RESEARCH PAPER

Formulation, Optimization, and In Vitro Evaluation of Brivaracetam-Loaded Solid Lipid Nanoparticlesusing Box–Behnken Design for Brain-Targeted Drug Delivery

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ABSTRACT
Brivaracetam is a hydrophilic antiepileptic drug with limited brain bioavailability due to poor permeability across the blood–brain barrier (BBB) and rapid systemic clearance. Solid lipid nanoparticles (SLNs) offer a promising strategy to enhance brain targeting by improving drug encapsulation, reducing particle size, and facilitating uptake. This study aimed to formulate, optimize, and evaluate Brivaracetam-loaded SLNs using a Box–Behnken experimental design for brain-targeted delivery.
SLNs were prepared by the solvent emulsification diffusion method. A three-factor, three-level Box–Behnken design was employed to investigate the influence of Compritol® 888 ATO, Precirol® ATO 5, and polyvinyl alcohol (PVA) on critical quality attributes. Entrapment efficiency, particle size, and zeta potential were selected as dependent responses. Drug–excipient compatibility was evaluated using Fourier Transform Infrared (FTIR) spectroscopy, and surface morphology was examined by Field Emission Scanning Electron Microscopy (FESEM). In-vitro characterization included particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, and drug release studies.
The optimized SLNs showed high entrapment efficiency (93–98%), particle size in the nanometric range (734–1189 nm), and negative zeta potential (−19.5 to −31 mV), indicating good stability. Statistical analysis revealed that lipid and surfactant concentrations significantly influenced particle size and entrapment efficiency. FTIR results confirmed drug–excipient compatibility, while FESEM images showed spherical nanoparticles with smooth surfaces. The formulations exhibited controlled drug release behavior.
Overall, Brivaracetam -loaded SLNs demonstrated favorable physicochemical properties and sustained release, indicating their potential for effective brain-targeted drug delivery.
Keywords: Brivaracetam, Solid Lipid Nanoparticles, Box–Behnken design, Field emission Scanning Electron Microscopy,
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INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, requiring long-term pharmacotherapy for effective management. However, successful treatment is often limited by inadequate drug delivery to the brain due to the presence of the blood–brain barrier (BBB), a highly selective barrier that restricts the entry of many therapeutic agents. Hydrophilic drugs, in particular, exhibit poor permeability across the BBB, resulting in reduced brain bioavailability and compromised therapeutic efficacy.

Brivaracetam is a second-generation antiepileptic drug that selectively binds to synaptic vesicle protein 2A (SV2A), offering improved seizure control. Despite its pharmacological advantages, Brivaracetam shows limited brain targeting due to its hydrophilic nature and rapid systemic clearance. These challenges necessitate the development of advanced drug delivery systems to enhance its transport across the BBB and maintain sustained drug levels in the brain.

Nanotechnology-based carriers, particularly solid lipid nanoparticles (SLNs), have emerged as promising systems for brain-targeted drug delivery. SLNs are composed of physiologically compatible lipids that remain solid at body temperature, providing a stable matrix for drug incorporation. They offer several advantages, including

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improved drug stability, controlled release, enhanced permeability, and reduced toxicity. Their nanoscale size and surface characteristics facilitate uptake via endocytosis, thereby improving drug delivery to the brain.

The physicochemical properties of SLNs, such as particle size, zeta potential, and entrapment efficiency, are significantly influenced by formulation variables like lipid concentration and surfactant levels. Therefore, systematic optimization is essential for developing an efficient formulation. The Box–Behnken design (BBD), a response surface methodology, is widely used to evaluate the effects of multiple variables and their interactions with a reduced number of experimental runs.

MATERIALS

Brivaracetam was obtained from Yarrow Chemicals (Mumbai, India). Precirol ATO5, Compritol® 888 ATO, Polyvinyl Alcohol were procured from sigma Aldrich (Bangalore, India). All reagents were of analytical grade and used as received without further purification.

Drug and Excipient compatibility studies by FTIR

FTIR analysis was performed using the KBr pellet method by scanning samples in the range of 4000–400 cm^{-1}. The spectra of drug, excipients, and formulation were compared to identify any possible interactions.

Formulation Of Brivaracetam Solid Lipid Nanoparticles By Solvent Emulsion- Diffusion Method:

Weighed required quantity of drug and lipids and dissolved in O organic solvent (DCM) at 80 C in water bath. Prepare aqueous solution containing (polyvinyl alcohol), Tween 80, and PEG- 400 and continuous stirring for 90minutes at room temperature and emulsion is formed.Organic solvent containing drug and lipid was injected in to the aqueous phase drop by drop and stir continuously at 500 RPM and white milky suspension was formed. The formed suspension was dried for further process

Entrapment Efficiency (EE%)

Entrapment efficiency of Brivaracetam solid lipid nanoparticles is determined by an indirect method using centrifugation or ultrafiltration. A known quantity of SLN dispersion is taken and centrifuged at 10,000–15,000 rpm for about 30–45 minutes to separate the free drug from the nanoparticle-bound drug. The supernatant containing the unentrapped drug is carefully collected and analyzed using a UV spectrophotometer wavelength. The entrapment efficiency is then calculated by subtracting the amount of free drug from the total drug used and expressing it as a percentage. This parameter indicates the drug loading capacity and efficiency of the formulation.

Particle Size, Polydispersity Index (PDI) and Zeta Potential

The particle size, PDI, and zeta potential of Brivaracetam SLNs are measured using a Zetasizer based on dynamic light scattering and electrophoretic mobility principles. The SLN dispersion is suitably diluted with distilled water to avoid multiple scattering effects and then placed in a cuvette or capillary cell. The instrument measures the average particle size in nanometers, PDI indicating size distribution, and zeta potential representing surface charge. A PDI value below 0.3 indicates uniform distribution, while zeta potential values greater than ±30 mV suggest good stability of the nanoparticle system.

Surface Morphology (FESEM)

Surface morphology of the prepared SLNs is examined using Field Emission Scanning Electron Microscopy (FESEM). A small amount of nanoparticle dispersion is placed on a metallic stub and allowed to dry under vacuum or in a desiccator. The sample is then coated with a thin layer of gold or palladium to enhance conductivity. The prepared sample is scanned under FESEM at an appropriate accelerating voltage. The obtained images provide information about the shape, size, and surface characteristics of the nanoparticles, which are typically expected to be spherical with a smooth surface.

In-vitro Diffusion Study

The in-vitro diffusion study of Brivaracetam SLNs is carried out using a Franz diffusion cell or dialysis bag method. In the dialysis method, the SLN formulation is placed inside a pre-soaked dialysis membrane, which is then immersed in a receptor compartment containing phosphate buffer pH 7.4. The system is maintained at 37 ± 0.5°C with continuous stirring to simulate physiological conditions. At predetermined time intervals, samples are withdrawn from the receptor compartment and replaced with fresh buffer to maintain sink conditions. The collected samples are analyzed using a UV spectrophotometer, and the cumulative percentage of drug release is calculated over time to assess the release profile.

Drug Release Kinetics

The release kinetics of Brivaracetam from SLNs are evaluated by fitting the in-vitro diffusion data into various mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The cumulative drug release data is plotted against time according to each model, and the correlation coefficient (R^2) is determined. The model with the highest R^2 value is considered the best fit, indicating the mechanism of drug release. The release exponent (n) from the Korsmeyer–Peppas model is used to interpret the mechanism, where values indicate Fickian diffusion, non-Fickian transport, or case-II transport. This analysis helps in understanding and optimizing the controlled release behavior of the formulation.

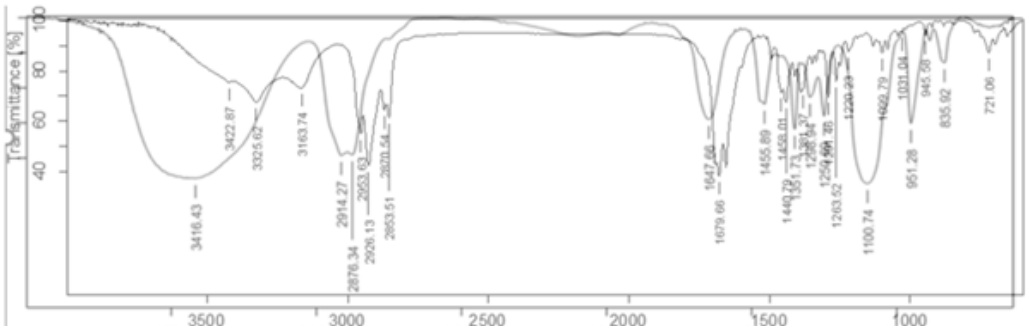

Fig:1 a) FTIR spectra of Brivaracetam pure drug,b) FTIR spectra of Brivaracetam solid Lipid Nanoparticle

The FTIR spectra of Brivaracetam (a) and Brivaracetam-loaded solid lipid nanoparticles (b) were compared to evaluate possible drug–excipient interactions. The characteristic peaks of Brivaracetam were observed at around 3422 cm^{-1} (N–H stretching), 2950–2850 cm^{-1} (C–H stretching), and 1679 cm^{-1} (C=O stretching), along with other fingerprint region peaks. In the SLN formulation, these प्रमुख peaks were retained with slight shifts and minor changes in intensity, which may be attributed to physical interactions or encapsulation within the lipid matrix. Importantly, no significant disappearance or formation of new peaks was observed, indicating the absence of chemical interaction between the drug and excipients. Thus, the FTIR results confirm that Brivaracetam remains chemically stable and compatible within the solid lipid nanoparticle formulation.

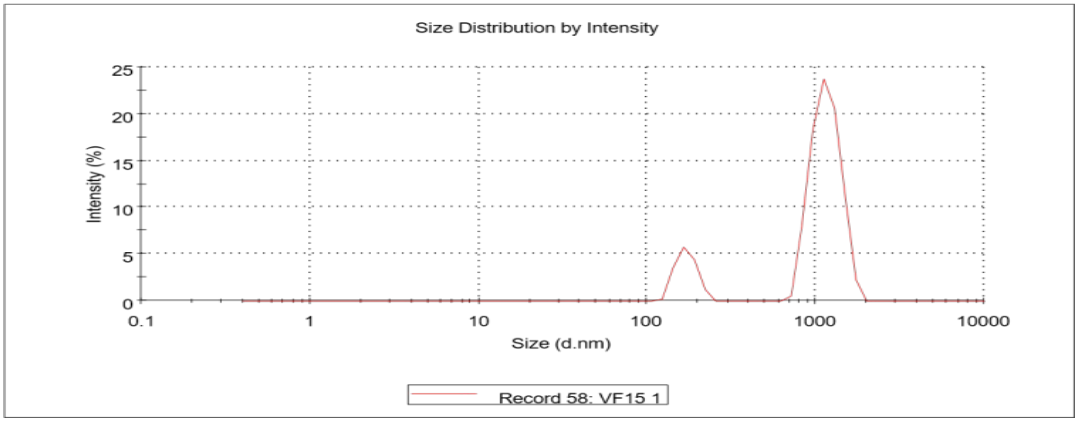

Fig 2a: Particle size of F15 formulation

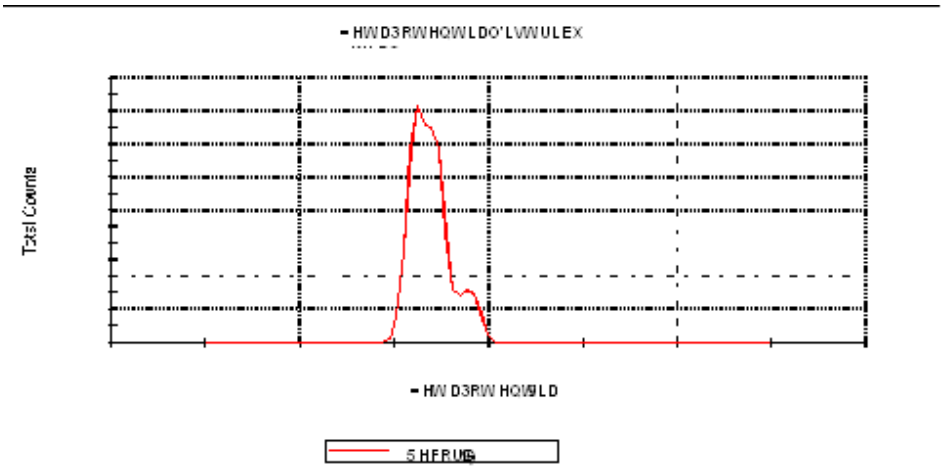

Fig 2b: Zeta Potential of F15 formulation

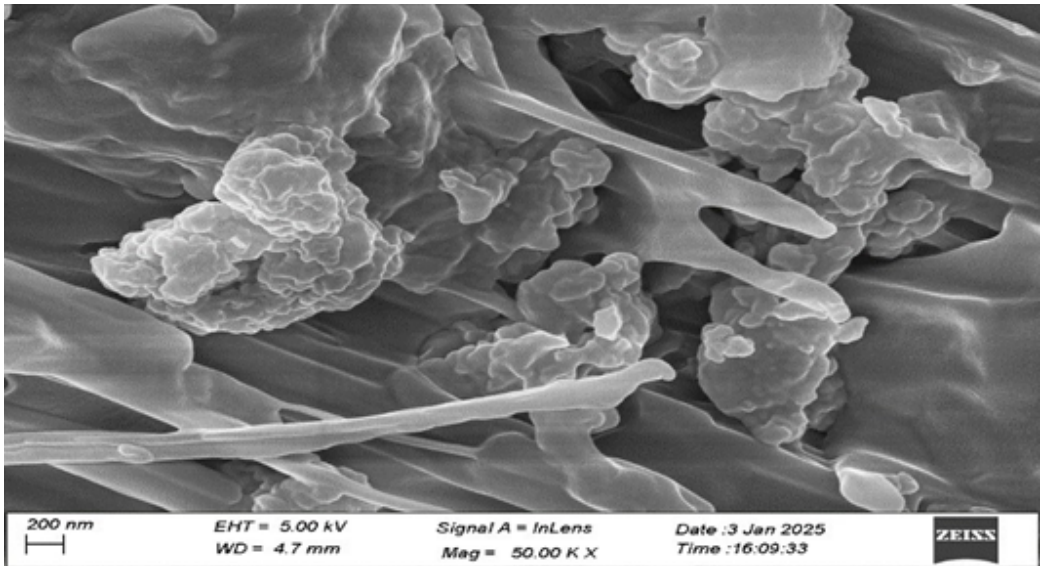

Fig: 3. Field Emission Scanning electron microscopy of F14

FESEM images show the surface morphology and particle characteristics of the slns formulation. Particles are spherical to irregular in shape. Surface texture presents both smooth and slightly rough regions, which may give evidence of successful encapsulation of active components. The size distribution appears fairly uniform. Images thus prove the nanoscale structure of the slns further supporting their suitability for enhanced drug delivery applications.

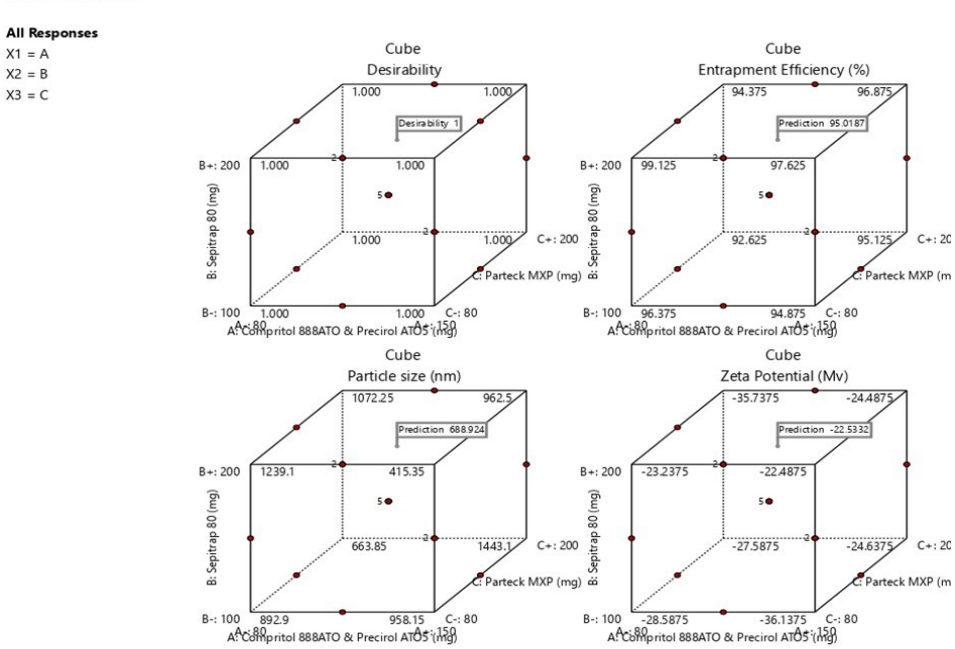

Fig :4 Desirability graph of all responses Entrapment efficiency, Particle size, Zetapotential

The desirability plot indicates that the optimized formulation achieved a maximum desirability value of 1.000, confirming the suitability of the selected factor levels for achieving the desired responses. The entrapment efficiency plot shows a predicted value of approximately 95.01%, demonstrating high drug incorporation within the SLNs. The response surface suggests that the independent variables significantly influence the entrapment efficiency. Overall, the optimization results confirm that the formulation variables were effectively tuned to obtain an optimal and stable nanoparticle system.

Table:1 *in vitro* Drug release kinetics of optimized formulation

Formulation code	Zero order		First order		Higuchi model		Korsmeyerpeppas		Release Mechanism transport
	Slope	R^2	Slope	R2	Slope	R^2	N	R^2	Non-fickian
F14	8.033	0.997	0.069	0.939	22.93	0.975	0.834	0.993	transport mechanism

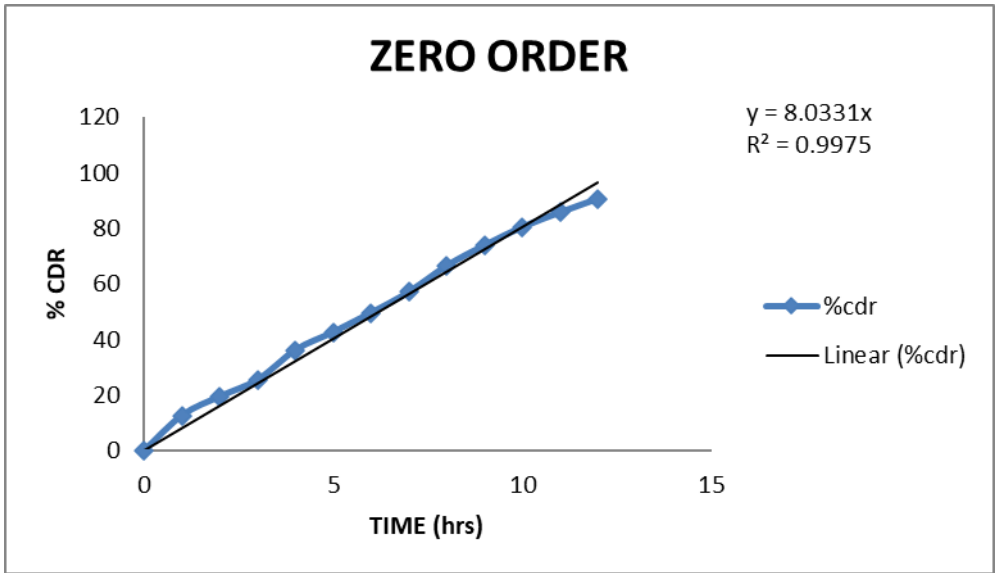

Fig: 5a) Zero order kinetics of optimized formulation

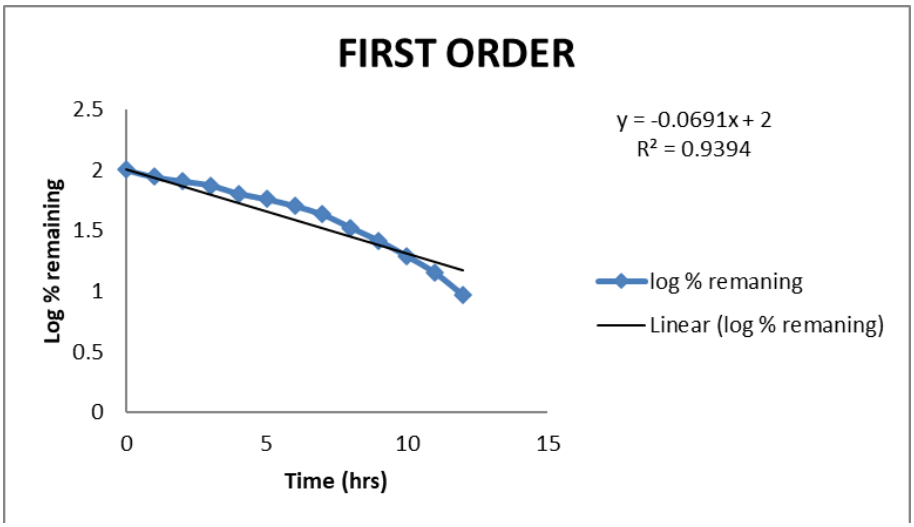

Fig: 5b) First order kinetics for optimized formulation

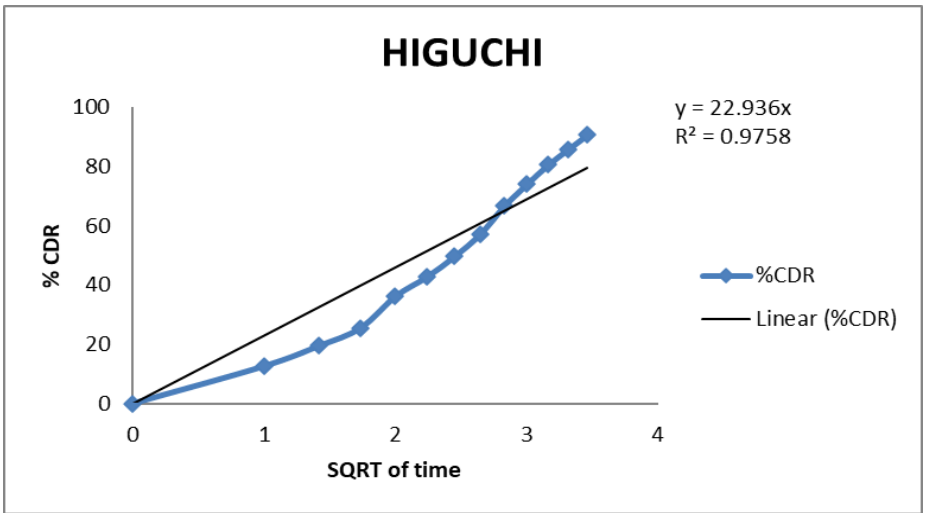

Fig: 5c). Higuchi model of optimized formulation

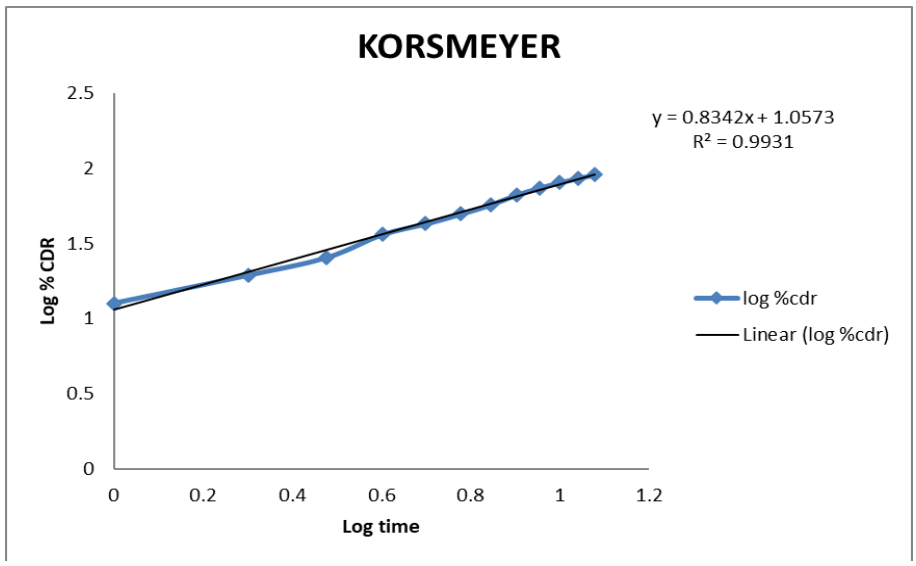

Fig: 5d). Korsmeyer-peppas model of optimized formulation Validation of

DISCUSSION

Brivaracetam-loaded solid lipid nanoparticles (SLNs) were successfully developed using the solvent emulsification–diffusion method with Compritol and Precirol as lipids, Tween 80 as surfactant, and PVA as stabilizing polymer. The calibration curve of Brivaracetam in pH 6.8 phosphate buffer showed good linearity between concentration and absorbance, with an R^2 value of 0.9961, confirming adherence to Beer–Lambert's law.

FTIR analysis confirmed the presence of characteristic functional groups of Brivaracetam, including O–H, N–H, C–H, and C=O stretching vibrations. The spectra of excipients (Compritol, Precirol, Tween 80, and PVA) showed corresponding peaks without significant shifts or disappearance, indicating no chemical interaction and good compatibility between drug and excipients. Minor shifts observed in thermograms further supported compatibility.

The prepared formulations were evaluated for entrapment efficiency (EE), particle size, and zeta potential. Among all formulations, F14 exhibited the highest entrapment efficiency (97%) with acceptable particle size and zeta potential. In vitro drug release studies over 12 hours revealed that F14 showed maximum drug release (90.06%), following a non-Fickian (anomalous) diffusion mechanism. Another formulation, F16, showed 77.65% drug release, also following non-Fickian transport.

Optimization was carried out using Design-Expert software (Version 13.0.5.0), where responses were fitted into quadratic and linear models. Various statistical plots (normal, predicted vs. actual, contour, and 3D plots) confirmed model suitability. By applying constraints on formulation variables, the optimized formulation was obtained containing lipid (150 mg), Sepitrap (150 mg), and PVA (150 mg).

The optimized formulation demonstrated desirable physicochemical properties with 94% entrapment efficiency, particle size of 68 nm, and drug release of 90.06%. The experimental values were in close agreement with predicted values, with minimal relative error,

confirming the validity and reliability of the optimization model.

CONCLUSION

The study successfully developed and optimized Brivaracetam-loaded SLNs with high entrapment efficiency, nanoscale particle size, and controlled drug release, making them a promising system for improved drug delivery.

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