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FORMULATION DEVELOPMENT OF DOLUTEGRAVIR SODIUM LOADED NANO LIPID CARRIERS FOR IMPROVED SOLUBILITY AND PERMEABILITY

N. A. Shaikh and R. R. Lala *

Department of Pharmaceutics, Prin. K. M. Kundnani College of Pharmacy, Cuffe Parade, Mumbai - 400005, Maharashtra, India.

Keywords:

Nano Lipid Carriers, Dolutegravir Sodium, Melt Emulsification Sonication, Flux

Correspondence to Author:
Dr. Rita R. Lala

Associate Professor,
Department of Pharmaceutics,
Prin. K. M. Kundnani College of Pharmacy, Cuffe Parade, Mumbai - 400005, Maharashtra, India.

E-mail: r_r_lala@yahoo.co.in

ABSTRACT: Dolutegravir sodium (DTG) is a poorly soluble antiretroviral drug that belongs to BCS class II approved by the FDA for treatment of HIV infections; however, DTG has several shortcomings, including low solubility in water, low oral bioavailability, hepatotoxicity, and instability in an acidic environment. After oral administration, 84% of the dose is excreted from the body in an unchanged form due to its poor solubility. To overcome the above mentioned difficulties, Nano Lipid Carriers (NLCs) are selected as a potential drug delivery system for the present research work. NLC suspension was formulated using melt emulsification sonication technique using a combination of solid lipid (8% w/v), *i.e.*, Glyceryl monostearate (GMS), Gelucire 50/13, Dynasan 118, and liquid lipid Capmul MCM EP along with a blend of Tween 80 and Span 80 as a surfactant, Sodium cholate (0.4 w/v) as surface charge modifier and BHT (0.01%w/v) as a preservative. Response surface methodology using 2^3 factorial designs with three independent variables, that is, lipid concentration (A), surfactant concentration (B), sonication time (C) was applied to determine the optimum levels for particle size, entrapment efficiency. Optimized batch NLC-F2 suspension was composed of an 80:20 ratio of solid to liquid lipid and 5% w/v of Tween 80: Span 80 blend in a 70:30 ratio. NLCs were characterized by Scanning Electron Microscopy. The average Particle size of the optimized batch was 123.1 nm with a polydispersity index value of 0.406 and zeta potential -16.1 mV. The DTG loaded NLCs suspension formulation offered good *in-vitro* release (96.32 % in 48 h) and permeability of (94.02% in 8 h) using the rat intestinal model.

INTRODUCTION: In recent years, Nano-particulate carriers have shown great promise as Nano drug delivery systems with their nanoscale dimensions, large surface area, and distinct properties. Their advantages include protection of the active ingredient from the harsh gastrointestinal environment and enzymes.

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Nanocarriers help in the enhancement of bioavailability, dose reduction, controlled drug release, prolonged circulation time, improved intracellular penetration.

Targeted drug delivery is a modern approach by surface modifications of the carriers to specific sites or organs [1, 2, 3]. They also act as carriers for a variety of molecules, including poorly soluble drugs, peptides and proteins, antibodies, RNA, *etc*. [4, 5] Lipidic drug delivery systems such as Solid Lipid Nanoparticles (SLN) and Nano Lipid Carriers (NLC) have gained the attention of researches in the past few decades due to their non-

immunogenicity, biocompatibility as compared to polymeric and inorganic nanoparticulate delivery systems, in addition to their capability of permeating physiological barriers, especially the blood-brain barrier (BBB) due to their lipophilic nature. Further, ecofriendly, ease of preparation, cost-effectiveness, and the feasibility of large-scale production is making these delivery systems more attractive [6, 7, 8]. NLCs are a new generation of Solid Lipid Nanoparticles that were developed to overcome the limitations of SLN. However, instead of using only a solid lipid, a portion is replaced by an oil resulting in a less ordered lipid matrix providing enhanced drug loading and preventing leaching out of the drug during storage [9, 10]. The oral route is the most imperative route for administering a variety of drugs. It has been extensively used for both conventional and novel drug delivery systems. In spite of the wide success with some other routes for drug administration, the oral route is still the most preferred route for its vast qualities.

Dolutegravir sodium (DTG) is a poorly soluble drug as it belongs to the class II category according to BCS classification. DTG has an oral bioavailability of only 16% [11]. Therefore, it is necessary to increase the solubility and dissolution rate of DTG, which leads to improvement in oral bioavailability. Enhancement in oral bioavailability with conventional dosage form can be enhanced by any suitable novel drug delivery system such as prodrug concept or using a novel lipid-based system such as lipid nanoparticles [12, 13]. Compared to other nanoparticles, NLCs gain some advantages in less toxicological risk because of natural origin lipids. As an effect, Nanostructured Lipid Carriers (NLCs) have been developed, which to some extent can avoid the mentioned limitations. NLCs can be defined as the second generation of SLNs having solid lipid and liquid lipid matrix that creates a less ordered or imperfect structure which helps in improving drug loading and decreasing the drug expulsion from NLCs during storage period [14, 15].

In the present work, DTG loaded NLCs were developed by melt emulsification sonication method as this technique has several remarkable advantages such as avoidance of organic solvents, use of simple equipment and accessories, ease in handling, and rapid manufacturing process [16].

MATERIALS AND METHODS:

Materials: Dolutegravir sodium was obtained as a gift sample from Cipla Ltd. Mumbai, Softemul SE from Mohini organics Mumbai, Gelucire from Gattefosse India Pvt. Ltd., Dynasan 118 from Chika Pvt. Ltd. Mumbai, Capmul MCM EP from Abitec corp. Tween 80, Span 80, Sodium Cholate, was purchased from S.D. Fine Mumbai, Propylene glycol and PEG 6000 was purchased from chemco chemicals. All the excipients used were pharmaceutically approved, complying with I.P./ B.P./U.S.P. or in-house specifications. Current Research work was performed in the year 2018-2019 at the Department of Pharmaceutics, Prin. K.M. Kundnani College of Pharmacy, Mumbai.

Method: NLCs were prepared by melt emulsification sonication technique. The solid and liquid lipid in a different ratio (80:20, 70:30) were used in the formulation of NLCs along with the Surfactant mixture [(Tween 80: Span 80 (70:30)]. The drug was dispersed and dissolved in liquid lipid by using vortex cyclomixer, propylene glycol BHT, and solid lipids were added and melted (80 °C) then oil-soluble surfactant, *i.e.*,, span 80 was added in lipid melt. The simultaneously aqueous phase was prepared by adding a weighed amount of water-soluble surfactant, *i.e.*, tween 80, PEG 6000, and bile salt, and heated at the same temperature as the oil phase. The aqueous phase was transferred quickly in the drug-containing melted lipid phase and stirred on a magnetic stirrer at 700 rpm for 20 min. Then obtained coarse emulsion was sonicated using probe sonicator to obtain Nanoemulsion, which gets converted to NLCs after solidification of lipid at room temperature.

TABLE 1: FORMULA OF NANO LIPID CARRIER SUSPENSION

S. no.	Ingredient	Quantity
1	Lipid (Solid + Liquid)	8% (w/v)
2	Surfactant mixture (Tween 80: Span 80)	70:30 ratio
3	PEG 6000	1% (w/v)
4	Propylene glycol	1% (v/v)
5	Sodium cholate	0.4 % (w/v)
	Butylated hydroxy toluene	0.01 % (w/v)
7	Dolutegravir sodium	2.5 mg /ml

Drug Solubility Studies:

Solubility of Drug in Liquid lipid/Oil/ Surfactant: Solubility of drug was checked by dissolving excess amount of drug in a fixed amount

(2 ml) of different liquid lipids/oils and stirred for 48 h by maintaining the temperature between 60-70 ºC to form a supersaturated solution, the Super saturated solution was centrifuged, and supernatant was diluted with methanol, and then the amount of drug was determined using UV VIS spectrophotometer at 258 nm [17, 18].

TABLE 2: SOLUBILITY OF DRUG IN LIQUID LIPID /SURFACTANT

S. no.	Lipid	Solubility (mg/ml)
1	Capmul MCM EP	29.36±1.14
2	Soyabean oil	Practically Insoluble
3	Sunflower oil	Practically Insoluble
4	Maize oil	Practically Insoluble
5	Lipophile 1944	Practically Insoluble
6	Labrafil 2124	5.03±0.86
7	Transcutol HP	Practically Insoluble
8	Labrafac PG	Practically Insoluble
9	Capryol 90	Practically Insoluble
10	Span 20	12.14±0.92
12	Span 80	14.86±1.55
13	Tween 80	15.92±1.01

Solubility of Drug in Solid lipid: Fixed amount of drug (10 mg) was taken, and solid lipid was added in increments, melted till it forms clear liquid/total drug dissolved, mixed properly with Vortex cyclomixer. Melted lipid was spread over the wall of a test tube. When it solidified from the upper part of the test tube fixed amount of lipid was taken and extracted with methanol, and drug was quantified using UV VIS spectroscopy at 258nm [19].

TABLE 3: SOLUBILITY OF DRUG IN SOLID LIPID

S. no.	Lipid	Solubility (mg/gram)
1	Glyceryl Monostearate	6.5±0.10
2	Compritol 888	2.9±0.17
3	Gelucire 50/13	6.5±0.15
4	Dynasan 118	5.3±0.12
5	Precirol ATO	4.2±0.15
6	Stearic Acid	3.8±0.14

Experimental Design: Response surface methodology using 2^3 factorial design by using Design-Expert software (11) of Stat -Ease lnc. Minneapolis, USA, with three independent variables was applied to determine the optimum levels for the particle size, entrapment efficiency. The selected numeric factors were the lipid concentration (A), surfactant concentration (B), sonication time (C). Each numeric factor was varied over 2 levels: plus and minus (factorial points). RLRS type selected factors were ranges in terms of +1, -1 level. By selecting small RLRS designs, 8 experiments were generated by the software; individual experiments were carried out in random order. From the preliminary studies, batches containing 8% of total lipid were selected for further optimization.

TABLE 4: INDEPENDENT VARIABLES AND THEIR RANGES FOR OPTIMIZATION OF NLC FORMULATION

S. no.	Variable/Factor	Lower value(-1)	Upper value(+1)
1	Solid: Liquid lipid ratio	70:30	80:20
2	Surfactant Concentration	4%	5%
3	Sonication time	5 min	10 min

TABLE 5: RLRS DESIGNS 8 EXPERIMENTS GENERATED BY THE DESIGN-EXPERT SOFTWARE (11) SOFTWARE

Batches	Actual batches		
	A	B	C
F1	70:30	4	5
F2	80:20	5	10
F3	70:30	5	10
F4	80:20	5	5
F5	80:20	4	5
F6	80:20	4	10
F7	70:30	5	5

Characterization of Nano Lipid Carriers:

Particle Size and Zeta Potential Measurement: The average particle size, Polydispersity index and zeta potential of optimize batch was determined by using Zeta sizer and particle size analyzer (Malvern Instruments Ltd). Prior to measurement sample was diluted with double distilled water to produce a suitable scattering intensity.

Entrapment Efficiency: This parameter was calculated to know the amount of drug present inside the NLCs. Entrapment efficiency was determined by refrigerated centrifugation separation technique in which NLCs were centrifuged at 15000 rpm for 45 min and free unentrapped drug in the supernatant after sedimentation of NLC was collected, diluted with methanol, and analyzed by UV-VIS spectroscopy at 258 nm.[20]

The entrapment efficiency was calculated by the indirect method as follows:

% Entrapment efficiency = ([DTG] total-[DTG] supernatant / [DTG] total) × 100

TABLE 6: PARTICLE SIZE, PDI AND %EE

Batch	Particle size	PDI	%Entrapment Efficiency
NLC-F1	123.3	0.301	75.42
NLC-F2	123.1	0.406	88.09
NLC-F3	127.1	0.356	72.50
NLC-F4	153.9	0.412	87.80
NLC-F5	181.0	0.368	85.60
NLC-F6	152.2	0.510	84.50
NLC-F7	159.1	0.477	71.40
NLC-F8	127.1	0.321	74.20

Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FTIR): FTIR measurement of DTG, excipient and the drug-excipient mixture was obtained on FTIR spectrometer (Bruker) in the 400-4000 cm^{-1} range, and major bands were recorded. The presence and absence of these bands and appearance of any new band were observed in the IR absorption spectrum.

Differential Scanning Calorimetry (DSC): DSC spectrum of drug and formulation was obtained by Exstar DSC by placing 5-10 mg of a sample against a reference. The equipment was provided with an auto cooling accessory for programmed cooling.

The sample was weighed into a standard aluminum pan, hermetically sealed, and heated from 25 ºC - 300 ºC at a constant rate of 10 ºC/min under constant purging with nitrogen at 80 ml/min. An empty aluminum sealed pan was used as a reference. DSC graphs of drug, Solid lipid mixture, solid + liquid lipid mixture, blank, and drug containing NLCs were recorded. The presence and absence of endothermic and exothermic peaks were observed in DSC graphs.

Scanning Electron Microscopy: Scanning electron microscopy of suspension was done to study the surface morphology of Nano Lipid Carriers. Nano Lipid Carrier's suspension was dried on carbon tube at room temperature; after drying sample, tube was coated with gold using sputter coater under vacuum and analyzed under an electron microscope at different magnifications.

***In-vitro* Release:** Dialysis membrane method was carried out to determine the release of drug from NLCs. Dialysis membrane 50 (Hi-Media, MW cut off 12-14K) was used in this study, the permeation studies [21] were carried out in 100 ml of phosphate buffer (pH 6.8). 1 ml of NLC suspension (2.5 mg/ml) was transferred in a one-end sealed dialysis membrane bag, and a pouch was prepared by closing another end with thread. Dialysis membrane pouch containing drug-loaded NLCs was suspended in release media and was stirred using a magnetic stirrer (Remi, India) at 100 rpm while the temperature was maintained at 37±0.5 ºC. 5 ml of aliquots were withdrawn and immediately replenished at 0, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 24, 48 h. Aliquots were filtered after withdrawal using Millipore Millex-HV(Hydrophilic) PVDF 0.45 µm filter and suitably diluted with distilled water (if required), and drug was quantified by using a UV-visible spectrophotometer at 257 nm.

***Ex-vivo* Release:** *Ex-vivo* permeation study was carried out using previously scarified Albino male Wistar rat of approved protocol in institute animal house. The ileum part of the small intestine of a rat was collected in phosphate buffer (pH 6.8) and gently cleaned using buffer solution to remove intestinal food content. The permeation studies were carried out in 100 ml of 6.8 phosphate buffer. 1 ml of NLC suspension (2.5 mg/ml) was transferred in one end sealed ileum part of intestine, and the pouch was prepared by closing another end with thread. Ileum pouch containing drug-loaded NLCs was suspended in release media. Air was gently bubbled in it with stirring using magnetic stirrer (Remi, India) at 100 rpm. At the same time, the temperature was maintained at 37±0.5 ºC. 5 ml of aliquots were withdrawn and immediately replenished at 0, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8 h. Aliquots were filtered after withdrawal using Millipore Millex-HV(Hydrophilic) PVDF 0.45 µm filter and suitably diluted with distilled water (if required), and drug was quantified by using UV-visible spectrophotometer at 257 nm.

Flux and permeability coefficient of drug from optimized batch and drug suspension 2.5 mg/ml (Drug in distilled water with 0.1% tween 80) was calculated as follows:

$$\text{Flux (J)} = \text{Slope (m)}/SA$$

$$\text{Permeation coefficient (Kp)} = J/Co$$

Where, SA=Surface area of the intestine ($2\pi rh$)
Co = Concentration of drug

$$(SA) = 2\pi rh$$

Where, r = radius of intestine (0.2 cm), h = height of intestine (8 cm)

$$\text{Surface area of the intestine (SA)} = 2\pi rh$$
$$= 2\times3.14\times0.2\times8$$
$$= 10.04\ cm^2$$

Flux and permeability coefficient of optimized batch and drug suspension was calculated by plotting time *vs*. cumulative amount permeated data.

Stability Studies: The optimized batch of Nano Lipid Carrier suspension was stored at room temperature for three months and observed for any changes Like drug content, lump formation,, oil separation, color change.

RESULTS AND DISCUSSION:

Statistical Analysis: The Nano Lipid Carrier suspension was optimized using response surface methodology. The quantitative effect of these factors at different levels was predicted by using polynomial equations. The polynomial equations generated explain the interaction effects of the variables on the response.

Final Equation in Terms of Coded Factors

Particle Size = +147.89+0.9625A-19.86B-6.34C
Entrapment Efficiency = +79.90+6.60A-0.0262B-0.1512

The coded factors comprising equation can be used to predict the response for given levels of each factor. +1 is coded as the high-level value of each factor and -1 as the low level. A coded equation is a suitable tool for identifying the relative impact on factors by comparing the factor coefficients.

P-values < 0.0500 in ANOVA after calculation using particle size and Entrapment efficiency data **Table 6,** respectively, indicate model terms are significant.

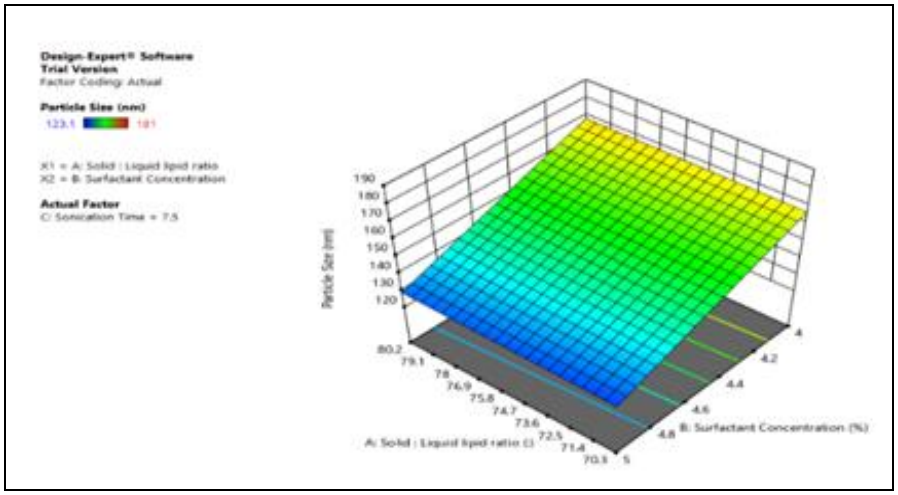


FIG. 1: 3D RESPONSE SURFACE PLOT OF PARTICLE SIZE *vs.* VARIABLE FACTORS

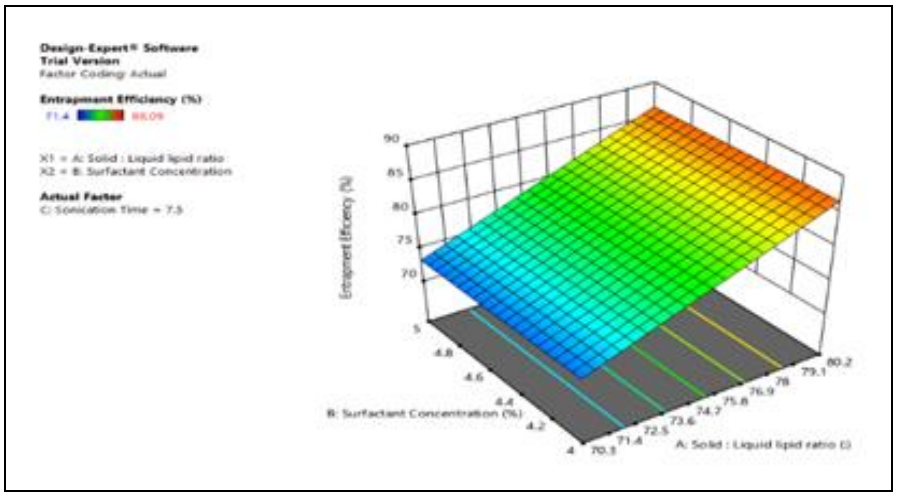


FIG. 2: 3D RESPONSE SURFACE PLOT OF % ENTRAPMENT EFFICIENCY *vs.* VARIABLE FACTORS

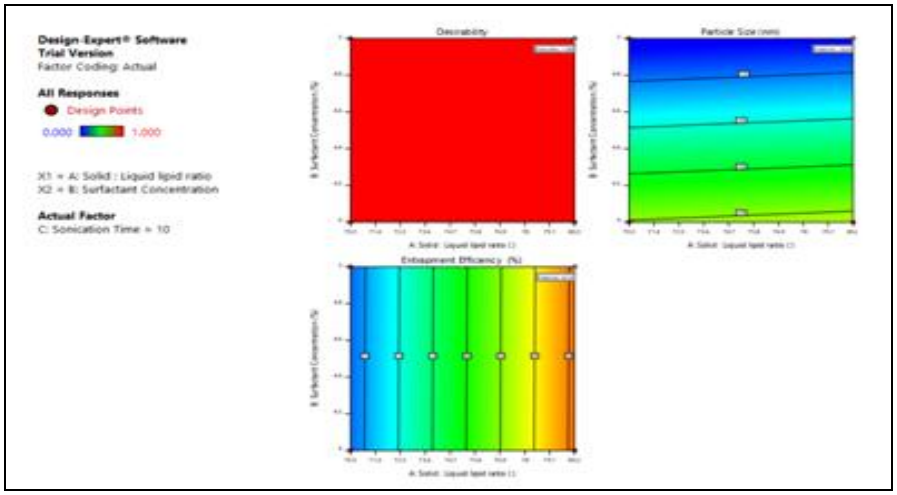


FIG. 3: CONTOUR PLOT INDICATING THE POINT OF DESIRABILITY

Numerical optimization was then used to predict the levels of the factors A, B, and C required for obtaining an optimum formulation with all excipient concentrations lying within the range with drug entrapment efficiency (maximum) and particle size (minimum). The optimal formulation of NLCs was composed of solid to liquid lipid ratio (80:20) A, surfactant concentration (5%) B and sonication time (10 min) C.

Validation of Predicted Formulation: Since there was a minute difference between values of the formulation variables from which 100 solutions were generated during numerical optimization, following batch **Table 7** is predicted by Design - Expert Software as an optimized batch.

TABLE 7: NLC BATCH PREDICTED BY DESIGN - EXPERT SOFTWARE AS OPTIMIZED BATCH

Solid: Liquid lipid ratio	80:20
Surfactant Concentration	5
Sonication Time	10
Particle Size(nm)	122.65
%Entrapment Efficiency	86.32
Desirability	1.000

TABLE 8: % ERROR BETWEEN PREDICTED AND ACTUAL FORMULATION RESPONSE VALUES

Variables	Predicted Value	Observed Value	Response	Predicted Value	Observed Value	% Error
Solid: Liquid lipid ratio	80:20	80:20	Particle Size(nm)	122.65	123.1	0.36
Surfactant Concentration	**5**	**5**	%Entrapment Efficiency	86.32	88.09	2.05
Sonication Time	10	10				

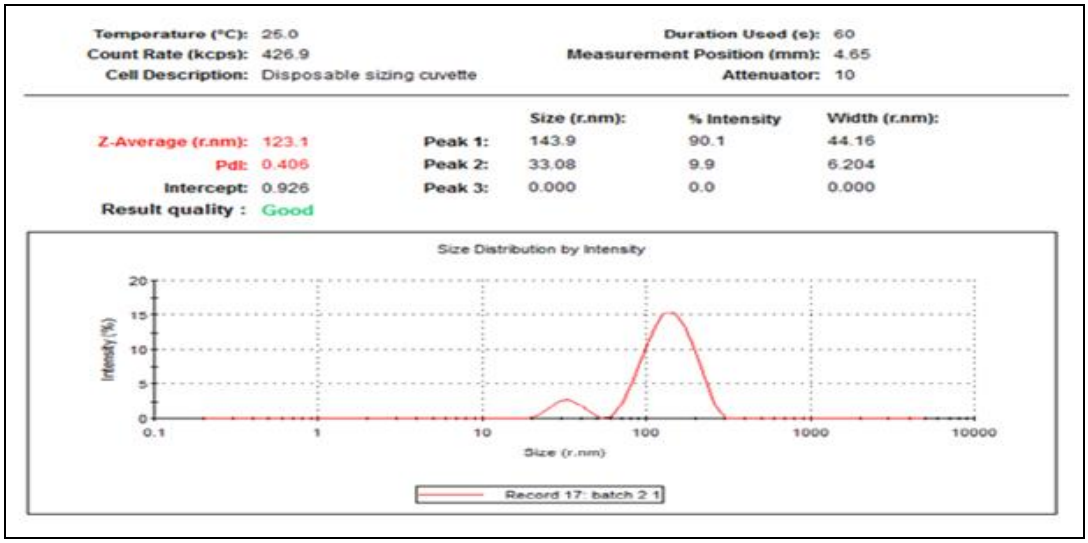


FIG. 4: PARTICLE SIZE OF OPTIMIZED NLC-F2 FORMULATION

Particle Size and Polydispersity Index: Nano Lipid Carriers under optimized conditions showed a small homogeneous particle size of (123.1 nm) and a polydispersity index of 0.406.

Zeta Potential: Zeta potential of optimized of nano lipid carriers was found to be -16.6 mV.

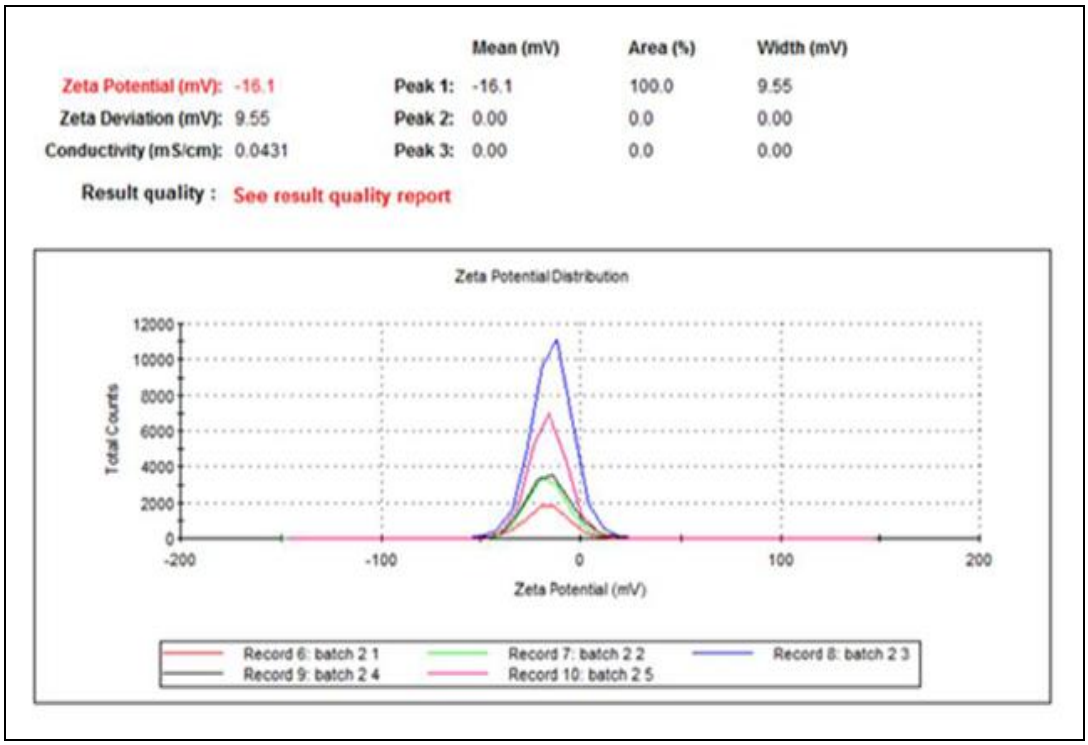


FIG. 5: ZETA POTENTIAL OF OPTIMIZED NLC-F2 FORMULATION

Entrapment Efficiency: Optimized batch NLC-F2 showed entrapment efficiency of 88.09% **Table 6**.

Scanning Electron Microscopy: SEM images indicated that the particles were round and spherical in shape, as shown in **Fig. 14**.

Compatibility Studies: DSC thermogram of physical mixture of solid lipids **Fig. 7** showed crystallization/endothermic peak at 149 C, which is not observed in the physical mixture of solid and liquid lipid **Fig. 8**; instead it showed melting/ exothermic peak at 149.8 C, which indicate conversion of crystalline nature of solid lipid to amorphous form due to addition of liquid lipid.

In DSC thermogram of blank formulation **Fig. 9**, it showed all exothermic peak at 67.2,82 and 107.2 C, which slightly shifted with more intensity peak in DSC thermogram of drug-loaded formulation **Fig. 10** it could be due to presence of the drug.

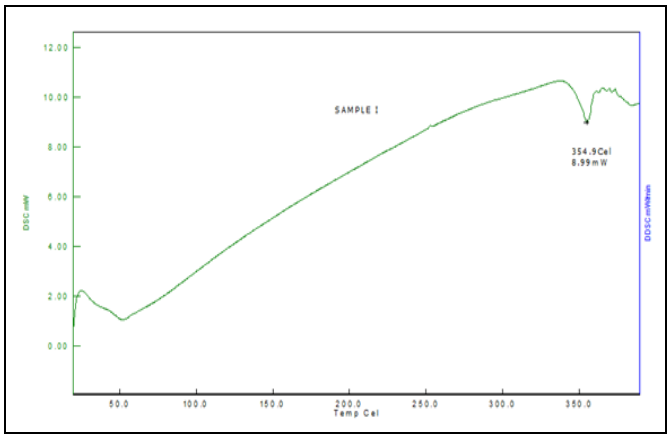


FIG. 6: DSC THERMOGRAM OF DTG

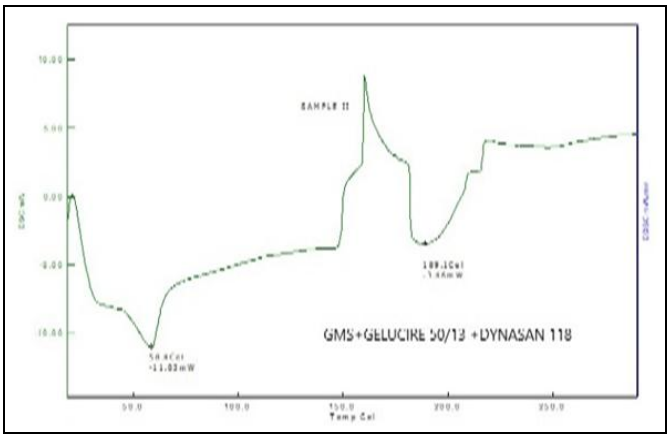


FIG. 7: DSC THERMOGRAM OF SOLID LIPID MIXTURE

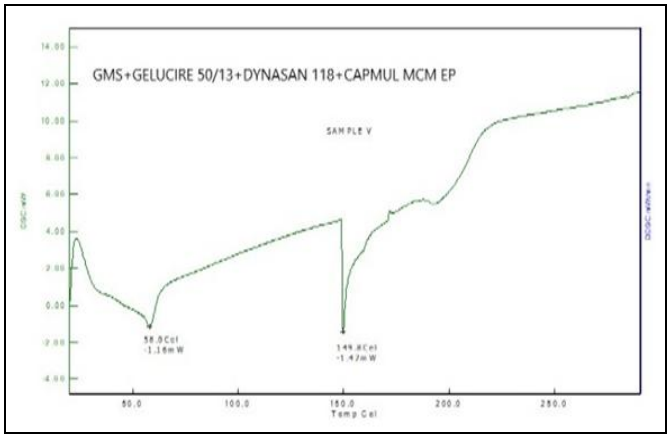


FIG. 8: DSC THERMOGRAM OF SOLID LIPID+LIQUID LIPID MIXTURE

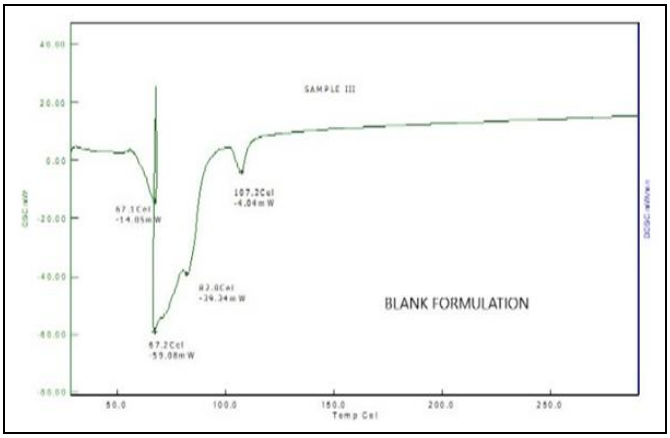


FIG. 9: DSC THERMOGRAM OF BLANK FORMULATION

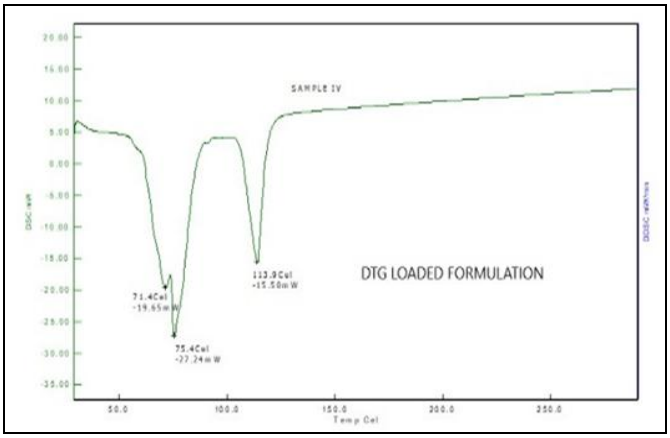


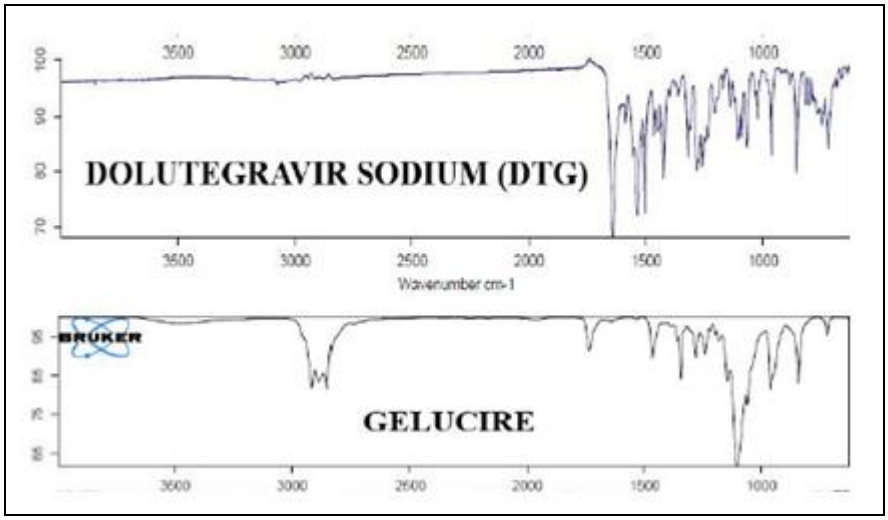
FIG. 10: DSC THERMOGRAM OF DTG LOADED FORMULATION

DSC analysis indicated that there was no chemical interaction between the drug and excipients; thus, it could be concluded that DTG is compatible with all the excipients.

FTIR: All the characteristics peak of excipient mixture was observed after physical mixing DTG with as shown in **Fig. 11**.

There is no change observed in any functional group of excipient mixture after the addition of DTG, which confirms the compatibility of the drug with all excipients.

Investigation of drug-excipient/s interactions using FTIR, DSC studies confirmed the compatibility of Dolutegravir sodium with the excipients.



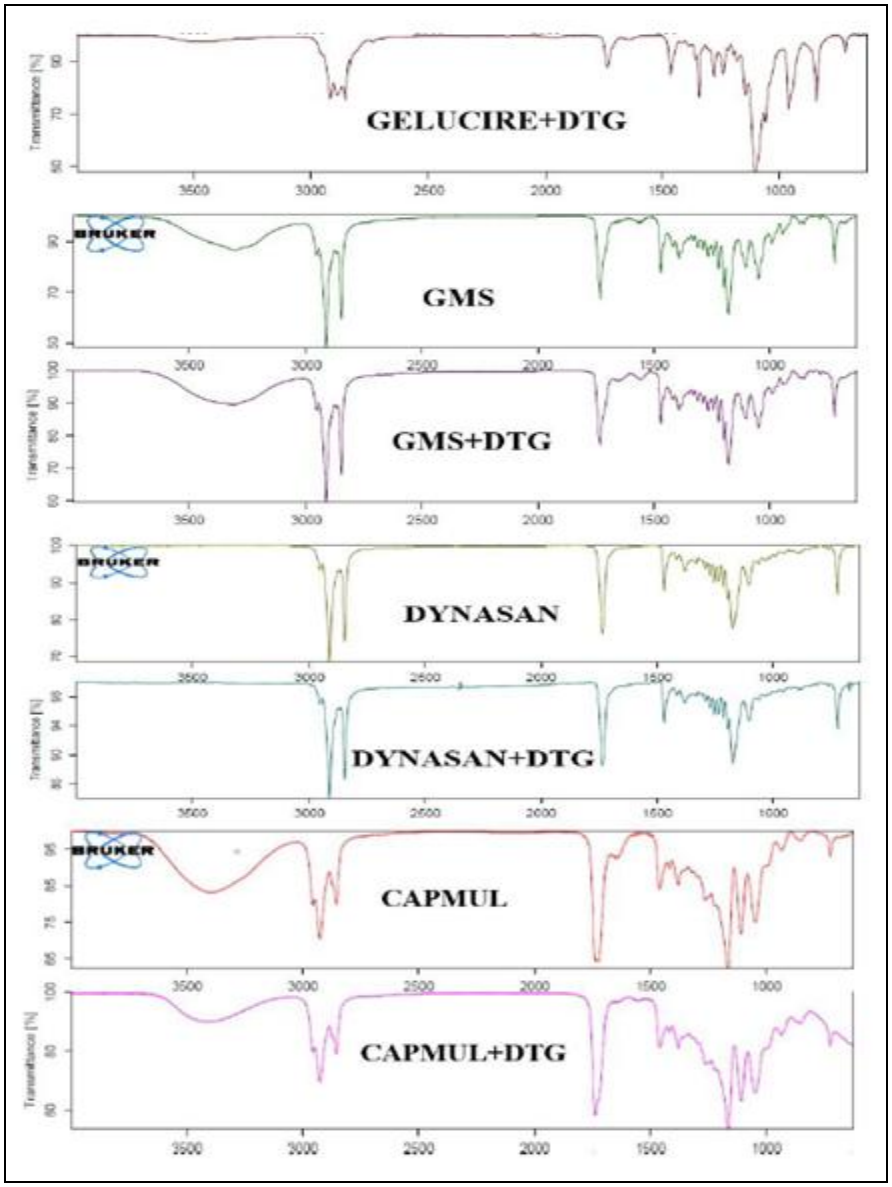


FIG. 11: FTIR SPECTRA

***In-vitro* Release:** *In-vitro* drug release using dialysis membrane demonstrated that the optimized NLC formulation (NLC-F2) showed sustained drug release over a period of 48 h with a maximum drug release of 96.32%.

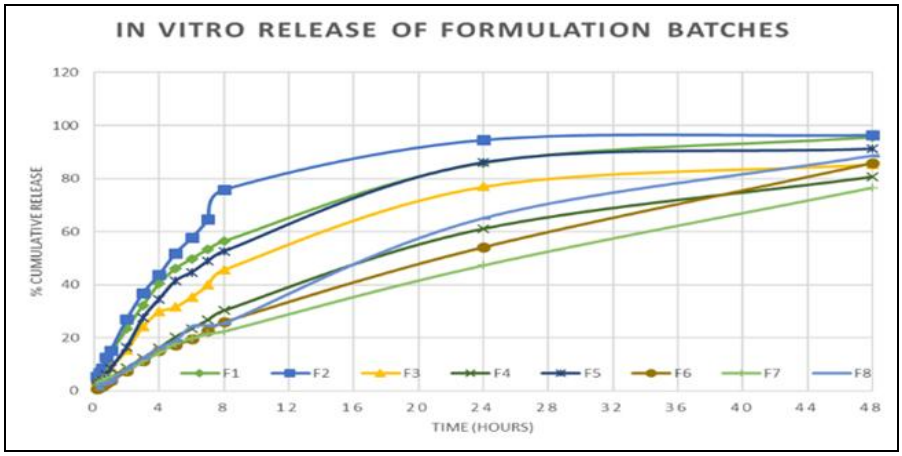


FIG. 12: *IN-VITRO* RELEASE OF FORMULATION BATCHES

***Ex-vivo*:** In *ex-vivo* studies, about 94.02% of drug permeated through rat intestine while it was only 55.62% in the case of plain DTG suspension during 8 h.

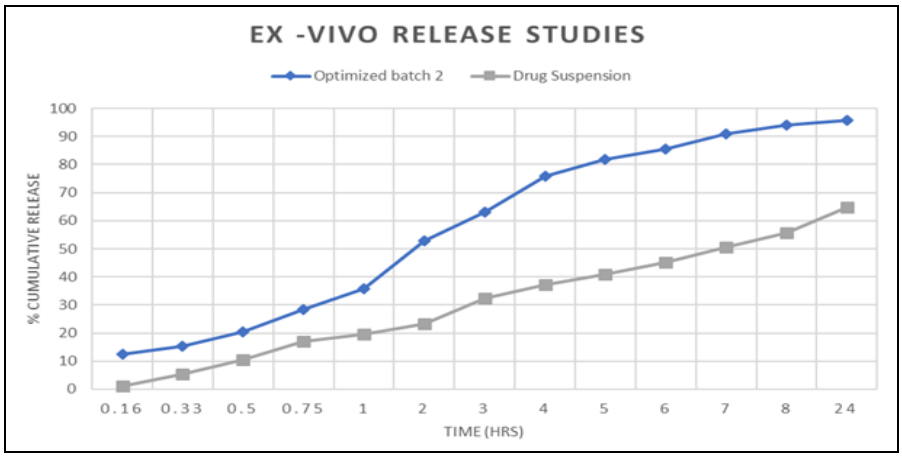


FIG. 13: *IN-VIVO* RELEASE OF NLC-F2 BATCH AND DRUG SUSPENSION

Flux: Flux of optimized batch and drug suspension through intestinal permeation was found to be 8.73 µg cm^{-2} hr^{-1} and 6.35 µg cm^{-2} hr^{-1} respectively, the Permeability coefficient of optimized batch and drug suspension was 0.349 and 0.254, which indicates a 1.374-fold increase in drug permeation **Table 9** when incorporated in Nano Lipid Carriers.

TABLE 9: FLUX AND PERMEATION COEFFICIENT DATA

	Concentration of drug (mg)	Slop (m)	Flux (J) µg cm^{-2} hr^{-1}	Permeation coefficient (K.p)	Ratio of permeation of drug
NLC-F2		87.662	8.73	0.349	= $Kp_{(NLC)}$ / $Kp_{(DS)}$
Drug Suspension (DS)	25	63.789	6.35	0.254	= 0.349/0.254
					1.374

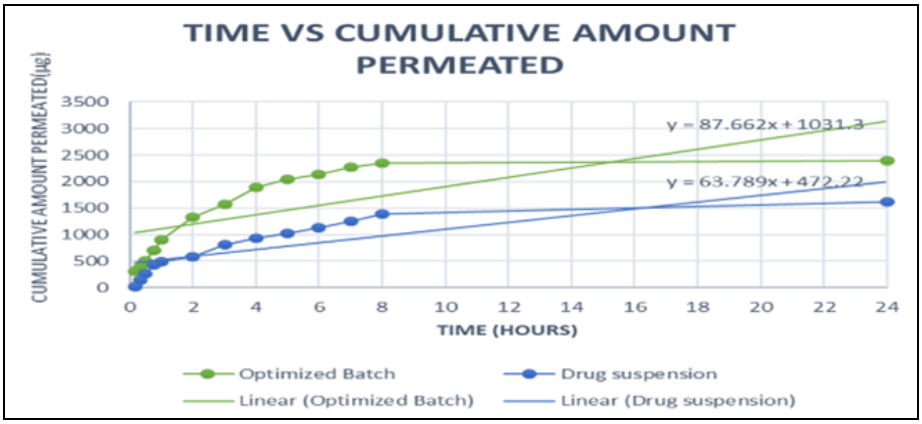


FIG. 14: TIME *vs.* CUMULATIVE AMOUNT PERMEATED FOR *EX-VIVO* STUDIES

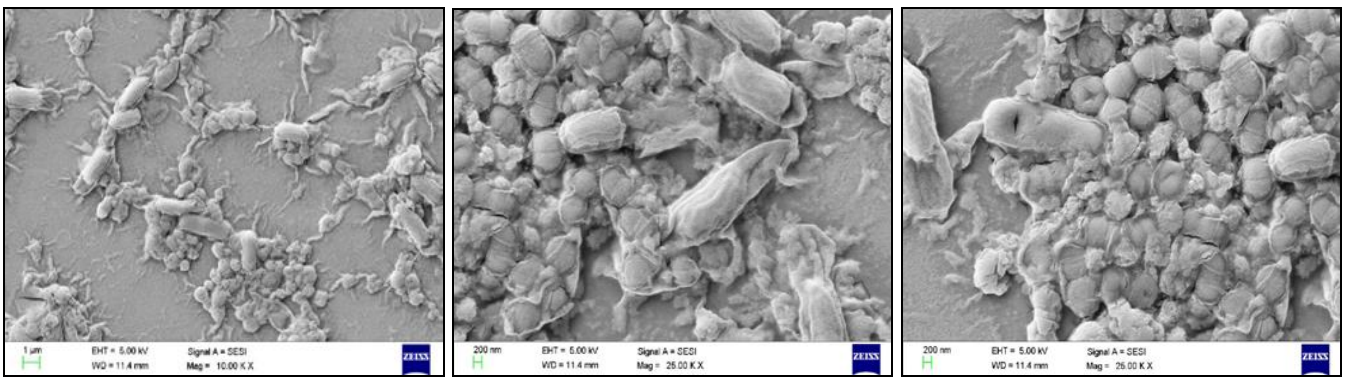


FIG. 15: SCANNING ELECTRON MICROSCOPY

Stability Studies: The optimized Nano Lipid Carrier formulation was found to be physically stable for 3 months at room temperature.

CONCLUSION: In this study, Dolutegravir sodium loaded oral Nano Lipid Carrier formulation as a suspension was successfully prepared by melt emulsification sonication technique.

Glyceryl monostearate, Gelucire 50/13, Dynasan 118 were selected as solid lipids, and Capmul MCM EP as liquid lipid, Tween 80 and Span 80 as surfactants, PEG 6000 for PEGylation of lipid, propylene glycol as drug solubilizer, and sodium cholate as charge modifier for the preparation of Nano Lipid Carriers.

Nano Lipid Carriers under optimized conditions showed small homogeneous particle size (123.1 nm) and entrapment efficiency (88.09%) by melt emulsification sonication technique. Observed responses were in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing Nano Lipid Carriers.

Since the rate of release of drug from the NLC formulation was found to be significantly higher, the results suggest that it takes time for DTG to be released when encapsulated in the NLC because of its high solubility in liquid lipid and the lipid layer is stabilized by Dynasan 118 (solid lipid) which plays a major role in prolonging the release. From the above results, it can be suggested that the drug would be stable in the intestine as the study was carried out in phosphate buffer pH 6.8, which mimics the intestinal condition.

In *ex-vivo* studies, permeation of drug from intestine was enhanced with Nano Lipid Carrier, which fulfilled our objective of solubility enhancement of drug and increased intestinal permeability, which would lead to enhancement in the bioavailability of DTG.

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