, improved stability, greater permeability and bioavailability, reduced side effects, prolonged half-life, and targeted drug delivery. In recent years, they have gained significant attention for both pharmaceutical and cosmetic applications [11].

2. Materials and Methodology

2.1 Materials

API Fosphenytoin procured from Trifarma Italy. GMS, OA, Isopropyl alcohol,HCL, Poloxamer-407 -All these chemicals were procured from Bharat Chemicals Hosur Tamilnadu.

2.2. Methods

2.2.1 Preparation of NLC loaded with Fosphenytoin

Nanostructured lipid carriers were developed through solvent injection method. GMS and OA were mixed into the solution of Fosphenytoin sodium API (15 mg) and Specified amount of 100 mg GMS, 30 mg OA in beaker with adding 2 ml isopropyl alcohol (boiling point 81-83’c) while heating utensil at melting temperature of GMS. GMS is fully soluble in IPA, although some heat will aid and speed up the solubilisation process. In order to form the resulting solution is instantly drop-wise added into 10 ml of aqueous phase containing certain amount of poloxamer 407 (0.8%). To lower the pH to 1.5–2 for encouraging NLCs aggregation to facilitate its separation, 0.1N HCL (4ML) was incorporated into the dispersion and stirred continuously at 400rpm for 30min on a magnetic stirrer. Then the dispersion was centrifuged in REMI cooling centrifuge (Model C24BL, Vaco-779, Vasai, India) at 10,000rpm for 30 min at 10 °C and re-suspended on aggregates in 10ml double distilled water containing poloxamer407 (4%, by weight) as stabilizer with stirring at1000 rpm for 10 min.

2.2.2 Characterization of Fosphenytoin loaded NLC

UV–Visible Spectroscopy

3. Results and Discussion

3.1 UV-Visible Spectrophotometer

The UV–Visible absorption spectrum of the NLC dispersion was recorded using a UV–Visible spectrophotometer in the wavelength range of 280–400 nm. The sample was placed in a quartz cuvette with a path length of 1 cm, and the characteristic absorption

maximum (λmax) was noted to confirm the presence of fosphenytoin in the formulation.

Dynamic Light Scattering (DLS)

Futher the particle size and polydispersity index (PDI) of NLC formulation were determined using dynamic light scattering (DLS). Each sample were analyzed by triplicate manner.

FTIR Analysis

Fourier transform infrared (FTIR) spectroscopy was employed to assess the chemical compatibility between fosphenytoin and the excipients used in the NLC formulation. FTIR spectra of the pure drug and the formulated NLCs were recorded over the range of 4000–400 cm^{-1} using the KBr pellet method. The characteristic peaks were compared to identify any potential chemical interactions or structural changes following formulation.

Entrapment efficiency

The entrapment efficiency of formulated fosphenoytoin loaded NLC was calculated by the following equation:

$$\%EE = Wa - (Ws + Wp) / Wa \times 100 \quad (1)$$

where Wa is the amount of drug added in system, Ws is the amount of drug in supernatant after the centrifugation, and Wp is the amount of drug in the purification medium.

In vitro drug release study

The in vitro drug release analysis of fosphenytoin loaded NLCs was carried out using dialysis bag diffusion technique. 5 mg of fosphenytoin loaded NLCs was placed in a dialysis bag and dipped into the receptor verified in 100 ml of phosphate buffer, pH 7.4 at a speed of stirring 100rpm at 37°C.[20]. This compartment was sealed to prevent evaporation of the medium. At different time intervals (1,2,3,4,5,8,10,15,20 mins), 5 ml of aliquots were removed and replaced with fresh volume of dissolution medium which was then diluted proportionally concentration obtained using UV-Visible spectrophotometer at 239 nm.

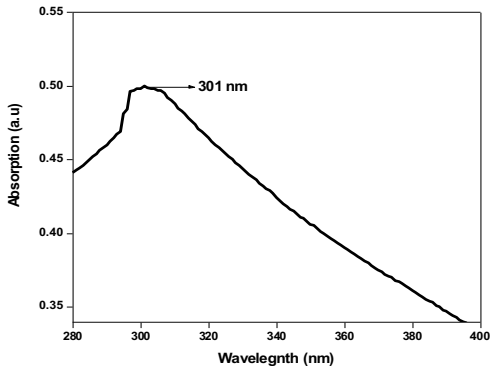


Fig. 1 UV-Visible spectrophotometer of NLC

Optical property of prepared NLCs were analysed using UV–Visible spectrophotometer. Sample was placed in a quartz cuvette, and the absorption spectrum was recorded. The maximum wavelength was observed at 301 nm indicating the characteristic electronic transition of the formulation. The absorption band suggests successful incorporation of the drug within the lipid nanocarrier.

3.2 Particle Size Analyzer

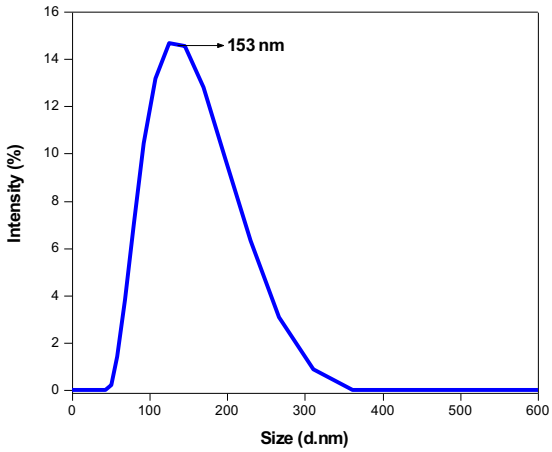


Fig. 2 DLS image of NLC

The size of NLC was observed at 153 nm, which indicates the average particle size of the formulation. It indicates a relatively uniform particle distribution between 100 - 200 nm and the intensity distribution gradually decreased beyond 200 nm.

Zeta Potential

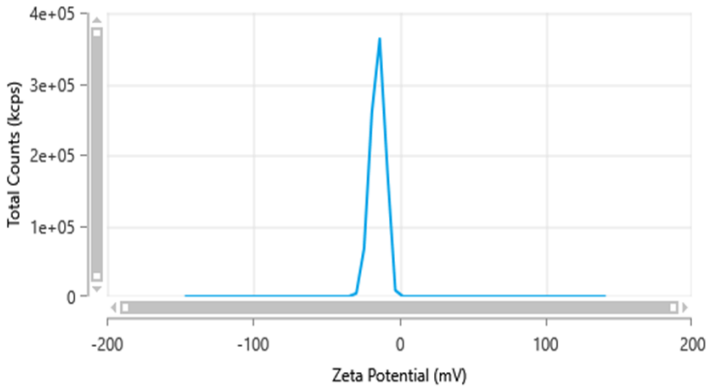


Fig. 3 Zeta Potential of NLC

In zeta potential analysis, surface charge and the stability of the prepared NLCs were evaluated. The peak was observed at -19 mV showing sharp and narrow peak indicates a negative surface charge.

3.3 FTIR

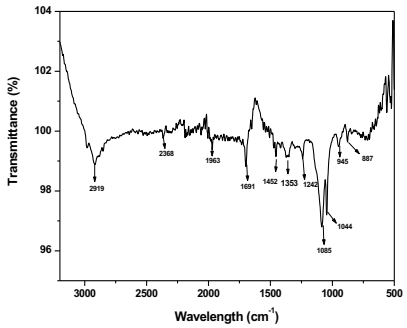


Fig. 3 FTIR image of NLC

The formulated NLCs was further recorded by FTIR spectrum to identify the characteristic functional groups and evaluate possible interactions.The bands were observed at 2919 cm^{-1}, corresponding to C–H asymmetric stretching vibrations of aliphatic $–CH_2$ groups, indicating the presence of lipid chains. A distinct peak at 1691 cm^{-1} was attributed to C=O stretching, suggestive of amide or carbonyl groups. The band at 1452 cm^{-1} corresponded to C–H bending of $–CH_2$/$–CH_3$ groups, while peaks at 1353 cm^{-1} and 1242 cm^{-1} were assigned to C–N stretching (amide III), indicating possible protein or surfactant contributions. Peaks at 1085 cm^{-1} and 1044 cm^{-1} were related to C–O–C and C–O stretching vibrations, characteristic of glycosidic linkages or ester functionalities. Additional signals at 945 cm^{-1} and 887 cm^{-1} corresponded to C–H bending vibrations, further confirming the presence of lipid/surfactant moieties. The peak at 2368 cm^{-1} was attributed to adsorbed atmospheric CO_2, and the weak overtone band at 1963 cm^{-1} indicated aromatic/conjugated C=C contributions.

S. No	Peak position (cm^{-1})	Group	Peak details
1	2919	C–H stretching	Asymmetric stretching of aliphatic $–CH_2$ groups (lipids, fatty acids)
2	2368	O=C=O stretching	Adsorbed CO_2 molecules / atmospheric carbon dioxide
3	1963	C=C	Overtone/combination band of conjugated/aromatic C=C bonds
4	1691	C=O stretching	Amide I band (proteins) / carbonyl groups of aldehydes, ketones, carboxylic acids
5	1452	C–H bending	Scissoring vibrations of $–CH_2$/$–CH_3$ groups; aromatic ring vibrations
6	1353	C–N stretching	Amide III band (proteins) / symmetric stretching of $–COO^-$ groups
7	1242	C–N stretching	Amide III band (proteins) / asymmetric phosphate (P=O) stretching
8	1085	C–O–C stretching	Glycosidic linkages in polysaccharides; also P–O stretching (phosphates)
9	1044	C–O stretching	Stretching vibrations of alcohols, polysaccharides, and glycosidic bonds
10	945	C–H bending	Out-of-plane bending of =CH (alkenes) / skeletal vibrations of polysaccharides
11	887	C–H bending	Out-of-plane aromatic C–H bending / β-glycosidic linkages in polysaccharides

3.4 Entrapment Efficiency

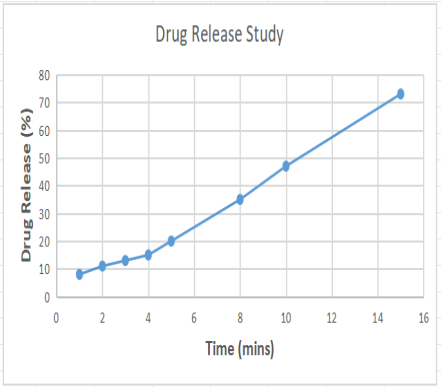
An entrapment efficiency of about 80% was obtained for the NLC-loaded fosphenytoin formulation, reflecting good compatibility between the drug and lipid components. The high entrapment efficiency confirms the ability of the nanostructured lipid carrier system to accommodate a substantial amount of the drug, which may contribute to enhanced therapeutic performance.

3.5 Drug Release Study

In vitro release study of fosphenytoin from prepared NLCs was performed by using dialysis bag diffusion technique. A desired amount of NLC dispersion corresponding to the calculated drug content was introduced into a pre-wetted dialysis membrane (molecular weight cut-off 12,000–14,000 Da). The sealed dialysis bag was placed in 100 mL of release medium at a constant temperature of 37 ± 0.5 °C and continuously stirred at a speed of 100 rpm to mimic physiological conditions. and to mimic the nasal and physiological environment, phosphate buffer saline (PBS, pH 6.4/7.4) was used as the release medium. At different time intervals (1,2,3,4,5,8,10,15 and 20 min), aliquots of 2 ml were withdrawn from release medium

and replaced with equal volume of fresh buffer to maintain sink condition. Following the collection of the samples, UV–Visible spectrophotometry was performed on the samples at a previously established λmax for fosphenytoin. The release profile was obtained by calculating and plotting the cumulative percentage of drug released at different time intervals.

				Blank 0.024			OD Before	0.5		0.476	
	Time	OD 300 nn	OD-Blank		Drug Release %				Time	Drug Release %	
	1	0.062	0.038	0.079832	7.983193277				1	8	
	2	0.079	0.055	0.115546	11.55462185				2	11	
	3	0.083	0.059	0.12395	12.39495798				3	13	
	4	0.098	0.074	0.155462	15.54621849				4	15	
	5	0.12	0.096	0.201681	20.16806723				5	20	
	8	0.147	0.123	0.258403	25.84033613				8	35	
	10	0.248	0.224	0.470588	47.05882353				10	47	
	15	0.374	0.35	0.735294	73.52941176				15	73	
	20	0.465	0.441	0.926471	92.64705882						



4. Conclusion

The present study demonstrates the successful development of fosphenytoin-loaded nanostructured lipid carriers (NLCs) designed for intranasal administration with the aim of enhancing brain delivery and improving anticonvulsant efficacy. The formulated NLCs exhibited favorable physicochemical characteristics, including nanoscale particle size, acceptable zeta potential, and high entrapment efficiency, which are considered essential parameters for efficient nose-to-brain transport and formulation stability.

The mean particle size of approximately 153 nm obtained by DLS analysis indicates that the formulation falls within the optimal nanometric range reported for intranasal drug delivery systems. Nanoparticles below 200 nm are known to facilitate transport across the nasal epithelium and enhance uptake through olfactory and trigeminal nerve pathways. The relatively narrow size distribution observed in the present work suggests good homogeneity of the formulation, which is critical for reproducible biological performance and consistent drug delivery. The negative zeta potential (−19 mV) further supports moderate colloidal stability of the NLC dispersion, minimizing particle aggregation during storage and administration.

High entrapment efficiency (~80%) reflects the suitability of the lipid matrix composition and preparation method for accommodating fosphenytoin within the NLC system. The combination of solid and liquid lipids likely created imperfections in the lipid matrix, enabling higher drug loading and reducing drug expulsion during storage. Efficient encapsulation is advantageous for intranasal delivery, as it allows administration of therapeutically relevant doses within the limited volume that can be applied to the nasal cavity.

FTIR analysis indicated the absence of significant chemical interactions between fosphenytoin and the excipients used in the formulation, suggesting that the drug remained chemically stable within the NLC matrix. This compatibility is important for preserving the pharmacological activity of the drug and ensuring formulation safety. UV–Visible spectroscopic analysis further confirmed successful incorporation of the drug into the nanocarrier system.

The in vitro drug release profile of NLC formulation showed a slight burst followed by sustained release up to 24 h respectively. The early release can be ascribed to drug presented in an adsorbed state on or proximal to the particle surface (the so-called "burst effect"), whereas the delayed release phase likely can be explained by diffusion of the drug from the lipid matrix. This biphasic release pattern is beneficial for antiepileptic therapy, allowing rapid drug delivery for the acute treatment of seizures but over long enough time periods to maintain therapeutic concentrations to prevent recurrence. The prolonged drug release of NLCs can also lead to fewer doses and higher patient compliance.

Overall, the findings of this study suggest that intranasal delivery of fosphenytoin using NLCs represents a promising strategy for rapid and efficient brain targeting in the management of epileptic seizures. However, the study is limited by the lack of pharmacokinetic and biodistribution data. Future investigations should focus on in vivo brain targeting efficiency, nasal mucosal safety, long-term stability of the formulation, and comparative efficacy with conventional dosage forms in higher animal models. These studies will be crucial to establish the translational potential of the developed intranasal NLC system for clinical application.

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