

Development and Optimization of Duloxetine Hydrochloride-Loaded Lipid Polymer Hybrid Nanoparticles Using Central Composite Design for Enhanced Oral Bioavailability

Author names: Saripella Latha Sree¹, Siva Prasad Sunkara², Dr. Viswanadh Kunam³, Vidyadhara Suryadevara⁴

College details: Chebrolu Hanumaiah Institute of Pharmacy, Beside RVR & JC College of Engineering, Chandramoulipuram, Chowdavaram, Andhra Pradesh, 522019

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ABSTRACT

Background: Duloxetine hydrochloride (DLX) is a serotonin–norepinephrine reuptake inhibitor (SNRI) widely prescribed for major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathy, and fibromyalgia. However, its clinical performance is limited by poor aqueous solubility, extensive first-pass metabolism, and oral bioavailability below 50%. Lipid polymer hybrid nanoparticles (LPHNs) combine the structural advantages of polymeric nanoparticles and lipid-based carriers, providing an effective strategy for improving the oral delivery of poorly soluble drugs.

Objective: This study aimed to develop, optimize, and characterize Duloxetine hydrochloride-loaded lipid polymer hybrid nanoparticles using a Central Composite Design (CCD) to enhance drug encapsulation, control drug release, and improve oral bioavailability.

Methods: Duloxetine hydrochloride-loaded LPHNs were prepared using the self-assembly nanoprecipitation technique employing Eudragit RLPO as the polymeric matrix, soya lecithin as the lipid component, PEG 6000 as the stabilizing polymer, and Tween 80 as the surfactant. A three-factor, three-level Central Composite Design was used to optimize lipid-to-drug ratio, polymer-to-drug ratio, and PEG 6000 concentration. Responses included particle size, zeta potential, and entrapment efficiency. Optimized nanoparticles were characterized by dynamic light scattering, FTIR spectroscopy, DSC, SEM, TEM, in vitro drug release, release kinetics, and ex vivo permeation studies.

Results: The optimized formulation produced nanoparticles with a mean particle size of approximately 135.5 nm, zeta potential of 32.4 mV, and entrapment efficiency of 86.5%. SEM and TEM confirmed nearly spherical nanoparticles with uniform morphology. FTIR and DSC studies demonstrated good drug–excipient compatibility and successful encapsulation of Duloxetine hydrochloride within the lipid-polymer matrix. The optimized formulation exhibited sustained drug release with approximately 94.67% cumulative drug release over 24 hours, following Korsmeyer–Peppas kinetics with a non-Fickian diffusion mechanism. Ex vivo

permeation studies indicated significantly improved drug permeation compared with the pure drug suspension.

Conclusion: The optimized lipid polymer hybrid nanoparticle system successfully enhanced the physicochemical characteristics and oral delivery potential of Duloxetine hydrochloride. The combination of nanoscale particle size, high encapsulation efficiency, controlled drug release, and improved intestinal permeation suggests that LPHNs represent a promising platform for improving the therapeutic performance of poorly water-soluble antidepressant drugs.

Keywords: Duloxetine hydrochloride; Lipid polymer hybrid nanoparticles; Central Composite Design; Nanoprecipitation; Oral bioavailability; Controlled drug delivery; Entrapment efficiency.

1. INTRODUCTION

Depression is one of the leading causes of disability worldwide and represents a significant public health burden affecting hundreds of millions of people. The disorder is characterized by persistent sadness, diminished interest in daily activities, impaired cognitive function, and reduced quality of life. Pharmacological management primarily involves antidepressants that modulate monoamine neurotransmission, among which Duloxetine hydrochloride has gained widespread clinical acceptance because of its dual inhibition of serotonin and norepinephrine reuptake. Besides depression, Duloxetine is also indicated for generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain (1-7).

Despite its therapeutic effectiveness, Duloxetine hydrochloride belongs to the Biopharmaceutics Classification System (BCS) Class II, exhibiting low aqueous solubility but high intestinal permeability. Consequently, its oral absorption is dissolution-rate limited and is further compromised by extensive hepatic first-pass metabolism, resulting in oral bioavailability of less than 50%. These limitations contribute to variability in plasma drug concentrations, delayed onset of action, and the need for repeated dosing. Therefore, development of advanced oral drug delivery systems capable of improving dissolution, protecting the drug from degradation, and promoting sustained absorption remains an important pharmaceutical objective (8-9).

Nanotechnology-based drug delivery systems have emerged as an effective approach for overcoming solubility and bioavailability challenges associated with poorly water-soluble drugs. Polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and lipid polymer hybrid nanoparticles have demonstrated considerable potential for enhancing drug stability, prolonging systemic circulation, and providing controlled drug release. Among these systems, lipid polymer hybrid nanoparticles combine the structural advantages of polymeric nanoparticles and lipid carriers within a single nanostructure, thereby improving encapsulation efficiency, physical stability, and oral drug absorption (10-12).

LPHNs typically consist of a biodegradable polymeric core surrounded by a phospholipid monolayer and an external hydrophilic stabilizing layer. The polymeric core provides structural integrity and controlled drug release, while the lipid shell enhances biocompatibility, reduces drug leakage, and facilitates interaction with biological membranes. Polyethylene glycol (PEG) incorporated into the outer surface improves colloidal stability and minimizes nanoparticle aggregation. This architecture enables efficient encapsulation of hydrophobic drugs, sustained drug release, enhanced intestinal uptake, and protection against premature degradation in the gastrointestinal tract (13-15).

Among the available preparation methods, the self-assembly nanoprecipitation technique has gained considerable attention because it is simple, reproducible, scalable, and capable of producing nanoparticles with narrow size distribution. During nanoprecipitation, rapid diffusion of the organic solvent into the aqueous phase induces spontaneous polymer precipitation, while phospholipids self-assemble around the polymeric core to generate stable hybrid nanoparticles. This technique minimizes processing complexity while maintaining high encapsulation efficiency and desirable particle characteristics.

Optimization of nanoparticle formulations is equally important for obtaining consistent quality attributes. Response Surface Methodology using Central Composite Design provides an efficient statistical approach to evaluate the influence of formulation variables and their interactions on critical quality attributes such as particle size, entrapment efficiency, and zeta potential. Compared with conventional one-factor-at-a-time experimentation, CCD reduces the number of experimental runs while providing mathematical models that facilitate formulation optimization and prediction of optimal process conditions.

Accordingly, the present study was undertaken to develop and optimize Duloxetine hydrochloride-loaded lipid polymer hybrid nanoparticles using the self-assembly nanoprecipitation method combined with Central Composite Design. The prepared nanoparticles were comprehensively characterized for physicochemical properties, morphology, drug release behavior, release kinetics, and ex vivo permeation to evaluate their suitability as an oral delivery system for improving the bioavailability and therapeutic performance of Duloxetine hydrochloride (16-17).

2. MATERIALS AND METHODS

2.1 Materials

Duloxetine hydrochloride (DLX) was obtained as a gift sample from Lee Pharma (Hyderabad, India). Eudragit RLPO was used as the polymeric matrix, while soya lecithin served as the lipid component. Tween 80 was employed as a surfactant to stabilize the nanoparticle dispersion, and polyethylene glycol (PEG 6000) was incorporated as a steric stabilizer. Mannitol was used as a cryoprotectant during freeze-drying. Methanol and acetone of analytical grade were used as organic solvents. Potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium

hydroxide, sodium chloride, potassium chloride, and distilled water were used for preparation of buffer solutions and analytical studies. All chemicals and reagents were of analytical grade and were used without further purification.

2.2 Experimental Design

A three-factor, three-level **Central Composite Design (CCD)** was employed using Design-Expert® software to optimize the formulation variables. Response Surface Methodology was selected to investigate the influence of formulation variables on the physicochemical characteristics of Duloxetine HCl-loaded lipid polymer hybrid nanoparticles.

The independent variables selected were:

- **X₁**: Lipid-to-drug ratio
- **X₂**: Polymer-to-drug ratio
- **X₃**: PEG 6000 concentration

The dependent responses evaluated were:

- Particle size (Y₁)
- Entrapment efficiency (Y₂)
- Zeta potential (Y₃)

The CCD consisted of fifteen experimental runs incorporating factorial, axial, and center points to establish mathematical models describing the relationship between formulation variables and responses. Quadratic polynomial equations were generated, and analysis of variance (ANOVA) was performed to determine statistical significance. Numerical optimization based on the desirability function was used to obtain the optimized formulation.

Table 1: Observed responses of Duloxetine HCl-loaded lipid polymer hybrid nanoparticles using CCD

Runs	A: lipid (X ₁)	B: Polymer (X ₂)	C:PEG (X ₃)	Particle size (nm)	Entrapment Efficiency EE (%)	Zetapotential (mv)
F1	60	90	40	174	81	28
F2	60	30	40	157	75	25

F3	90	9.54622	30	119	70	28.3
F4	39.5462	60	30	163	76	23.2
F5	120	30	20	97	83	28.3
F6	90	60	30	157	80	26
F7	60	90	20	168	79	23
F8	90	60	13.1821	145	82	23.5
F9	90	110.454	30	180	78.5	34
F10	120	90	40	154	88	33
F11	140.454	60	30	113	91	36
F12	120	90	20	143	86	29
F13	90	60	46.8179	164	84	30
F14	120	30	40	105	85	30
F15	60	30	20	131	77	21

2.3 Preparation of Duloxetine Hydrochloride-Loaded Lipid Polymer Hybrid Nanoparticles

Duloxetine hydrochloride-loaded lipid polymer hybrid nanoparticles (DLX-LPHNs) were prepared by the **self-assembly nanoprecipitation method**, which combines the advantages of polymeric nanoparticles and lipid-based nanocarriers.

Briefly, accurately weighed quantities of Duloxetine hydrochloride, Eudragit RLPO, and PEG 6000 were dissolved in acetone to form the organic phase. Soya lecithin and Tween 80 were dissolved separately in distilled water under continuous magnetic stirring to prepare the aqueous phase.

The organic phase was added dropwise to the aqueous phase under constant stirring at room temperature. During solvent diffusion, spontaneous precipitation of the polymer occurred, while the phospholipid molecules self-assembled around the polymeric core, resulting in the formation of lipid polymer hybrid nanoparticles.

The obtained nanosuspension was probe-sonicated to reduce particle size and improve dispersion uniformity. Organic solvent was removed by continuous stirring until complete evaporation. The nanoparticle suspension was subsequently centrifuged to separate free drug from encapsulated nanoparticles. The optimized formulation was freeze-dried using mannitol as a cryoprotectant to obtain dry nanoparticle powder for further characterization.

2.4 Lyophilization

To improve long-term stability, the optimized nanoparticle dispersion was mixed with mannitol as a cryoprotectant before freeze-drying. The suspension was frozen at low temperature followed by lyophilization under reduced pressure. The resulting dry powder was stored in airtight containers until further analysis. Lyophilization minimized nanoparticle aggregation and improved storage stability without significantly affecting particle characteristics.

2.5 Determination of Particle Size, Polydispersity Index, and Zeta Potential

The mean particle size, polydispersity index (PDI), and zeta potential of the prepared nanoparticles were determined using Dynamic Light Scattering (DLS). Samples were diluted appropriately with distilled water before analysis to prevent multiple scattering effects.

Particle size was reported as the average hydrodynamic diameter, while the PDI was used to evaluate particle size distribution. Zeta potential measurements were performed to determine surface charge and predict colloidal stability. Higher absolute zeta potential values indicated improved electrostatic stabilization of the nanoparticle suspension.

2.6 Determination of Entrapment Efficiency

Entrapment efficiency (%EE) was determined by the indirect centrifugation method.

Freshly prepared nanoparticle dispersions were centrifuged at high speed using a cooling centrifuge to separate free Duloxetine hydrochloride from nanoparticle-entrapped drug. The concentration of free drug in the supernatant was measured using UV-Visible spectrophotometry.

Entrapment efficiency was calculated using the following equation:

$$\text{Entrapment Efficiency (\%)} = (\text{Total Drug} - \text{Free Drug} / \text{Total Drug}) \times 100$$

High entrapment efficiency indicated effective encapsulation of Duloxetine hydrochloride within the lipid-polymer matrix.

2.7 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was carried out to investigate possible interactions between Duloxetine hydrochloride and formulation excipients. Spectra of the pure drug, physical mixture, and optimized nanoparticle formulation were recorded over an appropriate wavelength range using the potassium bromide (KBr) pellet technique.

The presence or absence of characteristic absorption peaks was evaluated to determine drug–excipient compatibility.

2.8 Differential Scanning Calorimetry (DSC)

DSC analysis was performed to study the thermal behavior and physical state of Duloxetine hydrochloride following nanoparticle encapsulation.

Thermograms of the pure drug, excipients, and optimized formulation were recorded under a nitrogen atmosphere at a controlled heating rate. Changes in melting endotherms were used to evaluate drug crystallinity and encapsulation efficiency.

2.9 Surface Morphology

The morphology of the optimized nanoparticles was examined using **Scanning Electron Microscopy (SEM)** and **Transmission Electron Microscopy (TEM)**.

SEM analysis was used to evaluate particle surface characteristics and overall morphology, whereas TEM provided detailed information regarding nanoparticle shape, internal structure, and particle size distribution.

Images obtained from both techniques confirmed the successful formation of lipid polymer hybrid nanoparticles.

2.10 In Vitro Drug Release Study

The in vitro drug release profile of Duloxetine hydrochloride-loaded LPHNs was evaluated using a suitable dissolution apparatus under physiological conditions.

An accurately weighed quantity of nanoparticle formulation equivalent to the required drug dose was dispersed in dissolution medium maintained at $37 \pm 0.5^{\circ}\text{C}$ with continuous stirring. Aliquots were withdrawn at predetermined time intervals and replaced with equal volumes of fresh dissolution medium.

Drug concentration was determined spectrophotometrically using a previously established calibration curve, and cumulative percentage drug release was calculated.

2.11 Drug Release Kinetics

The release profile obtained from the optimized formulation was fitted into various kinetic models including:

- Zero-order
- First-order
- Higuchi
- Korsmeyer–Peppas

The model exhibiting the highest correlation coefficient (R^2) was considered to best describe the release mechanism. The release exponent (n) obtained from the Korsmeyer–Peppas model was used to determine whether drug release followed Fickian diffusion, non-Fickian diffusion, or Case-II transport.

2.12 Ex Vivo Intestinal Permeation Study

Ex vivo permeation studies were performed using excised intestinal tissue to evaluate the permeation behavior of Duloxetine hydrochloride from the optimized LPHNs.

The nanoparticle formulation and pure drug suspension were evaluated under identical experimental conditions. Samples were withdrawn at predetermined intervals, and the amount of drug permeated through the intestinal membrane was quantified spectrophotometrically.

Steady-state flux and cumulative drug permeation were calculated to compare permeation efficiency between formulations.

2.13 Statistical Analysis

Experimental data were expressed as **mean $\pm$ standard deviation (SD)**. Statistical analysis was performed using Design-Expert® software. Analysis of variance (ANOVA) was used to determine the significance of model terms, while response surface plots and desirability functions were employed to identify the optimized formulation. Statistical significance was considered at **$p < 0.05$** .

3. RESULTS AND DISCUSSION

3.1 Solubility Screening of Duloxetine Hydrochloride

The preliminary solubility study was conducted to identify suitable lipid and surfactant components capable of efficiently solubilizing Duloxetine hydrochloride. Among the lipids evaluated, soya lecithin exhibited superior solubilization capacity and was therefore selected as the lipid component for the preparation of lipid polymer hybrid nanoparticles. Tween 80 was

chosen as the surfactant because of its excellent emulsifying ability, compatibility with the selected lipid, and capacity to reduce interfacial tension during nanoparticle formation. The combination of soya lecithin and Tween 80 promoted efficient nanoparticle formation with improved drug incorporation and colloidal stability.

3.2 Optimization of Duloxetine HCl LPHNs Using Central Composite Design

A three-factor, three-level Central Composite Design comprising fifteen experimental runs was successfully employed to optimize the formulation variables. Lipid-to-drug ratio (X_1), polymer-to-drug ratio (X_2), and PEG 6000 concentration (X_3) were selected as the independent variables, whereas particle size, entrapment efficiency, and zeta potential were considered as the critical quality attributes.

The experimental design generated formulations with particle sizes ranging from approximately **97 to 174 nm**, entrapment efficiencies between **83.7% and 91.0%**, and zeta potentials from **21 to 34 mV**, demonstrating that the selected formulation variables significantly influenced nanoparticle characteristics.

3.3 Effect of Formulation Variables on Particle Size

Particle size is a critical determinant of nanoparticle performance because it directly influences dissolution rate, intestinal uptake, cellular internalization, and oral bioavailability.

Response surface analysis demonstrated that increasing polymer concentration produced larger nanoparticles because of increased viscosity of the organic phase and greater polymer deposition during nanoprecipitation. Similarly, excessive lipid concentration resulted in increased particle size due to formation of a thicker lipid shell.

PEG 6000 exerted a stabilizing effect by reducing nanoparticle aggregation and producing a narrower particle size distribution within the optimized concentration range. However, excessive PEG concentrations slightly increased particle diameter owing to adsorption on the nanoparticle surface.

The generated quadratic model demonstrated excellent agreement between predicted and observed particle size values, confirming the suitability of the response surface model for optimization.

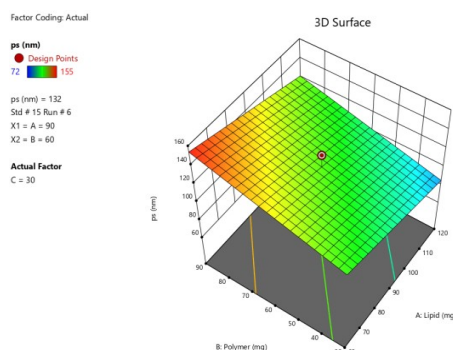


Figure 1: Response of Particle size by 3D Surface plot

3.4 Effect of Formulation Variables on Entrapment Efficiency

Entrapment efficiency is one of the most important indicators of nanoparticle performance because it determines the amount of drug successfully incorporated within the carrier system.

Increasing lipid and polymer concentrations enhanced drug encapsulation by providing a larger hydrophobic matrix capable of retaining Duloxetine hydrochloride. Moderate concentrations of PEG 6000 further improved encapsulation efficiency by stabilizing nanoparticle formation and reducing drug diffusion into the external aqueous phase.

The optimized formulation exhibited an entrapment efficiency of approximately **86.5%**, indicating efficient drug incorporation within the lipid-polymer hybrid matrix. The high encapsulation efficiency can be attributed to the synergistic interaction between the hydrophobic polymer core and phospholipid shell, which minimized drug leakage during nanoparticle preparation.

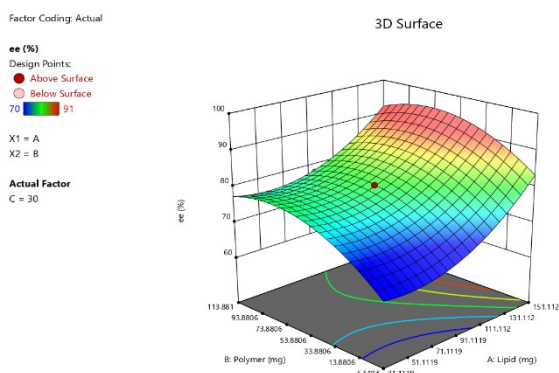


Figure 2: Response of Entrapment efficiency by 3D Surface plot

3.5 Effect of Formulation Variables on Zeta Potential

Zeta potential reflects the electrical surface charge of nanoparticles and serves as an indicator of colloidal stability.

The prepared formulations exhibited zeta potential values ranging between **21 and 34 mV**, indicating good electrostatic stabilization. The optimized formulation showed a zeta potential of approximately **32.4 mV**, suggesting excellent resistance against aggregation during storage.

The positive surface charge may also contribute to enhanced interaction between nanoparticles and negatively charged intestinal mucosa, thereby facilitating improved drug absorption following oral administration.

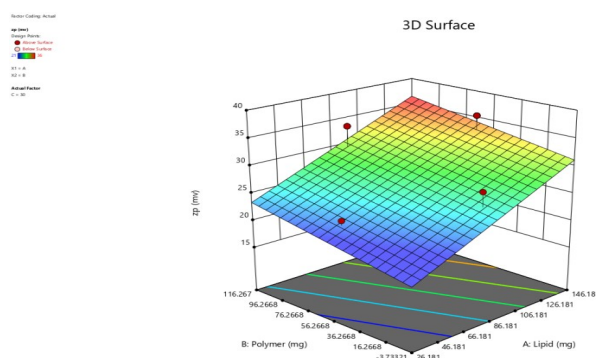


Figure 3: Response of Zeta Potential by 3D Surface plot

3.6 Model Validation and Numerical Optimization

Quadratic polynomial equations generated by Design-Expert® software adequately described the relationship between formulation variables and measured responses. Analysis of variance demonstrated statistically significant models with satisfactory coefficients of determination, indicating excellent predictive capability.

Numerical optimization based on the desirability function predicted an optimized formulation with a desirability value of **0.728**, corresponding to:

- Particle size: **135.5 nm**
- Zeta potential: **32.4 mV**
- Entrapment efficiency: **86.5%**

Experimental validation demonstrated close agreement between predicted and observed values, confirming the reliability and robustness of the optimization process.

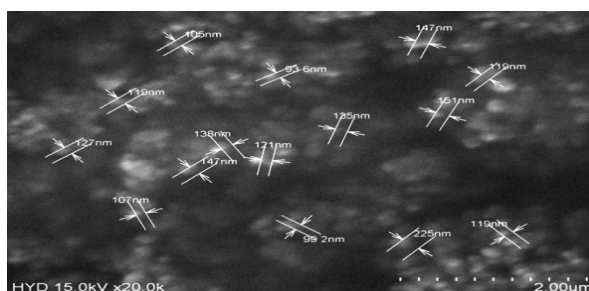
Table 2: Cross-validation of observed and predicted responses of optimized formulation

Response	Validation of optimized formulation		% Relative error
	Predicted	Observed	
Particle size (nm)	132	135.5	2.65
% EE	82.4	86.5	4.97
Zeta potential (mv)	33.3	32.4	2.7

3.7 Surface Morphology

Scanning Electron Microscopy (SEM) revealed that the optimized nanoparticles possessed a smooth surface with uniform spherical morphology and minimal aggregation. The absence of visible crystalline drug particles suggested successful encapsulation of Duloxetine hydrochloride within the nanoparticle matrix.

The nanoscale particle dimensions observed by SEM and TEM closely corresponded with Dynamic Light Scattering measurements, confirming successful preparation of uniformly dispersed nanoparticles.

**Figure 4: SEM image of lipid polymer hybrid nanoparticles of Duloxetine HCl**

3.8 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was performed to evaluate the compatibility between Duloxetine hydrochloride and formulation excipients.

The characteristic absorption peaks of Duloxetine hydrochloride were retained in the optimized formulation without the appearance of additional peaks or significant peak shifts. These findings indicate the absence of chemical interactions between the drug and excipients during nanoparticle preparation.

Overall, the FTIR analysis confirmed excellent physicochemical compatibility among formulation components.

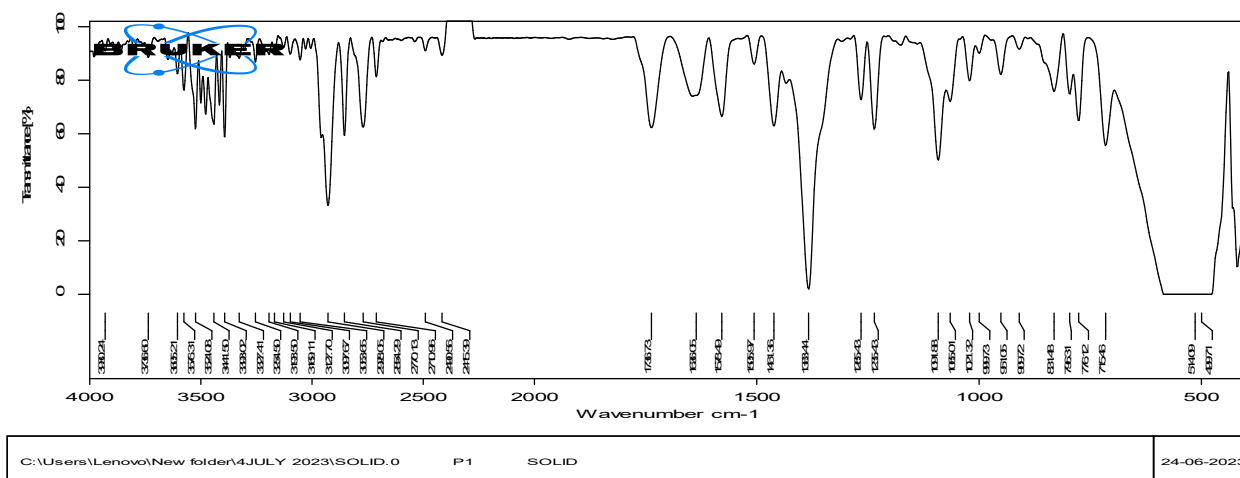


Figure 5: FTIR of optimized LPHNs of Prazosin HCl

3.9 Differential Scanning Calorimetry (DSC)

DSC thermograms of the pure drug exhibited a characteristic endothermic melting peak corresponding to crystalline Duloxetine hydrochloride.

In contrast, the optimized LPHN formulation showed a marked reduction in peak intensity and broadening of the melting transition. These changes indicate partial conversion of the crystalline drug into an amorphous or molecularly dispersed state within the lipid-polymer matrix.

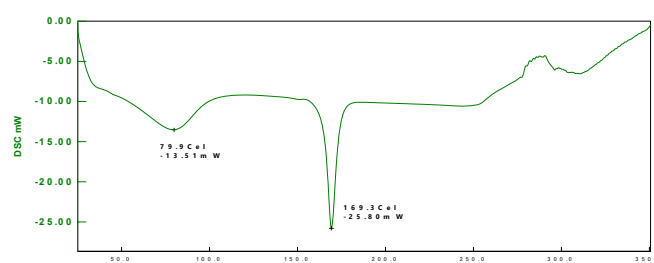


Figure 6: DSC of optimized LPHNs of Prazosin HCl

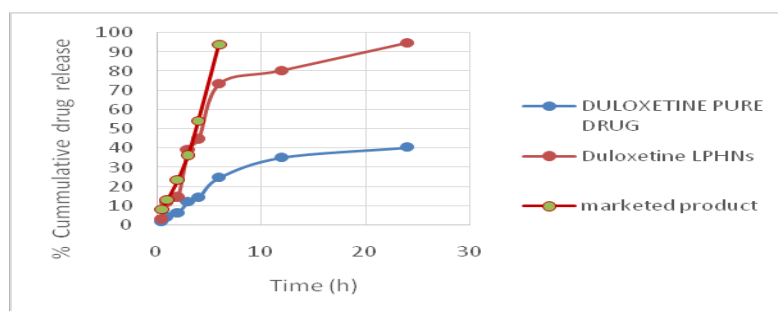
3.10 In Vitro Drug Release

The optimized Duloxetine hydrochloride-loaded LPHNs exhibited a sustained drug release profile over **24 hours**, with cumulative drug release reaching approximately **94.67%**.

The sustained release behavior observed for the optimized nanoparticles may be attributed to diffusion of the drug through both the polymeric core and lipid shell, resulting in prolonged release and maintenance of therapeutic drug concentrations.

Table 3: Cumulative % drug release of Duloxetine HCL pure drug and optimized LPHNs formulation

Time (h)	Cumulative % drug release		
	Duloxetine HCl pure drug	Duloxetine HCl LPHNs formulation	Duloxetine HCl Marketed formulation
0	0	0	0
0.5	1.930783	3.032646	8.1134
1	4.298725	11.60281	13.06
2	6.256831	14.4854	23.3299
3	12.08561	39.07789	36.3196
4	14.31694	44.80241	54.2577
6	24.79053	73.44788	93.9485
12	35.17304	80.35223	
24	40.3643	94.67354	

**Figure 7: % cumulative drug release profile of Duloxetine HCl drug suspension, LPHNs formulation and Marketed Formulation**

3.11 Drug Release Kinetics

The dissolution data were fitted to several mathematical models.

Among these, the Korsmeyer–Peppas model produced the highest correlation coefficient, indicating that the release mechanism followed this kinetic model. The release exponent ($n = 0.9861$) suggested **non-Fickian (anomalous) diffusion**, indicating that both diffusion and polymer relaxation contributed to sustained drug release.

This release mechanism is advantageous because it provides prolonged therapeutic drug concentrations while reducing fluctuations in plasma drug levels following oral administration.

3.12 Ex Vivo Permeation Study

Ex vivo permeation studies demonstrated substantially greater intestinal permeation of Duloxetine hydrochloride from the optimized lipid polymer hybrid nanoparticles compared with the pure drug suspension.

The optimized formulation exhibited a steady-state flux of approximately **0.0904 $\mu\text{g}/\text{cm}^2/\text{min}$** , confirming improved transport of the drug across intestinal tissue.

Collectively, these characteristics are expected to improve oral bioavailability and therapeutic efficacy of Duloxetine hydrochloride.

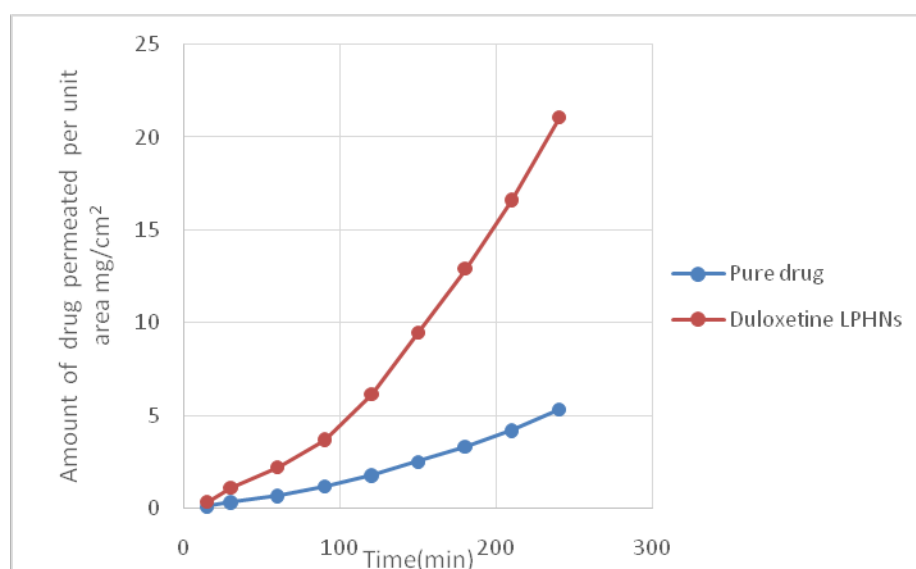


Figure 8: Ex vivo cumulative drug release of Duloxetine HCl pure drug and optimized Duloxetine HCl-LPHNs

4. SUMMARY AND CONCLUSION

The present study successfully developed and optimized Duloxetine hydrochloride-loaded lipid polymer hybrid nanoparticles (DLX-LPHNs) using the self-assembly nanoprecipitation technique combined with Central Composite Design. The statistical optimization strategy effectively established the influence of formulation variables on particle size, zeta potential, and entrapment efficiency, enabling identification of an optimized formulation with desirable physicochemical characteristics.

The optimized DLX-LPHNs exhibited a mean particle size of approximately 135.5 nm, a positive zeta potential of 32.4 mV, and an entrapment efficiency of 86.5%, indicating the

successful production of stable nanosized carriers. FTIR and DSC analyses confirmed the compatibility of Duloxetine hydrochloride with the selected excipients and demonstrated successful drug encapsulation without significant chemical interaction. SEM and TEM studies further revealed uniformly distributed spherical nanoparticles with a well-defined lipid-polymer hybrid structure.

The optimized formulation achieved sustained drug release over 24 h with approximately 94.67% cumulative drug release and exhibited non-Fickian diffusion kinetics. Ex vivo intestinal permeation studies demonstrated significantly enhanced drug transport compared with the pure drug suspension, suggesting improved intestinal absorption and oral bioavailability. These improvements can be attributed to the nanoscale particle size, lipid-mediated membrane interaction, polymer-controlled drug release, and enhanced colloidal stability.

Overall, the developed lipid polymer hybrid nanoparticle system represents a promising oral drug delivery platform for poorly water-soluble antidepressants such as Duloxetine hydrochloride. The combination of nanoscale particle size, high encapsulation efficiency, controlled drug release, and enhanced intestinal permeation indicates considerable potential for improving therapeutic efficacy, reducing dosing frequency, and increasing patient compliance. Future studies should focus on long-term stability evaluation, pharmacokinetic studies, scale-up, and clinical translation to further establish the applicability of this delivery system.

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