RESEARCH ARTICLE

Preparation and Evaluation of Primidone Solid Lipid Nanoparticle for Alleviating Seizure Activity in Wistar Rats

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ABSTRACT

Introduction: In order to increase primidone's anticonvulsant action, the study set out to manufacture it in solid lipid nanoparticle form (PRI-SLN).

Method: Microemulsification and ultrasonication procedures were used to create 17 PRI-SLN formulations.

Results: The PRI-SLN displayed a high entrapment efficiency (46.37 ± 2.42% to 81.82 ± 1.21%), as well as small particle size (149.9 ± 6.72 to 188.8 ± 5.25 nm). According to the *in-vitro* release study, PRI from SLNs releases more slowly than PRI by itself. The thermal analysis showed the drug's compatibility with other substances and its presence in the more soluble amorphous state. Following a lethal and chronic dosage of picrotoxin, the PRI-SLN exhibited a higher anticonvulsant efficacy, according to *in-vivo* research on rats ($p < 0.05$).

Conclusion: SLN with stronger anticonvulsant action can be made from PRI.

Keywords: Epilepsy, Picrotoxin, Solid lipid nanoparticles, Primidone.

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INTRODUCTION

The hallmark of the central nervous system (CNS) illness known as epilepsy is an upsurge in the number of electrical impulses happening in one specific area of the brain and/or the entire brain, which results in partial or generalized seizures.[1]

Antiepileptic medications are often directed orally or intravenously. By the conclusion of their treatment, 40% of patients develop drug resistance. Uncontrolled seizures, a higher risk of brain damage, and higher mortality rates are all caused by drug resistance.[2] Patients with epilepsy experience behavioral and emotional changes, convulsions, sadness, and occasionally unconsciousness in addition to seizures.[3] Drug resistance causes epilepsy medications with low bioavailability to lose their effectiveness during the course of treatment.[4]

Treatment for epilepsy is frequently difficult because drugs only partially cross the blood-brain barrier; this problem can be solved by preparing drugs as solid lipid nanoparticles.

The best antiepileptic drugs are those that deliver localized and regulated drug release to specific brain locations, reducing medication-associated toxicities and increasing treatment efficacy.[5]

Primidone is a first-generation antiepileptic drug of the barbiturate type that was created to treat seizures, most frequently partial and generalized seizures. It may have an impact on convulsions and essential tremors by altering sodium and calcium channel transit and lowering the frequency of nerve firing. Active anticonvulsants include primidone and its metabolites phenobarbital and phenylethylmalonamide (PEMA). Primidone, unlike phenobarbital, does not directly interact with GABA-A receptors or chloride channels.

Alternative to the liposome, noisome, and polymeric nanoparticles are solid lipid nanoparticles (SLNs). When these SLN are distributed in water with a surfactant present, they act as a stabilizer. SLN has a high drug loading capacity, a big surface area, and a small size (nano range). Additionally, it enhances oral bioavailability of drugs with poor water solubility.[6,7] To enhance the medication's therapeutic efficacy, Qushawy *et al*. created carbamazepine SLN.[2,8]

The current investigation aimed to prepare primidone solid lipid nanoparticles (PRI-SLNs) as a new and different approach for other colloidal dispersion carriers. The study aimed to create PRI-SLNs that were more effective at entrapping PRI

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than free PRI while also having smaller particle sizes and higher anticonvulsant action.

MATERIALS AND METHODS

Materials

Primidone was obtained from sun pharmaceuticals, Ahmedabad, India. Poloxamer 188, glyceryl monostearate, and sunflower lecithin were procured from Hi-media, Mumbai, India. All of the substances and reagents utilized were of high analytical grade.

Methods

Preparation of solid lipid nanoparticle

SLN loaded with primidone prepared by microemulsification.[9,10] Initially required quantity of primidone, glyceryl monostearate (lipid) was dissolved in hot (45°C) organic solvent (ethanol). To that solution, soyabean lecithin was added as a co-emulsifier. Aqueous solution of poloxamer 188 was prepared in another beaker with a similar temperature of 45°C. The lipophilic drug phase was poured to the aqueous phase with continuous stirring (rpm mentioned in as the table) to obtain primary o/w emulsion. A probe sonicator was also used to ultrasonicate this coarse emulsion for 10 minutes (UAI-PS20khz-900W, Ultra Autosonic, India) at 45% amplitude for 10 minutes. To create SLN, the dispersion was freeze-dried in a lyophilizer (BK FD10, Biobase, China) for 24 hours at -80°C. The SLN were then kept at 4°C for additional analysis and processing.

Box-Behnken design

The effects of chosen independent variables were assessed using a 3-level, three-factor Box-Behnken experimental design in the current investigation. Consideration was given to three distinct components, including sodium glyceryl monostearate (A), RPM (B), and Poloxamer-188 (C). Particle size, drug release after 12 hours, and entrapment effectiveness (EE) are the reactions that were noted during the 17 experiment runs (Table 1). The polynomial equation carried out mathematical fitting and analysis.[2] The optimized formula was solved by utilizing a numerical method and a graphical optimization methodology with a confidence interval value of α 0.05.

Measuring Variables of Responses

- *Mean particle size*

In order to characterize formulations and characterize responses to all variables more thoroughly, mean particle size was assessed and used as a response in the optimization step. Another argument is that, according to Marianecci *et al*. (2014), particle size is regarded as a metric that provides reliable information concerning aggregation, nanoparticle stability, and electrostatic repulsion amid the dispersed nanoparticles. Using dynamic light scattering (DLS), the particle size distribution for each formulation was calculated.[11]

- *Entrapment efficacy (EE)*

A predefined volume of each created SLNs dispersion was subjected to cooling centrifuge model (Union 32 R, Hanil Science Ind. Ltd., Incheon, Korea) set at 2ºC and 10,000 rpm for 60 minutes after the development of PRI formulations. Next, free FP was removed from the dispersion through washing, and the washed centrifuged dispersion underwent additional centrifugation to produce a pure SL. To liberate the medication that had been imprisoned in the acquired SLNs, a lyses procedure was used. This process involved redispersing a specific weight of the washed SLNs in 10 mL of distilled water, then dissolving 1-mL of the resulting solution in 30 mL of ethanol and sonicating the mixture for 10 minutes using an ultrasonicator (Ultrasonicator, CPX3800-E, Branson). The created clear solution was then tested using a spectrophotometric analysis method[12-14] at wavelength 240 nm as a control for drug-free SLNs made and handled in the same manner.

$$EE\ (\%) = \frac{\text{Mass of drug in SLNs}}{\text{Initial mass of drug used in SLNs}} \times 100 \quad \text{.....(1)}$$

- *In-vitro release pattern and kinetic behavior*

Primidone was released from the SLNs *in-vitro* utilizing the Franz-diffusion cell and the diffusion technique. Prior to usage, the cellophane dialysis membrane was divided into equal pieces of 6 cm by 2.5 cm and saturated in distilled water for 12 hours. In 10 mL of phosphate buffer pH 6.8 saline kept at 37 ± 0.5°C with a magnetic stirrer and continual heating apparatus (IKA Auto Temp Regulator, Germany), primidone drug release tests are conducted. In the receptor compartment, 2 mL of SLN suspension sample was inserted. At regular intervals, 1-mL aliquot samples were taken out and substituted with an equal volume of new buffer.

UV spectrophotometer at 257 nm was used to measure the amount of medication that diffused through the membrane, while phosphate buffer (pH 6.8) served as the control. Kinetic modeling can be used with data from PRI release profiles of SLN formulations to learn more about the release mechanism. These results were adjusted to kinetic models to illustrate the mechanism of drug release from various carrier systems (zero-order, first-order, second-order, Higuchi, and Korsmeyer-Peppas models).[15,16]

Optimization of formulation variables

Based on factors including a high entrapment effectiveness percent, small particle size, a high zeta potential to prevent the aggregation of nanoparticles, and a high drug release after 12 hours, the optimum formulation was chosen to finish the *in-vivo* investigation.

Morphological Examination

- *Scanning electron microscope*

With the aid of poloxamer 188 and GMS, the optimized PRI-SLN (F8) formulation was created, and the surface morphology was observed using a scanning electron microscope (S3700N-Hitachi, Japan). On an aluminum stub, a single drop of the sample was applied, and it was let to dry

at a temperature of 25 ± 1ºC. A tiny layer of platinum was applied to the dried sample, and an SEM set to 30 KV was used to take the picture.

- *DSC of study of optimized SLN*

Shimadzu DSC-50 (Japan) was used to analyze the lyophilized samples of pure PRI, GMS, poloxamer 188, SLNs made with GMS, as well as SLNs made with poloxamer, for their thermotropic characteristics and phase transition behavior. In an aluminum pan, samples weighing about 3 mg were heated and sealed, ranging from 25 to 250ºC at a rate of 10°C/min while nitrogen gas was flowing. As a benchmark, an empty aluminum pan was employed.

Pharmacological Activity

- *Animals*

They were bought from the Jeeva Life Sciences, Hyderabad, Telangana, India. At the time of the experiment, male albino wistar rats weighing 200–250 g were utilized. They were housed six to a cage, with free access to food and water throughout the day. The research ethics committee gave its consent to each experimental procedure, and every attempt was made to lessen and eventually end animal suffering.

- *Seizure activity evaluation in rats*

In this investigation, 24 male albino mice were employed, and they were placed into 4 groups at random, each with six animals: Group I received the saline control group (administrated orally), group II disease control group received the picrotoxin (3.5 mg/kg, s.c.), Group III Standard group received diazepam dispersed in water (0.5 mg/kg, i.p.) 45 minutes before picrotoxin injection and group 4,5,6 treatment groups received the PRI-SLN formulation (5, 10, 50 mg/kg, p.o.) 45 minutes before picrotoxin injection.

After receiving a picrotoxin injection, each rat was monitored for convulsion activity for 30 minutes. Based on the Racine rating scale for seizure evaluation, a score was assigned to each mouse based on the severity of their seizures.

Rats were graded using the following standards: (1) If the rat was immobile, had closed eyes, twitched ears, and facial clonus; (2) If the rat nodded with severe facial clonus; (3) If the rat had a cloned forelimb; (3.5) If the rat had bilateral forelimb cloning without rearing; (4) If the rat had bilateral forelimb cloning with rearing; Rats dropping on one side (without raising) exhibit lack of the righting reflex together with general tonic-clonic seizures in condition (4.5), and rats dropping on the back while rearing exhibit general tonic-clonic seizures in condition (5.5). Following the final picrotoxin injection, the means of each group's 15 seizure scores were computed and compared.[17]

RESULTS AND DISCUSSION

Preparation of the PRI-SLN

The microemulsification and ultrasonication process was used to formulate seventeen different PRI-SLN formulations (F1–F17). Table 1 contains a list of the ingredients in the created formulations. The prepared PRI-SLN formulations were tested for EE%, particle size analysis, and *in-vitro* release to choose the optimal formulation.

Table 1: Formulation of primidone solid lipid nanoparticles

	Factor 1	*Factor 2*	*Factor 3*
Formulations	*Glyceryl Monostearate (mg)*	*rpm*	*Poloxamer-188 (%)*
F1	125	1000	0.1
F2	200	3000	2
F3	200	5000	1.05
F4	125	1000	2
F5	125	3000	1.05
F6	200	1000	1.05
F7	125	3000	1.05
F8	125	3000	1.05
F9	200	3000	0.1
F10	50	5000	1.05
F11	125	5000	2
F12	125	3000	1.05
F13	125	5000	0.1
F14	50	1000	1.05
F15	50	3000	0.1
F16	125	3000	1.05
F17	50	3000	2

Particle size, Entrapment Efficiency%

Formulations with high glyceryl monostearate (50%) content were discovered to have high EE. Maximum 89.33% of Formulation "F6" is trapped, while 87.39 and 82.59% of Formulations "F9" and "F3" are also trapped. Similar to this, the percentage amount of Poloxamer-188 indicated the EE as it can be observed that F9, which included 0.1% of Poloxamer-188, had the highest EE while F17, which contained 2% of Poloxamer-188, had a significantly lower EE of 47.18% This could be due to emulsifying property of poloxamer-188 which entrapped lesser amount of primidone. However, formulations with high amounts of glyceryl monostearate formed a hydrophobic barrier surrounding drug molecules in SLN formulation. Lastly it can be determined that, an appropriate blend of glyceryl monostearate and Poloxamer-188 with preferably less quantity can develop an SLN with good EE. Whereas, the RPM also contributed significantly; less processing at 1000 RPM developed SLN with improved EE as seen in "F6" possessed 81.82%. The EE% data, drug release at 12h, and particle size can be found in Table 2.

In-vitro Release Study of PRI from PRI-SLN

A SLN *in-vitro* dissolution study recommended by BBD was assessed. A maximum 15% of the medication was reported to be released in the first 30 minutes in all formulations. The largest amount of medication released by F17 throughout the 12-hour dissolving study was 99.98%. F9, on the other hand,

Table 2: The entrapment efficiency%, particle size, drug release at 12 hours and drug-loaded of prepared primidone solid lipid nanoparticle formulations

	Response 1	*Response 2*	*Response 3*	
Formulations	*EE (%)*	*Drug release at 12h (%)*	*Particle size (nm)*	*Drug loaded (%)*
F1	67.91	68.13	174.9	75.89
F2	70.62	62.38	179.6	81.22
F3	72.46	62.77	176.4	82.59
F4	64.38	82.15	169.3	75.21
F5	61.36	75.27	164.9	72.19
F6	81.82	65.22	188.8	89.33
F7	60.89	73.18	166.4	71.08
F8	62.17	72.18	165.1	73.81
F9	77.56	55.29	179.5	87.39
F10	46.37	97.29	148.1	57.64
F11	55.38	88.75	161.3	66.39
F12	62.34	72.17	165.3	72.06
F13	61.29	78.36	163.2	71.38
F14	52.18	89.13	157.1	63.46
F15	48.05	91.03	155.6	58.77
F16	63.11	70.14	166.2	73.39
F17	47.18	99.98	149.9	58.18

showed at least 55.29% of the medication in 12 hours. In the dissolving investigation, it was discovered that there is a clear correlation between the amounts of glyceryl monostearate and poloxamer-188. The higher amount of glyceryl monostearate delayed drug release; the similarly higher amount of poloxamer-188 fastened the drug release. It observed that F2, F3, F6 and F9 exhibited lesser drug release in 12 hours as they contained higher amount (200 mg) of glyceryl monostearate. It reveals that GMS can create a barrier around the drug particle, slowing the drug release process.

Poloxamer-188 was considered as an emulsifier while developing the formulation. It helps to emulsify and improve drug permeability across biological membrane. A comparison was made between "F2" and "F9"; it observed "F9" exhibited 55.29% of drug whereas "F2" highlighted a comparatively higher value of 62.38% drug release. This release could be the involvement of higher amount of poloxamer-188 in "F2". A similar pattern can be found in "F4" which contributed a higher amount of drug release of 82.15%. This data concluded the evidence of percentage poloxamer-188 in the drug release study. This gives poloxamer-188 its wetting property, which can emulsify drugs and hasten their release.

Similarly, a pattern of release can be observed from rpm. Higher rpm contributed faster than less RPM. It can be seen that, F14 contributed 89.13% of drug, whereas F10 exhibited a comparatively higher 97.29% of drug. The higher data could be the result of high processing rpm (5000). This provides evidence of RPM on drug release effect (Figures 1 and 2).

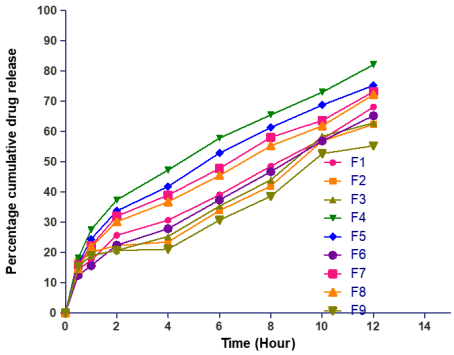

Figure 1: *In-vitro* drug release data of SLN F1-F10

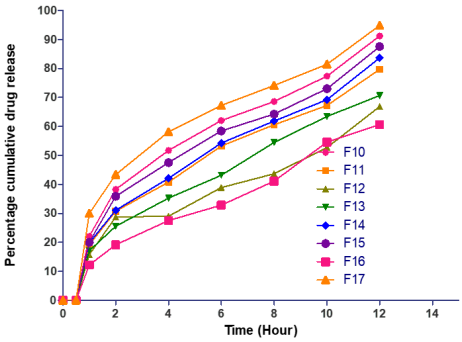

Figure 2: *In-vitro* drug release data of SLN F10-F17

Release Kinetics Study of PRI-SLN Formulations

Zero-order and first-order kinetic studies were used to determine the drug release kinetics. It discovered that every formulation followed the first order and had an R^2 value larger than zero, which shows that drug concentration and polymer concentration are the main determinants of drug release. In contrast, the Higuchi, Hixon-Crowell, and Korsemeyer peppas model determined the release mechanism. It observed that those formulations followed Higuchi pattern mechanism only shown in Table 3. The lipophilic nature of glyceryl monostearate contributes the insolubility.

Selection of the Optimized Formulation

Once the model polynomial equations were created, the approach was modified based on the interactions among the dependent and independent variables. The ultimate ideal investigational conditions were established using canonical analysis, which permits the compromise of multiple answers and searches for a combination of factor levels that jointly maximize a set of responses by satisfying the criterion for each response in the set. The improved formula is listed in Table 4.

Surface Morphology of the PRI-SLN

During SEM study it observed scattered dispersion of drug crystals and SLN. The study also revealed the appearances and surface of optimized SLN are symmetrical in nature. It observed in Figure 3, SLN are dispersed uniformly throughout the sample. In Figure 4 (3.0 µm resolution) it observed uniform particle size of optimized SLN formulation.[2,18]

Table 3: Release kinetics study from all formulations (F1-F17) prepared based on a suggestion from BBD

Formulation	*Zero*	*First*	*Higuchi*	*Hixson-Crowell*	*Korsemeyer peppas*	
					(R^2)	*N*
F1	0.908	0.950	0.986	0.939	0.778	0.317
F2	0.821	0.87	0.918	0.855	0.617	0.289
F3	0.856	0.901	0.931	0.888	0.637	0.401
F4	0.882	0.961	0.993	0.939	0.803	0.328
F5	0.899	0.963	0.994	0.946	0.810	0.416
F6	0.935	0.965	0.985	0.957	0.797	0.328
F7	0.896	0.956	0.992	0.941	0.802	0.371
F8	0.899	0.953	0.991	0.938	0.803	0.424
F9	0.813	0.857	0.910	0.844	0.612	0.269
F10	0.803	0.935	0.962	0.898	0.766	0.328
F11	0.846	0.941	0.983	0.914	0.793	0.411
F12	0.822	0.895	0.958	0.873	0.726	0.298
F13	0.895	0.963	0.993	0.945	0.803	0.341
F14	0.848	0.947	0.984	0.919	0.793	0.328
F15	0.812	0.929	0.966	0.896	0.775	0.427
F16	0.921	0.954	0.980	0.947	0.811	0.412
F17	0.757	0.925	0.943	0.877	0.702	0.237

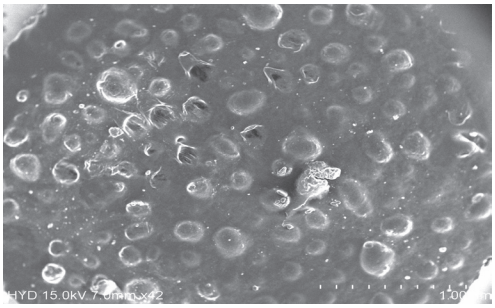

Figure 3: SEM study of optimized formulation (1.0 mm)

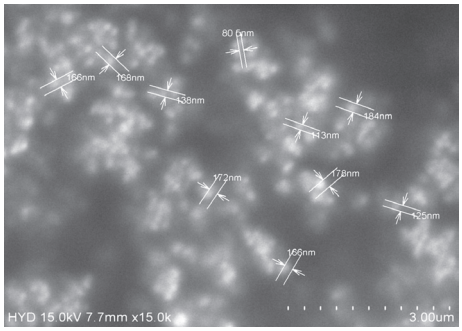

Figure 4: SEM study of improved formulation (3.0 µm)

DSC of Study of Optimized SLN

A DSC examination (Figure 5) revealed a clear endothermal peak at 282.7°C, which is close to the earlier measured value of 285.49°C for pure primidone. This determined that the endothermal peak had not changed much. It also implied that the pure medication in the SLN formulation was thermally stable. It also observed a broad peak at 61.54°C with onset at 50.64°C. This broadening of peak could be attributed to the formation of the complex by glyceryl monostearate and Poloxamer-188. It noted there is no such prominent peak appearing for sunflower lecithin. However, one newer and

Table 4: The composition, EE, drug release, particle size of optimized primidone solid lipid nanoparticles formulation

Factor	*Name*	*Level*	*Response*		
			EE (%)	*Drug release at 12h (%)*	*Particle size (nm)*
1	Glyceryl monostearate	97.35	64.21	83.18	182.6
2	rpm	1216.36			
3	Poloxamer-188	0.5732			

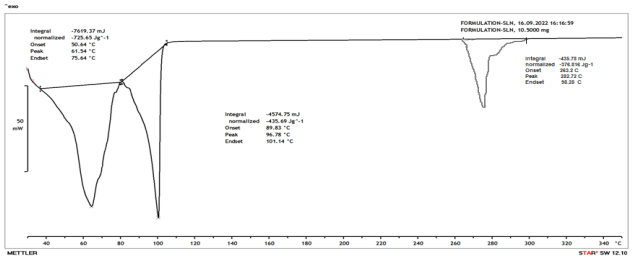

Figure 5: DSC thermogram of optimized formulation (SLN)

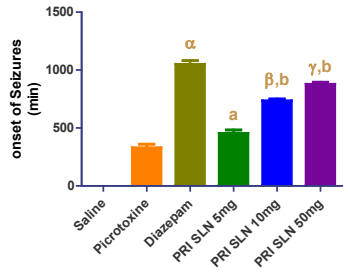

Figure 6: Onset of the seizure of PRI-SLN on picrotoxine-induced seizures. PRI-SLN significantly prolonged onset of the seizure ($p < 0.05$) in 50 mg/kg PRI-SLN ingested group. Data are presented as mean ± SD (n = 6) and were analyzed using an ANOVA followed by Tukeys post hoc test at $p < 0.05$, where $^{\alpha}P<0.001$, $^{\beta}P<0.01$, $^{\gamma}P<0.05$ vs picrotoxine. $^{a}P<0.001$, $^{b}P<0.01$ vs Diazepam

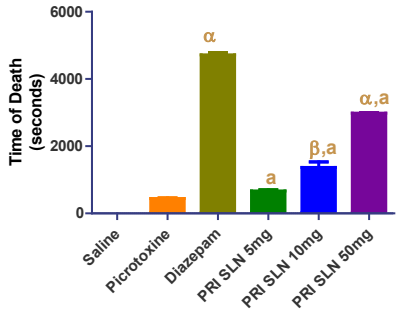

Figure 7: The effect of PRI-SLN on the time to death after the administration of Picrotoxine. PRI-SLN significantly prolonged time of the death ($p < 0.05$) in 50 mg/kg PRI-SLN ingested group. Data are presented as mean ± SD (n = 6) and were analyzed using an ANOVA followed by Tukeys post hoc test at $p < 0.05$, where $^{\alpha}P<0.001$, $^{\beta}P<0.01$ vs picrotoxine. $^{a}P<0.001$, vs Diazepam

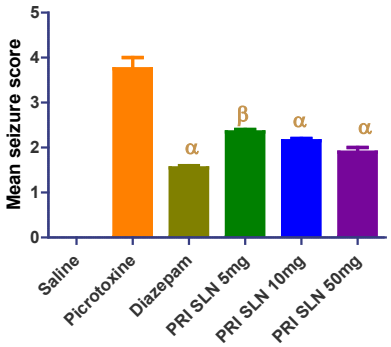

Figure 8: The effect of PRI-SLN on the mean seizure score after the administration of Picrotoxine. Data are presented as mean ± SD (n = 6) and were analyzed using an ANOVA followed by Tukeys post hoc test at p < 0.05, where $^{\alpha}P<0.001$, $^{\beta}P<0.01$ vs picrotoxine. $^{a}P<0.001$, vs Diazepam

more prominent peak appeared at 96.78°C. This could be due to the formation of an intermediate complex developed by quaternary ammonium ion in lecithin and long-chain fatty acid of glyceryl monostearate.[18,19]

Pharmacological Effect of PRI-SLN

Evaluation of the anticonvulsant activity

Development of picrotoxin-induced seizures is slower. Figure 6 illustrates how the produced PRI-SLN was discovered to successfully counteract picrotoxine's lethality. According to the findings depicted in Figure 7, the time-to-death estimate for the PRI-SLN group was substantially longer than the estimate for the picrotoxin groups. The time to death was discovered to be 400 ± 2.48, 3925 ± 140.71, and 2951 ± 244.95, respectively, for the picrotoxine, diazepam, and PRI-SLN high dosage groups, p <0.05. The continuous drug release from the SLN and the improved absorption of the produced PRI-SLN may be responsible for the prolonged anticonvulsant effect.[2,17]

As shown in Figure 8, the seizure score for the Picrotoxine group is 3.75 ± 0.35, the seizure score for the PRI-SLN of low, medium and high doses were 2.35 ± 0.07, 2.15 ± 0.08, and 1.9 ± 0.14 correspondingly, which is suggestively lower than that of the picrotoxine group. These outcomes might be attributable to the nanoparticles' smaller size and distinctive properties as compared to the drug's conventional form. Because of their nano size, nanoparticles can change their physicochemical characteristics and have greater permeability through biological membranes.

CONCLUSION

The present work successfully loaded primidone into rationally designed lipid-based nanovesicles. The microemulsification and ultrasonication process was used to formulate 17 different PRI-SLN formulations (F1–F17). Formulations with high glyceryl monostearate (50%) content were discovered to have high EE. SEM study revealed the appearances and surface of optimized SLN are symmetrical in nature. According to the *in-vitro* release study, PRI from SLNs releases more slowly than PRI by itself. The thermal analysis showed the drug's compatibility with other substances and its presence in the more soluble amorphous state. PRI-SLN exhibited a higher anticonvulsant efficacy, conferring to *in-vivo* research on rats (p< 0.05).SLN with stronger anticonvulsant action can be made from PRI.

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