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Review

Design Evaluation and Optimization of Novel Lipid Based Nanostructured Formulations for Enhancement of Oral Bioavailability of Dolutegravir

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Abstract

The oral delivery of Dolutegravir is limited by poor aqueous solubility and variable bioavailability, reducing therapeutic efficacy in long-term antiretroviral therapy. This study aimed to design, evaluate, and optimize lipid-based nanostructured formulations to enhance the oral bioavailability of Dolutegravir. Dolutegravir-loaded nanostructured lipid carriers (DNLCs) were prepared using a modified emulsification–evaporation method followed by low-temperature solidification. Nine formulations (DNLC1–DNLC9) were developed by varying lipid and surfactant concentrations and characterized for particle size, zeta potential, entrapment efficiency, morphology, in vitro drug release, release kinetics, and stability. The DNLCs exhibited nanoscale particle size, good entrapment efficiency, and adequate surface charge, indicating colloidal stability. DNLC5 was identified as the optimized formulation, showing the smallest particle size (121 ± 8.14 nm), highest entrapment efficiency (88 ± 1.74%), and favorable zeta potential (–22.5 mV). SEM confirmed spherical, uniformly distributed nanoparticles with minimal aggregation. In vitro drug release studies demonstrated sustained release over 24 hours, with DNLC5 achieving nearly complete drug release (99.04%). Release kinetics indicated diffusion-controlled mechanisms with near Zero-order release for DNLC5. Stability studies under accelerated conditions confirmed formulation stability for up to 180 days. Overall, lipid-based nanostructured carriers represent a promising strategy to enhance the oral bioavailability of Dolutegravir, with DNLC5 offering sustained delivery, reduced dosing frequency, and improved patient compliance.

Keywords: Dolutegravir, Nanostructured lipid carriers, Oral bioavailability. Lipid-based drug delivery, Antiretroviral therapy.

Introduction

Poor oral bioavailability remains a major challenge in the effective pharmacotherapy of many drugs, particularly those belonging to Biopharmaceutics Classification System (BCS) class II and IV. Factors such as low aqueous solubility, limited intestinal permeability, extensive first-pass metabolism, and efflux by transporters significantly compromise drug absorption following oral administration.[1] These limitations often result in variable plasma drug concentrations, reduced therapeutic efficacy, and the need for higher or frequent dosing, thereby affecting patient adherence and treatment outcomes.

Lipid-based drug delivery systems have emerged as a promising strategy to address the challenges associated with conventional oral dosage forms. Among various approaches, nanostructured lipid-based formulations have gained substantial attention due to their ability to improve solubilization of poorly water-soluble drugs, enhance intestinal absorption, protect drugs from enzymatic degradation, and modulate drug release characteristics.[2] Lipid-based nanocarriers, typically in the nanometer size range, can significantly alter the pharmacokinetic profile of drugs, leading to improved oral bioavailability and enhanced therapeutic performance.

Nanostructured lipid formulations are generally composed of physiological lipids, surfactants, and co-surfactants that are biodegradable and biocompatible. These systems can encapsulate lipophilic drugs within their lipid matrix, maintaining the drug in a solubilized state throughout the gastrointestinal tract.[3] Additionally, lipid-based nanocarriers can promote lymphatic transport, thereby by passing hepatic first-pass metabolism and further enhancing systemic drug availability.[4] The nanoscale size and lipidic nature of these systems also facilitate improved interaction with intestinal membranes, resulting in increased drug uptake.

Dolutegravir is a potent integrase strand transfer inhibitor widely used as a first-line. [5] However, dolutegravir suffers from poor aqueous solubility and variable oral bioavailability, which may limit its absorption and therapeutic consistency.[6] Additionally, food effects and gastrointestinal variability can influence its pharmacokinetic behavior, necessitating formulation strategies that ensure reliable and enhanced oral delivery.

To overcome these limitations, the development of novel lipid-based nanostructured formulations for oral delivery of dolutegravir represents a rational and effective approach. Incorporation of dolutegravir into lipid-based nanocarriers can improve its solubilization in the gastrointestinal environment, enhance membrane permeability, and reduce variability in absorption.[7] Such formulations can provide sustained drug release, improved bioavailability, and potentially reduced dosing frequency, thereby improving patient compliance in long-term antiretroviral therapy.[8]

Furthermore, lipid-based nanostructured formulations offer significant flexibility in formulation design parameters such as lipid composition, surfactant concentration, particle size, and surface characteristics. These parameters play a crucial role in determining drug loading, stability, release behavior, and in vivo performance of the formulation.[9] Systematic evaluation and optimization of these variables are therefore essential to develop a robust and efficient delivery system capable of consistent oral drug absorption.[10]

Consequently, the present study focuses on the design, evaluation, and optimization of novel lipid-based nanostructured formulations of dolutegravir to enhance its oral bioavailability. The developed formulations were subjected to comprehensive physicochemical characterization and in vitro evaluation, including particle size analysis, zeta potential determination, drug entrapment efficiency, morphological assessment, in vitro drug release studies, and optimization using appropriate experimental design approaches, to establish their potential as an effective oral nanocarrier system for improved antiretroviral therapy.[11]

Materials

All pharmaceutical-grade chemicals and excipients used in the present study were procured from reputed suppliers in the Hyderabad region. Dolutegravir sodium was obtained from a certified pharmaceutical manufacturer; glyceryl monostearate and Capryol® 90 were procured from Gattefossé; oleic acid was obtained from Loba Chemie Pvt. Ltd.; Tween® 80 and Span® 20 were purchased from Sigma-Aldrich; polyethylene glycol 400 (PEG 400) was obtained from Merck Life Science Pvt. Ltd.; and ethanol was procured from S.D. Fine Chemicals (SDFCL). All other chemicals, solvents, and reagents employed in the formulation development, evaluation, and

optimization studies were of analytical grade and were used as received without further purification.[12]

Methodology

Formulation of Dolutegravir loaded NLC

We prepared NLCs loaded with Dolutegravir by modified emulsification evaporation method at a high temperature and solidification at a low temperature [13]. Measured quantity of solid lipid GMS (glyceryl mono stearate)20mg, liquid lipid (Olive oil)3ml and Soya lecithin were weighed precisely and then co-dissolved into ethanol (30 ml) in water bath at 75°C. [14] The resultant organic solution was added drop wise into 40 ml of aqueous phase containing 1.5% Tween 80 was added under mechanical agitation with 1000 rpm in water bath maintained at 75 °C for 5 h. The nanoemulsion thus obtained was immediately dispersed into 40 ml of cold distilled water (0–2 °C) with constant stirring at 1000 rpm for 1 h to obtain the drug loaded NLCs dispersion.[15]

Table no. 1 Formulation Table for Dolutegravir loaded NLC

Ingredients	DNS1	DNS2	DNS3	DNS4	DNS5	DNS6	DNS7	DNS8	DNS9
Docetaxel(mg)	30	30	30	30	30	30	30	30	30
Eudragit RSPO(mg)	3	3.5	4	3	3.5	4	3	3.5	4
Tween 80(mL)	2	4.5	7	4.5	7	2	7	2	4.5
PVA (mg)	3	3	3	3	3	3	3	3	3
Solvent (Acetone: Water) 1:1 (ml)	10	10	10	10	10	10	10	10	10

DNLC= Dolutegravir Loaded Nano Lipidic Carrier

Evaluation Of Dolutegravir Loaded NLC

Particle Size and Polydispersity Index (PDI)

The mean particle size and polydispersity index of the prepared lipid-based nanostructured formulations were determined using dynamic light scattering (DLS) technique with a particle size analyzer. Samples were appropriately diluted with distilled water to avoid multiple scattering effects. Particle size analysis was carried out to ensure nanometric size range, which is critical for enhanced dissolution, intestinal uptake, and improved oral bioavailability. The polydispersity index was used to assess the uniformity of particle size distribution, with lower PDI values indicating homogenous formulations.[16]

Zeta Potential

Zeta potential was measured using a zeta potential analyzer to determine the surface charge and physical stability of the formulations. Adequate surface charge is essential to prevent particle aggregation during storage. Formulations exhibiting sufficiently high positive or negative zeta potential values were considered stable due to electrostatic repulsion between particles.[17]

Drug Entrapment Efficiency

Drug entrapment efficiency was determined by separating the free (unentrapped) Dolutegravir from the nanostructured lipid formulations using centrifugation at high speed. The supernatant containing free drug was analyzed spectrophotometrically at the predetermined λmax of Dolutegravir. Entrapment efficiency was calculated as the percentage of drug encapsulated within the lipid matrix relative to the total drug added. High entrapment efficiency indicates effective incorporation of Dolutegravir within the lipid system, which is essential for sustained release and enhanced bioavailability.[18]

In vitro drug release of Dolutegravir loaded nano lipidic carrier (DNLC)

All the formulation (DNLC1-DNLC9) evaluated for in vitro release by activated dialysis bag technique (molecular weight 12,000–14,000kDa) with slight modification from suggested methods. A known

volume containing Dolutegravir in both the formulation was placed in a dialysis bag, and both ends were tied to prevent any leakage. Samples were withdrawn at predetermined time intervals, filtered, and analyzed spectrophotometrically for Dolutegravir content The bag was dipped in 250ml phosphate buffer saline (pH 7.4) as release media at 37±2◦C with continuous stirring at 50rpm, DNLC5 showed best sustained release profile 97.52% in 24 hour.[19]

Drug Release Kinetic Studies

The in-vitro release data obtained from dissolution studies were fitted into various kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to elucidate the drug release mechanism and pattern. The best-fit model was selected based on correlation coefficient (R^2) values. Drug release kinetics provided insight into whether the formulation followed diffusion-controlled, erosion-controlled, or combined release mechanisms.[20]

Stability Studies

Stability studies of the optimized Dolutegravir-loaded lipid-based nanostructured formulation were conducted under accelerated storage conditions (40°C ± 2°C / 75% ± 5% RH).

RESULT & DISCUSSION

FTIR Study of pure Dolutegravir

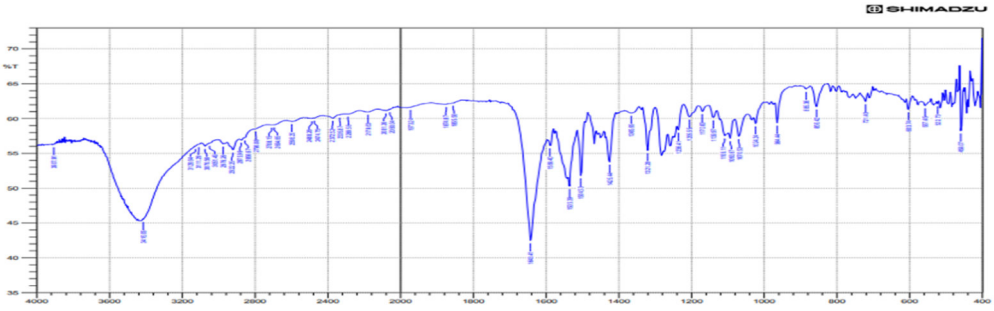


Figure no. 1 FTIR of Dolutegravir

The FTIR spectrum of Dolutegravir confirms (**Fig No: 1**) the presence of key functional groups essential to its pharmacological activity. Characteristic peaks include strong absorptions around 1700 cm^{-1}, indicating C=O stretching from carboxylic and amide groups, and bands near 1600 cm^{-1} corresponding to aromatic C=C stretching. Peaks around 3300 cm^{-1} suggest N–H or O–H stretching, consistent with amide or hydroxyl functionalities. Additional signals in the 1000–1300 cm^{-1} region reflect C–F and C–N vibrations, supporting the presence of fluorinated and nitrogen-containing moieties. These spectral features validate the structural integrity and functional group composition of Dolutegravir.

DSC Report of Dolutegravir

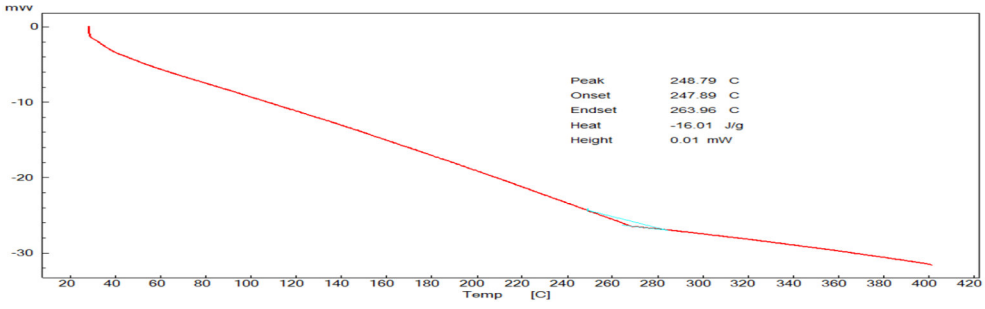


Figure no. 2 DSC Report of Dolutegravir

The Differential Scanning Calorimetry (DSC) (**Fig No: 2**) thermogram of Dolutegravir reveals a distinct thermal event with an onset at 247.89 °C, peak at 248.79 °C, and endset at 263.96 °C, indicating a sharp melting transition. The exothermic nature of the event, with a heat flow of –16.01 J/g, suggests a possible recrystallization or decomposition process post-melting. The narrow temperature range and minimal baseline shift reflect Dolutegravir's thermal stability and purity, supporting its suitability for solid dosage formulation.

Physicochemical characterization of Dolutegravir-loaded nanostructured lipid carriers

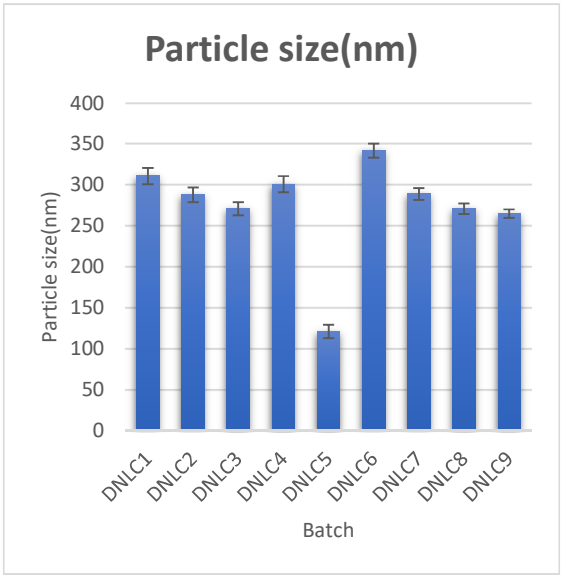
The physicochemical characterization of Dolutegravir-loaded nanostructured lipid carriers (DNLCs)(**Table no. 4**) revealed significant variation in particle size, entrapment efficiency (EE%), and zeta potential across batches DNLC1 to DNLC9. (Figure No: 3a, 3b, 3c) Particle sizes ranged from 121 nm (DNLC5) to 342 nm (DNLC6), indicating the influence of formulation parameters on colloidal stability and drug encapsulation. Notably, DNLC5 exhibited the smallest particle size (121 ± 8.14 nm), which is favourable for enhanced cellular uptake and bioavailability.

Entrapment efficiency varied between 68% and 88%, with DNLC5 achieving the highest EE% (88 ± 1.74%), suggesting optimal lipid–drug compatibility and efficient incorporation of Dolutegravir within the lipid matrix. This high EE% in DNLC5 may be attributed to its reduced particle size and optimized lipid composition.

Zeta potential values ranged from –21.3 mV to –32.1 mV, indicating moderate to good electrostatic stability of the formulations. DNLC1 showed the highest negative zeta potential (–32.1 mV), which contributes to particle repulsion and reduced aggregation, enhancing suspension stability. Most formulations maintained zeta potentials below –25 mV, supporting their colloidal integrity. Overall, DNLC5 emerged as the most promising formulation, combining minimal particle size, maximum entrapment efficiency, and sufficient zeta potential for stability. These findings underscore the importance of fine-tuning lipid composition and processing parameters to achieve optimal delivery characteristics for Dolutegravir.

Table no. 4 Characterization of Dolutegravir loaded NLC(DNLC)

Batch	Particle size(nm)	EE%	Zeta potential
DNLC1	311±10.01	72±1.02	-32.1
DNLC2	288±9.12	76±2.31	-21.3
DNLC3	271±8.74	74±1.14	-26.1
DNLC4	301±9.88	80±1.08	-25.4
DNLC5	121±8.14	88±1.74	-22.5
DNLC6	342±8.55	74±1.31	-29.1
DNLC7	289±7.03	77±3.01	-28.4
DNLC8	271±6.31	68±2.88	-26.4
DNLC9	265±5.24	69±2.14	-24.7



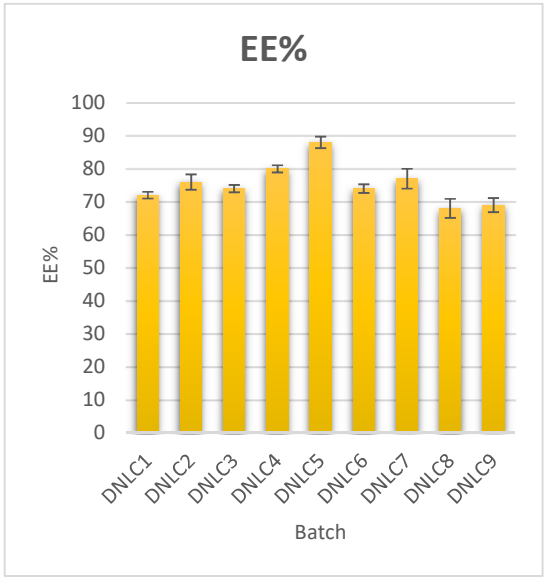


Figure no. 3(a) Particle size of DNLC

Figure no. 3(b) EE% of DNLC

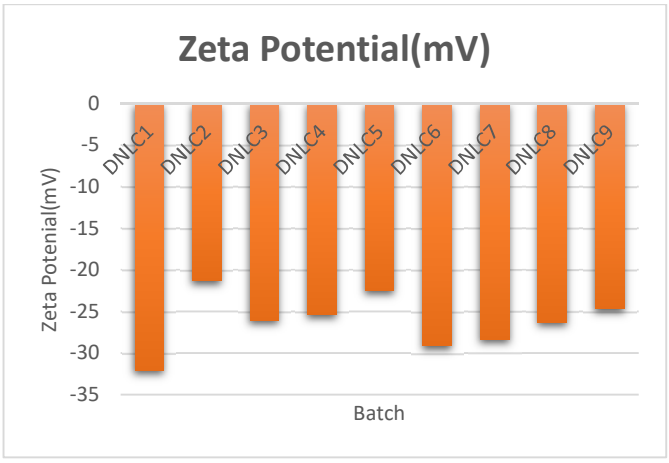


Figure no. 3(c) Zeta Potential of DNLC

Scanning Electron Microscope Image of Dolutegravir loaded NLC (DNLC5)

The Scanning Electron Microscope (SEM) image of Dolutegravir-loaded nanostructured lipid carrier (DNLC5) reveals a uniformly dispersed particulate morphology with spherical to slightly irregular shapes, indicative of successful nano formulation. (**Fig No: 4**) The particles exhibit a smooth surface texture, suggesting efficient lipid encapsulation and minimal aggregation. The absence of large clusters or crystalline residues supports the homogeneity and stability of the formulation. The nanoscale dimensions observed in the micrograph correlate well with the particle size data (~121 nm), reinforcing the suitability of DNLC5 for enhanced drug delivery and cellular uptake.

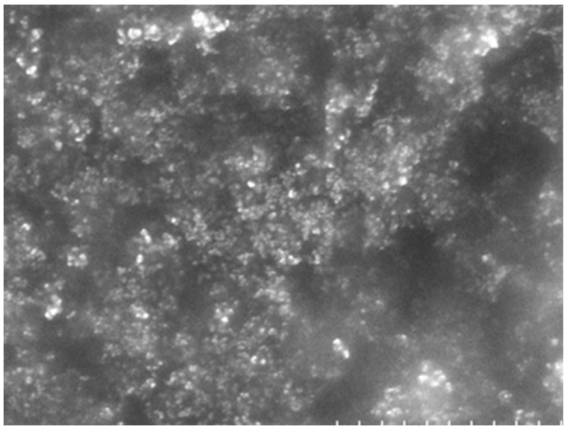


Figure no. 4 SEM Image of DNLC5

In vitro drug Release Study

The in vitro release study of Dolutegravir-loaded nanostructured lipid carriers (DNLCs) demonstrated a sustained and controlled release pattern across all nine formulations. (**Fig No: 5a, 5b**) Initial release within the first hour was minimal, ranging between 7–20%, indicating effective encapsulation and prevention of burst release. By 2–4 hours, cumulative release increased steadily, with values between 22–45%, reflecting gradual diffusion of the drug from the lipid matrix. A significant rise in release was observed at 8–12 hours, where formulations such as DNLC4 (90.81%) and DNLC5 (89.1%) showed rapid progression, while others like DNLC3 and DNLC8 maintained moderate release (~58–57%). This highlights variability in lipid composition and particle size influencing drug diffusion rates. At 24 hours, nearly all formulations achieved high cumulative release (>75%), with DNLC5 reaching 99.04% and DNLC4 97.52%, confirming their efficiency in delivering Dolutegravir over an extended period. The sustained release behavior suggests that these carriers can maintain therapeutic drug levels, reduce dosing frequency, and potentially improve patient compliance. Overall, DNLC5 emerged as the most promising formulation, combining small particle size, high entrapment efficiency, and near-complete drug release within 24 hours, making it a strong candidate for optimized Dolutegravir delivery.

Table no. 5 In vitro drug release of DNLC1-DNLC9

Time(Hr)	DNLC1	DNLC2	DNLC3	DNLC4	DNLC5	DNLC6	DNLC7	DNLC8	DNLC9
0	0	0	0	0	0	0	0	0	0
1	9.52	19.97	14.57	19.77	11.12	13.46	11.12	7.65	12.13
2	26.85	32.98	22.8	28.59	16.25	23.63	16.25	14.54	18.1
4	43.48	42.36	29.85	45.01	22.6	32.15	22.6	22.8	26.66
8	46.46	58.85	44.13	53.56	63.4	44.63	63.4	39.41	44.68
12	65.8	74.81	58.84	90.81	89.1	69.15	76.32	57.48	69.33
24	76.84	92.11	90.68	97.52	99.04	91.07	89.34	86.67	94.84

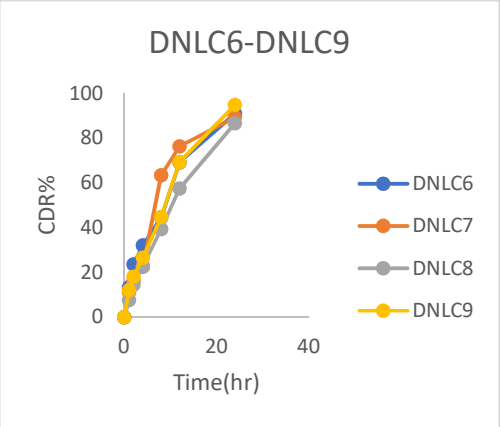


Figure no. 5(a) In vitro drug release of DNLC6-DNLC9

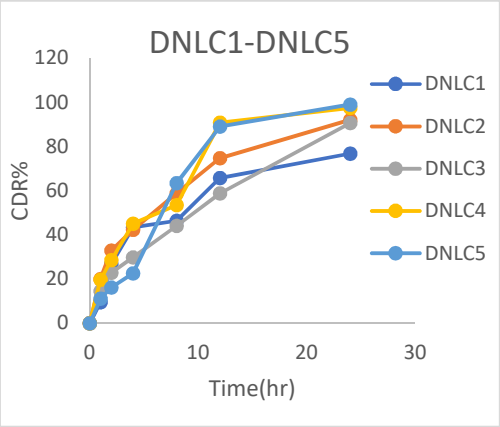


Figure no. 5(b) In vitro drug release of DNLC1-DNLC5

Release Kinetics of Dolutegravir-Loaded Formulations

The kinetic modeling of Dolutegravir-loaded formulations (DNLC1–DNLC9) highlights that drug release is best explained by the Korsmeyer–Peppas ($r^2 \approx 0.93–0.96$) and Higuchi models ($r^2 \approx 0.92–0.95$), confirming a diffusion-driven mechanism with contributions from polymer relaxation and matrix erosion. This indicates that the formulations follow anomalous transport behavior, where both diffusion and lipid degradation regulate sustained release.

Among all batches(**Table no:6**), DNLC5 demonstrated the strongest Zero-order fit ($r^2 = 0.99$), suggesting nearly constant release independent of concentration, which is highly desirable for maintaining steady therapeutic levels. Other formulations, such as DNLC2–DNLC6, showed strong Higuchi correlations, reinforcing the role of diffusion through the lipid matrix. Meanwhile, DNLC7–DNLC9 exhibited slightly lower Korsmeyer–Peppas values but still maintained good fits with Zero-order and Higuchi models, indicating mixed release mechanisms.

Overall, the data confirm that Dolutegravir-loaded NLCs achieve controlled and sustained release, with DNLC5 emerging as the most promising candidate due to its near-perfect Zero-order kinetics, ensuring predictable and prolonged drug delivery.

Table no. 6 Release Kinetics of Dolutegravir-Loaded Formulations

Batch code	r^2			
	Zero	First	Higuchi	Korsmeyer& Peppas
DNLC1	0.93	0.86	0.88	0.93
DNLC2	0.9	0.79	0.95	0.96
DNLC3	0.89	0.86	0.89	0.96
DNLC4	0.88	0.88	0.92	0.96
DNLC5	0.99	0.73	0.92	0.96
DNLC6	0.91	0.88	0.92	0.96
DNLC7	0.96	0.91	0.91	0.87
DNLC8	0.88	0.89	0.93	0.89
DNLC9	0.89	0.94	0.93	0.87

Stability Study

Formulation DNLC5 was subjected to different temperature and relative humidity (RH) conditions over four time intervals: 0, 30, 60, 90, and 180 days. Throughout the study, a slight increase in average particle size was observed, indicating minor aggregation or structural relaxation over time. Concurrently, the entrapment efficiency (EE%)

showed a marginal decline, suggesting minimal drug leakage or lipid reorganization under stress conditions. These changes remained within acceptable limits, confirming the physical and chemical stability of DNLC5 under accelerated storage conditions.

Table no. 7 Stability Results for best formula DNLC5

Days	25^0 C±2^0 C/60%±5%RH			40^0 C± 2^0C /75%±5% RH		
	Physical Appearance	**Particle size(nm)**	**EE%**	**Appearance**	**Particle size(nm)**	**EE%**
0	NC	121	88	NC	**121**	**88**
30	NC	132	86.1	NC	130	86
60	NC	140	86	NC	139	85.4
90	NC	141.2	85	NC	140	84
180	NC	142	84	NC	143	83

Conclusion

The present investigation successfully demonstrated the design, evaluation, and optimization of novel lipid-based nanostructured formulations for enhancing the oral bioavailability of Dolutegravir. Nanostructured lipid carriers (DNLCs) were effectively prepared using the modified emulsification–evaporation technique, yielding stable nanoscale formulations with controlled physicochemical properties. Systematic variation in lipid and surfactant composition significantly influenced particle size, entrapment efficiency, surface charge, and drug release behavior, underscoring the importance of formulation optimization. Among the nine developed formulations, DNLC5 emerged as the optimized formulation, exhibiting the smallest particle size (121 ± 8.14 nm), highest drug entrapment efficiency (88 ± 1.74%), and adequate negative zeta potential (–22.5 mV), indicative of good colloidal stability. Morphological evaluation by SEM confirmed spherical, uniformly distributed nanoparticles with minimal aggregation, corroborating the particle size analysis results. In vitro drug release studies revealed a sustained and controlled release pattern for all formulations over 24 hours, with DNLC5 achieving nearly complete drug release (99.04%), thereby ensuring prolonged drug availability. Release kinetic analysis indicated that drug release predominantly followed diffusion-controlled mechanisms, with DNLC5 showing an excellent fit to the Zero-order model, suggesting a near-constant release profile that is highly desirable for maintaining steady plasma drug concentrations. Stability studies conducted under accelerated conditions demonstrated that the optimized formulation DNLC5 remained physically and chemically stable over 180 days, with only marginal changes in particle size and entrapment efficiency, all within acceptable limits. These findings confirm the robustness and suitability of the formulation for further development. Overall, the results clearly indicate that lipid-based nanostructured carriers represent a promising oral delivery platform for Dolutegravir. The optimized DNLC5 formulation has the potential to enhance oral bioavailability, reduce dosing frequency, and improve patient compliance in long-term antiretroviral therapy. Further in vivo pharmacokinetic and bioavailability studies are warranted to establish the clinical applicability of the developed nanostructured lipid system.

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