IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Research Article
August 2016 Vol.:4, Issue:2

Nanostructured Lipid Carrier System for Dissolution Rate Enhancement of Irbesartan

IJSRM
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Submission: 31 July 2016
Accepted: 7 August 2016
Published: 25 August 2016

Keywords: Nanostructured Lipid Carrier, Solid lipid, Liquid Lipid, Irbesartan, optimization, dissolution

ABSTRACT

Present study deals with the formulation of nanostructured lipid carrier system (NLCs) for poorly water soluble drug Irbesartan (IBR). NLC is a lipid system which consists of a combination of liquid lipid and solid lipid creating a matrix imperfection, increasing drug entrapment. Based on the solubility study of Irbesartan in different excipients; Glycerol monostearate, Capryol 90 and Cremophore EL were selected as solid lipid, liquid lipid and surfactant respectively for formulating IBR-loaded NLC. Drug entrapment, drug loading and particle size were studied for the optimization of the formulation batch with maximum drug entrapment and drug loading and with minimum particle size was selected as an optimized batch for *in vitro* drug release study. IBR loaded NLC showed cumulative drug dissolution of 87% as compared to 45% for IBR suspension in water.

1. INTRODUCTION

Oral lipid-based products entered the market in 1981 and currently account for approximately 3% of commercially available oral formulations. Lipid-based formulations range in complexity from simple, one-excipient solutions based on e.g. sesame or corn oil to multi-excipient, self-emulsifying drug delivering systems (SEDDS) and nanostructured lipid carriers (NLCs) [1 and 3]. There are many natural and synthetic lipids aimed to improve oral bioavailability of poorly water-soluble drugs. When administered in hydrophilic form of solid formulations, these compounds exhibit low bioavailability as their absorption can be dissolution- and capacity-limited due to poor solubility [1]. Lipid formulations can reduce the inherent limitation of slow and incomplete dissolution of poorly water-soluble drugs and facilitate formation of solubilised phases from which absorption may occur. The solubilised phases most likely arise from intra-luminal processing after lipid absorption. The co-administration of lipids with drugs can also impact their absorption pathway. Although most orally administered compounds gain access to the systemic circulation via the portal vein, some highly lipophilic drugs are transported directly to the systemic circulation via intestinal lymphatic system, which improves oral bioavailability of active pharmaceutical ingredient (API) [2]. Compounds with a low aqueous solubility, i.e. belonging to the BCS class II and IV, are frequently discussed in relation to lipid based drug delivery system (LBDDS) [4].

Nanostructured lipid carriers (NLC) are considered to be the second generation of lipid nanoparticles. NLC show a higher loading capacity for active compounds by creating a less ordered solid lipid matrix, i.e. by blending a liquid lipid with the solid lipid, a higher particle drug loading can be achieved. Liquid lipids solubilize drugs to a much higher extent than solid lipids. In a preferred scenario, the liquid lipids form droplets within the solid lipid particles matrix. According to this model, the NLC nanoparticles would provide a high incorporation capacity (due to the liquid lipid) and control of drug release (due to the encapsulating solid lipid). NLC have also a lower water content of the particle suspension and a less tendency of unpredictable gelation [5-10].

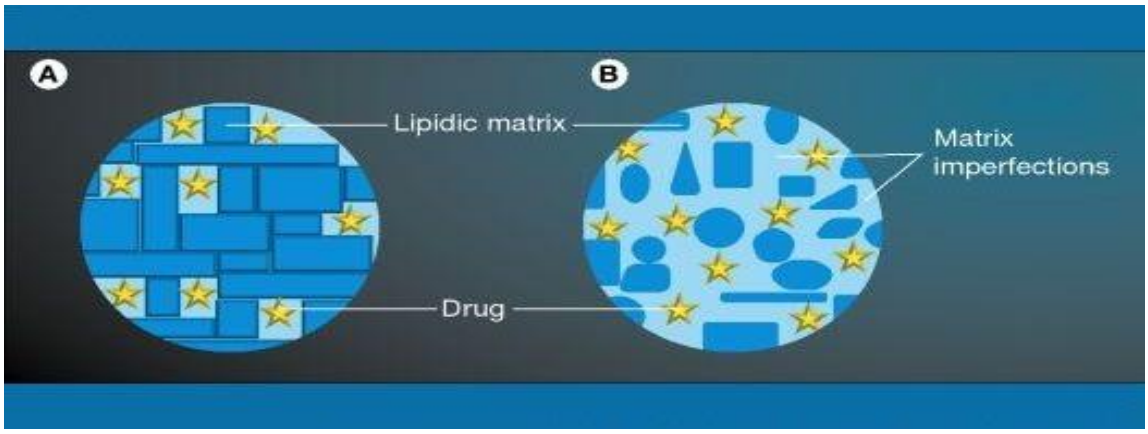

Figure 1: Matrix imperfections in Nanostructured lipid carrier system (B)

According to biopharmaceutical classification system, Irbesartan (IBR) has a low solubility and high permeability. IBR is non-peptide, angiotensin II receptor antagonist with high specificity for the AT1 subtype, used in the treatment of hypertension. The drug is lipophilic and practically insoluble in water. The low aqueous solubility and slow dissolution may lead to irreproducible clinical response or therapeutic failure. The plasma levels of this drug do not increase proportionally with the increase in dose. Thus theoretically IBR exhibits a solubility limited bioavailability**.** Hence, the main aim of present research project was to increase the dissolution and release properties of these drugs.

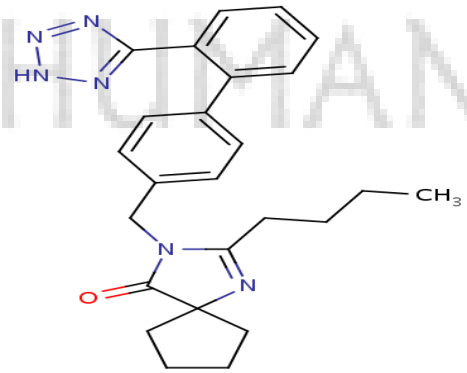

Figure 2: Structure of Irbesartan

The objective of the present research work was to design, prepare, and evaluate a nanostructured lipid carrier (NLC) formulation for Irbesartan using solid lipid, liquid lipid and surfactant in

combination which would enhance solubility, avoid first pass metabolism and thereby increase bioavailability of IBR and to study the *in-vitro* profile of the drug in the formulation.

2. MATERIAL AND METHODS

2.1 Materials:

Irbesartan (IBR) was kindly provided as a gift sample from Cadila Healthcare Ltd. Glycerol monostearate (GMS), Stearic acid, Tween 80 (polysorbate 80), Span 20, Methanol was purchased from S.D fine Chemicals. Precirol, Compretol, Maisine 35-1, Labrafac PG (propylene glycol caprylate/caprate), Labrafil M CS 1944 (oleoyl macrogolglycerides), Labrasol (Caprylo Caproyl macrogol glycerides), Gelucire 44/14 (Lauroyl polyoxyl-32 glycerides), Capryol 90 (Polypropylene glycol monocaprylate) and Transcutol P (purified diethylene glycol monoethyl ether) was provided as a gift sample from Gattefisse Saint Priest Cedex, France.

2.2 Solubility of Irbesartan in solid lipid:

Weighed quantity of drug was taken and mixed with melted solid lipid and the mixture was observed for any unsolubilized drug, this procedure was continued till no more drug goes into the lipid and unsolubilized drug was observed. Solubility of drug in different lipids such as Glycerol monostearate, Compretol, Precirol and stearic acid was determined. The experiment was repeated in triplicate and the results represent the mean value (mg/gm + SD) [11].

2.3 Solubility of Irbesartan in liquid lipid and surfactants:

An excess amount of the drug was added to 2 gm of oil in an Eppendorf. The mixture was vortexed to facilitate solubilization. The mixture was then shaken for 24 hours in a mechanical shaker at room temperature (to attain equilibrium) and centrifuged at 15000 rpm for 15 min. Supernatant was withdrawn and suitably diluted with methanol and the drug concentration was determined by UV-VIS spectrometer. The experiment was repeated in triplicate and the results were represented as mean value (mg/gm+ SD). Same procedure was followed to study solubility of drug in surfactants. Solubility of drug in different liquid lipids such as Labrafac P.G, Labrafil, maisine oil, and Capryol 90 was studied. Study was also performed on different surfactants such

as Tween 80, Span 80, Span 20, Solutol HS-15, Labrasol, Cremophore RH-40, Cremophore-EL and Transcutol-P [12].

2.4 Preparation method of IBR-NLC

The lipid and aqueous phases were prepared separately. The lipid phase was prepared in methanol with solid lipid (w/w) and liquid lipid (w/w). The aqueous phase consisted of distilled water (dH_2O) and emulsifier (w/w). IBR/OLM was dissolved in the lipid phase. Both the phases were heated separately to 85^0C. The aqueous phase was added to the lipid phase and mixed using a high-shear homogenizer at 4,000 rpm for 10 min and at 10,000 rpm for next 15 min. The mixture was further subjected to ultrasonication for 10 min. to obtain a translucent NLC [13-16].

2.5 Drug excipients compatibility studies:

Drug-excipient compatibility studies form an integral part of any pre-formulation study since even a minor incompatibility between the two could result in an altered release profile or degradation of the drug itself or the excipients ultimately leaving the dosage form below the therapeutic standard. The compatibility of Irbesartan and Medoxomil with excipients was studied by FTIR and DSC.

2.5.1. Fourier Transform Infra Red Spectroscopy (FTIR):

The samples of Irbesartan, excipients and NLC formulation (1mg) was finely grounded and intimately mixed with approximately 200 mg of dried KBr (kept at 100^oC for 8 h). Grinding and mixing were done in a mortar and pestle. The mixture was then pressed into a transparent disk in an evacuable die at a sufficient high pressure. The entire operation was conducted under controlled humidity. The sample was then scanned using spectrophotometer (Shimadzu, Japan) in the 400-4000 cm^{-1} range and major absorption bands were recorded. The presence and absence of these bands and appearance of any new band was observed in the FTIR absorption spectrum.

2.5.2. Differential Scanning Calorimetry (DSC):

DSC analysis was carried out in Mettler Toledo DSC 821e model, using data recording software STAR® SW 9.20 and calibrated with indium as per the standard procedure. The equipment was

provided with an auto-cooling accessory for programmed cooling. The sample was weighed accurately into a standard aluminum pan, hermetically sealed and heated from 25 to 300°C at a constant rate of 10°C /min under constant purging of nitrogen at 20 ml/min. An empty sealed pan was used as a reference. DSC graphs for Irbesartan, Olmesartan Medoxomil, excipients, and physical mixtures were recorded and the melting point, peak maxima, the presence and absence of endotherm peaks were observed in the DSC graphs.

Specifications:

a) Sample Holder: Perforated aluminum pans
b) Temperature range studied: 25-300^{o}C
c) Heating rate: 10^{o}C/ min
d) Reference sample: Blank perforated aluminum pans.

2.6 Computer Aided Optimization of IBR-NLC

In order to obtain optimal excipient concentrations of Irbesartan loaded NLC formulation, central composite rotatable design (CCRD) was applied. For this Design-Expert software (8.0.7.1 version) of Stat-Ease, Inc. Minneapolis, USA was used [17-22].

2.6.1 Selection of independent variables:

Preliminary experiments indicated that the three variables such as solid lipid, liquid lipid and surfactant were the main factors that affected the NLC formulation characteristics. A variation in the concentration of any of these components causes a change in the drug loading (DL), entrapment efficiency (EE) and other properties of the NLC. Thus, a central composite rotatable design–response surface methodology (CCRD–RSM) was used to systematically investigate the influence of these three critical formulation variables on particle size, drug loading and entrapment efficiency of the prepared NLC. Thus, concentration of solid lipid, liquid lipid and surfactant were chosen as the independent variables for the optimization. For each factor, the experimental range was selected on the basis of the results of preliminary experiments, literature survey and the feasibility of preparing the NLC at the extreme values. The value range of the variables was solid lipid concentration (A) of 2-6 %, liquid lipid concentration (B) of 0.8-2.4 % and surfactant concentration (C) of 1-3 %. As given in table 1.

Independent variables for Irbesartan:

1) Glycerol monostearate (solid lipid)
2) Capryol 90 (liquid lipid)
3) Cremophore-EL:Transcutol P (1:1) (surfactant and co-surfactant)

Table 1: Independent variables and their ranges for optimization of NLC formulation

Sr. No.	Variable/Factor	Lower limit	Upper limit
1.	Solid lipid (A)	2 %	6 %
2.	Liquid lipid (B)	0.8 %	2.4 %
3.	Surfactant (C)	1 %	3 %

2.6.2 Selection of response variables:

The response variables selected were the particle size, entrapment efficiency and drug loading. The various response variables selected are given in table: 2.

Table 2: Response variables selected for optimization of NLC formulation

Sr. No.	Response Variable	Unit	Type
1.	Particle size (Y_1)	Nm	Numeric
2.	Entrapment efficiency (Y_2)	%	Numeric
3.	Drug loading (Y_3)	%	Numeric

Percent quantity of the independent variables to study and optimized IRB loaded NLC obtained by using central composite rotatable design (CCRD), are given in table 3.

Table 3: Optimization batches for Irbesartan

Batch run	A	B	C
1	2	0.80	1
2	6	0.80	1
3	2	2.40	1
4	6	2.40	1
5	2	0.80	3
6	6	0.80	3
7	2	2.40	3
8	6	2.40	3
9	0.64	1.60	2
10	7.36	1.60	2
11	4	0.25	2
12	4	2.95	2
13	4	1.60	0.32
14	4	1.60	3.60
15	4	1.60	2

20 ml of the optimization batches given in table 3 were formulated for the study purpose. The ingredient and their quantity for formulating IBR-NLC is given in table 4.

Table 4: Pre-optimization batches formulated for total volume for 20 ml of IBR- NLC

Batch	GMS mg	Capryol 90 Mg	Cremophore EL: Transcutol p (1:1) mg	IBR Mg
OT1	0.4	0.16	0.2	150
OT2	1.2	0.16	0.2	150
OT3	0.4	0.48	0.2	150
OT4	1.2	0.48	0.2	150
OT5	0.4	0.16	0.6	150
OT6	1.2	0.16	0.6	150
OT7	0.4	0.48	0.6	150
OT8	1.2	0.48	0.6	150
OT9	0.128	0.32	0.4	150
OT10	1.472	0.32	0.4	150
OT11	0.8	0.05	0.4	150
OT12	0.8	0.59	0.4	150
OT13	0.8	0.32	0.064	150
OT14	0.8	0.32	0.736	150
OT15	0.8	0.32	0.4	150

2.7. Evaluation of pre-optimization batches

The pre-optimization batches obtained in the experimental design were evaluated for the responses, i.e. particle size, entrapment efficiency and drug loading.

2.7.1. Particle size:

The average particle size, size distribution and polydispersity index of OLM–NLCs and IRB-NLCs were determined using Zetasizer Ver. 6.34 (Malvern Instruments Ltd) and Nanophox Particle Size Analysis Windox 5. Prior to the measurements, all samples were diluted with double distilled water to produce a suitable scattering intensity.

2.7.2. Entrapment efficiency (EE) and drug loading (DL)

The encapsulation efficiency and drug loading were determined using centrifugation method. 2ml of drug loaded NLC was taken in Eppendorf and centrifuged at 15000 rpm for 20 min. After centrifugation supernatant was withdrawn and diluted suitably with methanol. The drug content in the supernatant (free drug) after centrifugation was measured by using UV-VIS spectrophotometer (Shimadzu vision pro software). Methanol was used as reference solution. The %EE and %DL in IBR-NLCs and OLM-NLCs were calculated from calibration equation.

$$\% \text{ EE} = \text{Wa} - \text{Ws} / \text{Wa} \times 100$$

$$\% \text{ DL} = \text{Wa} - \text{Ws} / \text{W}_\text{L} \times 100$$

Where, Wa, Ws and W_L were the weight of drug added to the system, free drug in supernatant and weight of lipid added in system, respectively [13, 14].

2.8. Lyophilization of optimized OLM-NLC and IBR-NLC:

The NLC precipitate was re-dispersed in lactose and glucose solution (5 % in water) in the lyophilization process to prevent the coagulation of the NLC in the aqueous suspension. It was fast frozen at -75^0 C in a deep-freezer for 5 h after which the sample was freeze dried. The drying time was 72 hrs. The NLC powder was subjected to DSC and SEM analysis.

2.9. Morphology of particles:

The surface morphology of optimized IBR-NLC and OLM-NLC was visualized by scanning electron microscopy (SSX-550, Shimadzu, Japan).

2.10. *In vitro* drug release studies:

The *in vitro* release studies of OLM and IBR from NLC were carried out by the bulk equilibrium dialysis technique. The release medium was 0.1 N HCl (pH 1.2) at 37^oC. The stirring speed was set at 50 rpm. The dialysis membrane (molecular weight cut off 12-14 kDa) was equilibrated in the release medium for 12 hr prior to experiment. 5 ml of IBR-NLC were directly placed into dialysis membrane, which was placed in 900 ml of the release medium. At intervals of 0, 15, 30, 60, 90, 120, 180 and 240 min, 5 ml of aliquot were withdrawn and same volume of medium was

replaced to maintain the constant volume. Then the aliquot was analyzed by UV-VIS spectrophotometer. Same procedure was followed for OLM-NLC [13-16].

3.1 RESULTS AND DISCUSSION

3.2 Solubility study of Irbesartan

From the solubility study conducted for IBR it was observed that IBR showed better solubility in GMS (48.6 ± 1.5 mg/gm) and compretol (39.1 ± 1.9mg/gm) as compared to other solid lipid used in the study. IBR also showed better solubility in Maisine 35-1 and caproyl 90 as compared to other liquid lipids used in study and also showed better solubility in cremophore –EL, span 80 and in Transcutol-P as compared to other surfactants. As given in table 5, 6 and 7.

Table 5: Solubility studies of Irbesartan in solid lipid excipients.

Sr. No.	Lipid (solid)	Solubility (mg/gm) ± SD
1.	Glycerol monostearate (GMS)	48.6 ± 1.5
2.	Stearic acid	23.4 ± 2.1
3.	Compretol	39.1 ± 1.9
4.	Precirol	11.15 ± 1.7

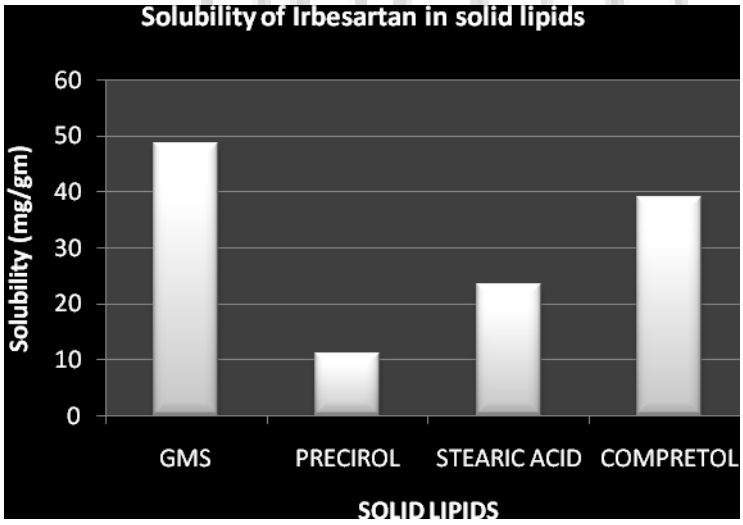

Figure 3: Solubility studies of Irbesartan in solid lipid excipients

Table 6: Solubility studies of Irbesartan in different liquid lipid excipients

Sr. No.	Lipid (liquid)	Solubility (mg/gm)) ± SD
1.	Labrafil M 1944 CS	32 ± 2.5
2.	Maisine 35-1	112 ± 0.5
3.	Capryol-90	98 ± 1.5
4.	Labrafac PG	41 ± 2.0

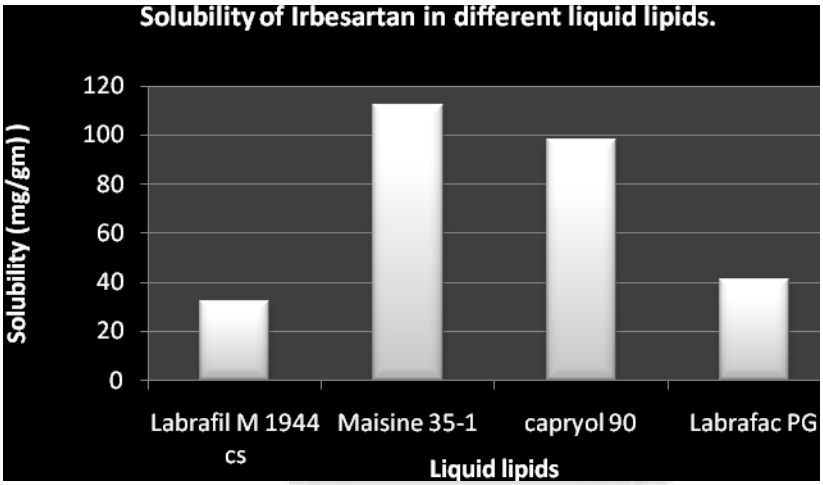

Figure 4: Solubility of Irbesartan in different liquid lipids

Table 7: Solubility of Irbesartan in different surfactants and co-surfactants

Sr. No.	Surfactant/co-surfactant	Solubility (mg/gm)) ± SD
1.	Tween 80	135 ± 2.4
2.	Span 80	142 ± 3.1
3.	Span 20	182 ± 3.5
4.	Solutol HS-15	140 ± 2.1
5.	Labrasol	121 ± 1.6
6.	Cremophore RH-40	111 ± 2.1
7.	Cremophore EL	250 ± 2.1
9.	Transcutol –p	283 ± 3.1

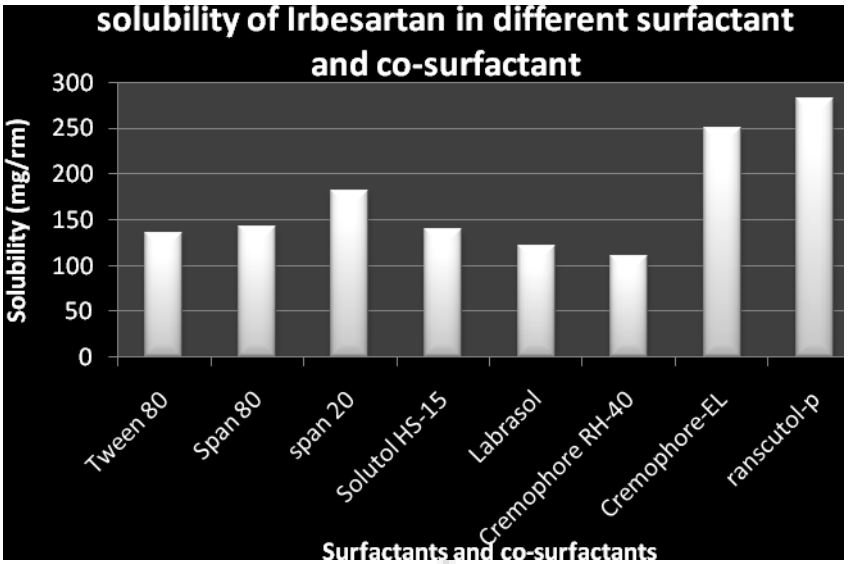

Figure 5: Solubility of Irbesartan in different surfactants and co-surfactants

3.3 Selection of excipients:

Final selection of excipients for formulation IBR-NLC was done on the basis of formulating IBR-NLC using excipients selected from solubility studies. Batches were formulated using different combinations of selected solid lipid, liquid lipid and surfactants, as given in table 9. Formulated batches were studied at the end of 15 days for appearance and stability of batches (cracked or stable) and batch containing GMS, caproyl 90 and chemophore –EL as solid lipid, liquid lipid and surfactant respectively were found to be more stable as given in Table 10, and the excipients were selected for formulating IBR-NLC for further studies.

Table 8: Selected excipients on the basis of solubility studies

DRUG	SOLID LIPID	LIQUID LIPID	SURFACTANTS
Irbesartan	Glycerol monostearate and compretol	Capryol 90 and maisine oil	Cremophore EL and span 20

Table 9: Table showing combinations of selected excipients for Irbesartan

Batch	Solid lipid	Liquid lipid	Surfactant
TC1	Compritol	Maisine oil	Cremophore EL
TC2	Compritol	Maisine oil	Span 20
TC3	Compritol	Capryol 90	Cremophore EL
TC4	Compritol	Capryol 90	Span 20
TG1	Glycerol monostearate	Maisine oil	Cremophore EL
TG2	Glycerol monostearate	Maisine oil	Span 20
TG3	Glycerol monostearate	Capryol 90	Cremophore EL
TG4	Glycerol monostearate	Capryol 90	Span 20

Table 10: Table showing stability of preliminary batches using selected excipient for Irbesartan.

Batch	Viscosity (CP)	Consistancy	Stability at the end of 15 days
TC1	0.975	Solidified	Not stable
TC2	1.763	Solidified	Not stable
TC3	1.412	Solidified	Not stable
TC4	1.725	Solidified	Not stable
TG1	1.050	Free flowing (cracked)	Nost stable
TG2	1.650	Solidified	Not stable
TG3	**0.563**	**Free flowing**	**Stable**
TG4	1.725	Solidified	Not stable

Batch TG3 was formulated using Transcutol-p to see the effect of co-surfactant on stability and entrapment of the drug in formulation and it was observed that batch formulated using Transcutol-p in the ration 1:1 with the selected surfactant i.e Cremophore –EL, was more stable and showed a good drug entrapment when observed visually as shown in Table 11.

Table11: Table showing batches formulated using Transcutol-P as a co-surfactant.

SR. NO.	DRUG	SURFACTANT	CO-SURFACTANT	RATIO OF SURFACTANT :CO-SURFACTANT	DRUG ENTRAPED
1	Irbesartan	Cremophore-EL	----------	----------	Drug not completely incorporated
2	Irbesartan	Cremophore-EL	Transcutol –p	1:1	Drug was completely incorporated

From the above study Glycerol monostearate, Capryol 90, Cremophore EL and Transcutol –p (in 1:1 ratio) were selected as solid lipid, liquid lipid, surfactant and co-surfactant for formulation of IRB loaded NLC.

3.4 Drug Excipient Compatability Studies for Irbesartan

3.4.1 DSC studies

Figures: 6, 7 and 8 show the DSC thermograms for IBR, GMS and mixture of excipients and drug . DSC thermogram of IBR showed a sharp melting endothermic peak at 186^0C.

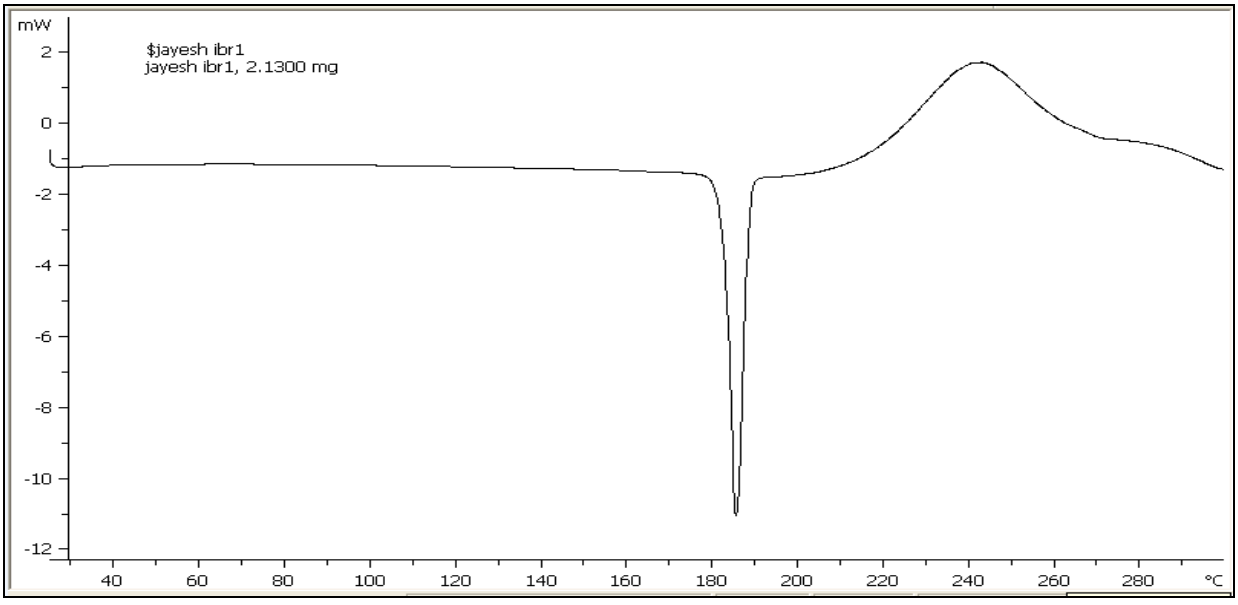

Figure 6: DSC of IBR

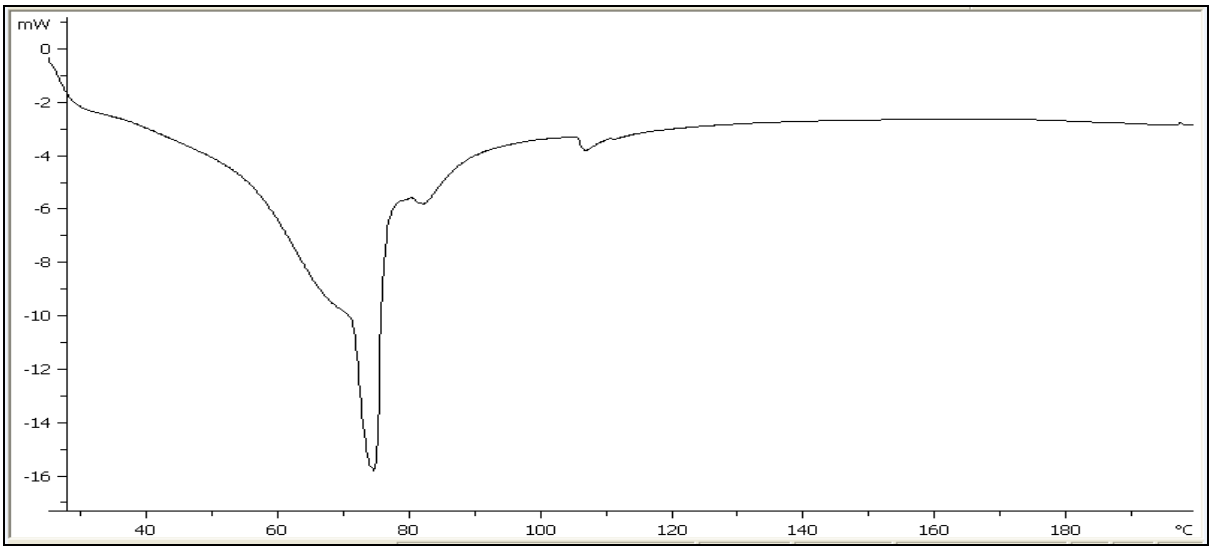

Figure: 7: DSC of GSM

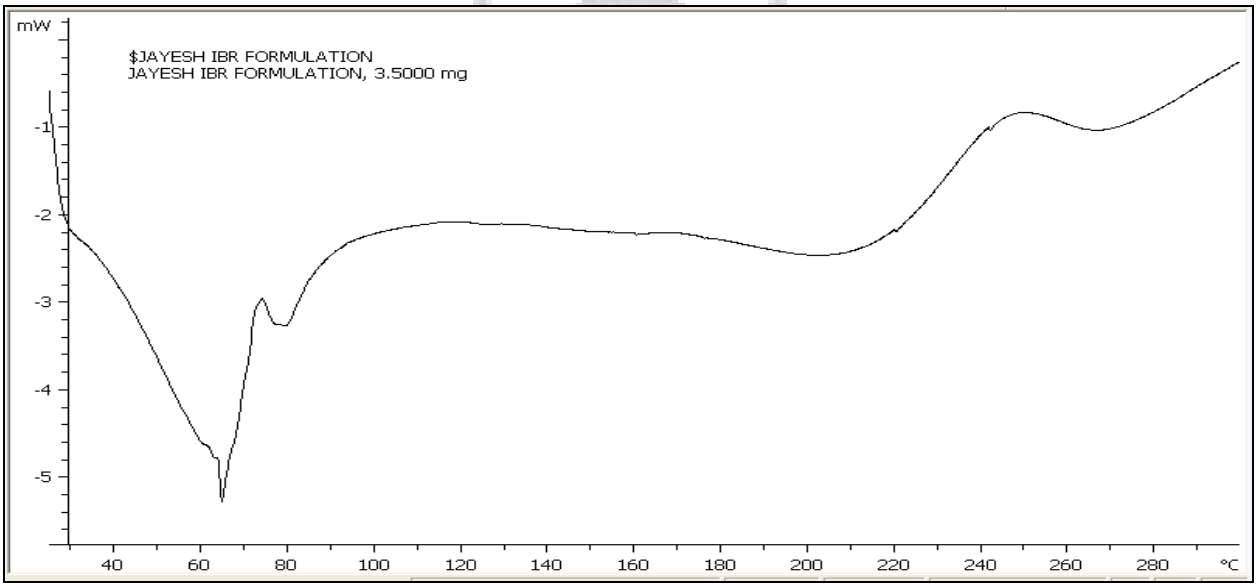

Figure: 8: DSC of mixture of excipient and drug(IBR)

From DSC graphs it was concluded there is absence of IBR peak in the mixture of excipients, indicating that the drug has dissolved in the excipients of formulation.

3.4.2 FTIR studies:

All the characteristic peaks representing respective functional groups for IBR are present in the spectra of the mixture of excipients. Results of the IR studies are shown in figures: 9, 10 and 11.

No additional peak was found in the spectrum of mixture of excipients which indicates absence of incompatibility between IBR and other excipients.

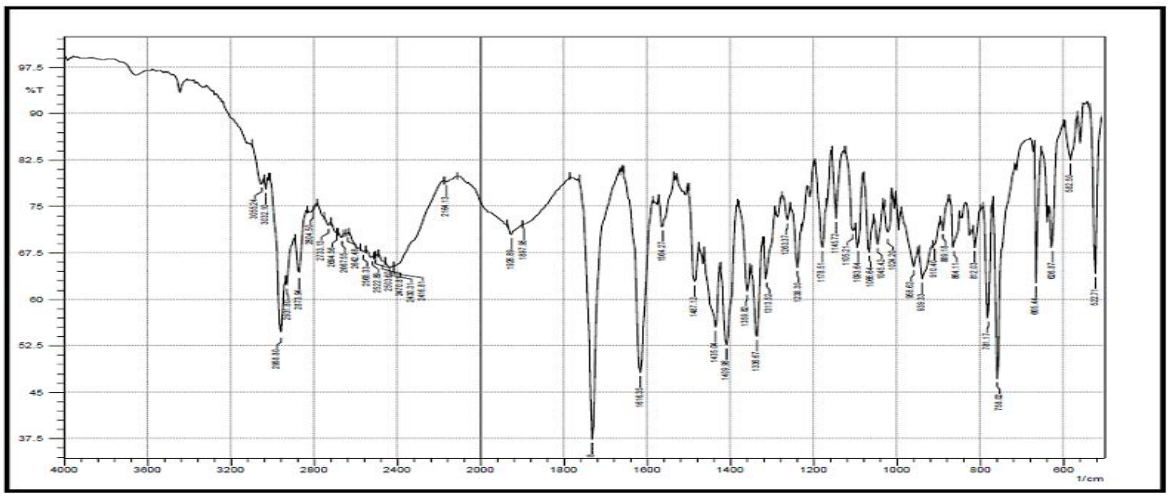

Figure: 9: FTIR of IBR

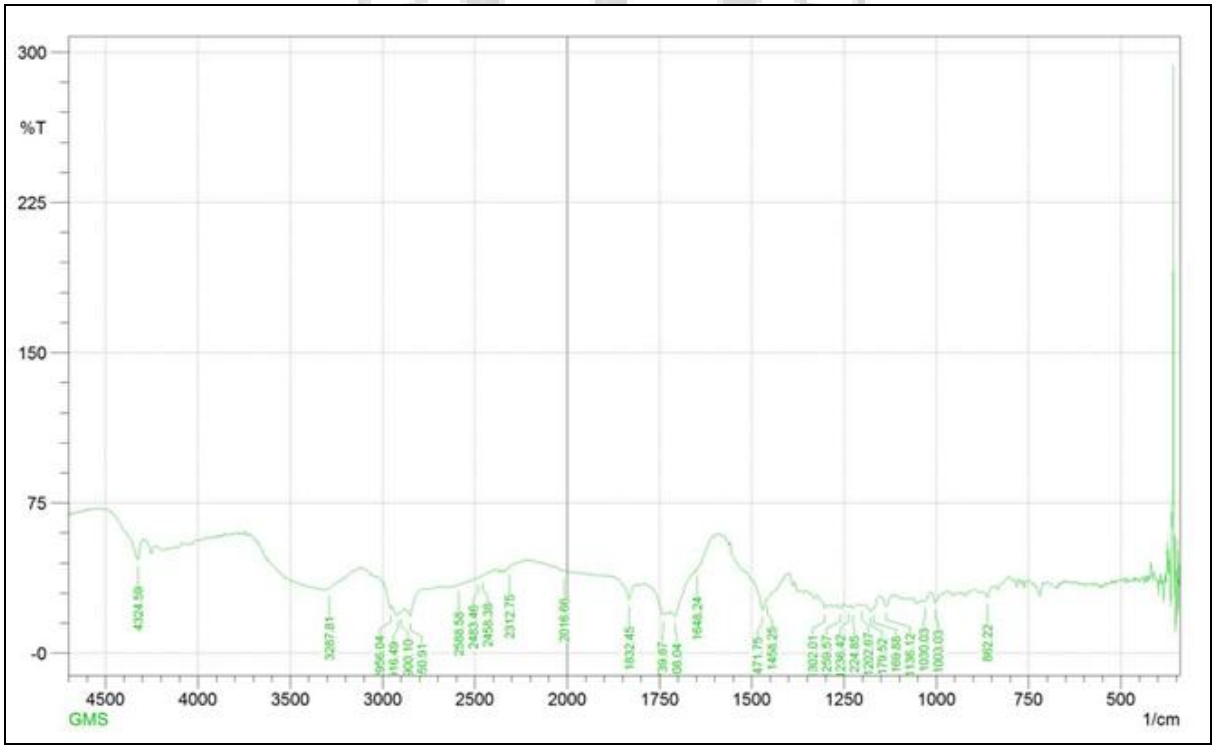

Figure: 10: FTIR of GMS

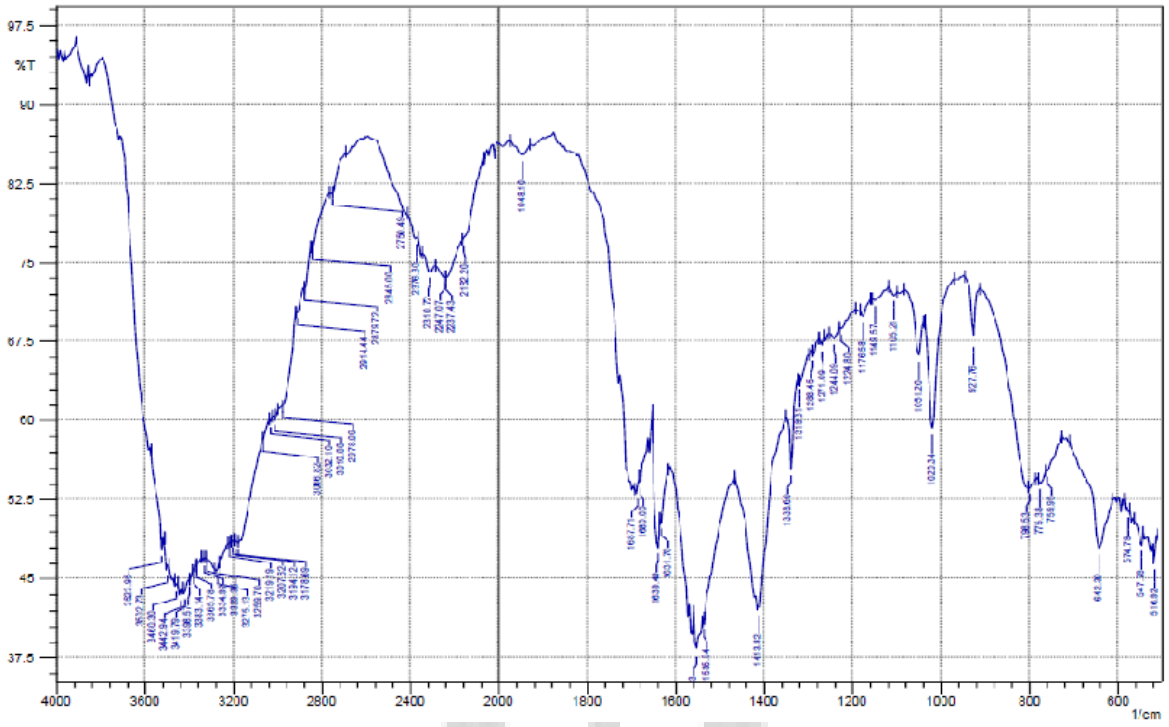

Figure 11: FTIR of mixture of excipients and drug (IBR)

3.5 Observation for pre-optimization batches for Irbesartan

Evaluation of the pre-optimized batches of IBR loaded NLC concluded that batch number OT7 which composed of GMS 0.4 mg , Caproyl 90 0.48 mg, surfactant (Cremophore EL: Transcutol P (1:1)) 0.6 mg and IBR 150 mg, showed smallest particle size and comparatively better drug loading and drug entrapment as shown in Table 12 and was considered as the optimized batch and used for further studies.

Table 12: Table showing observation for pre-optimization batches for Irbesartan

Batch	E.E %	D.L %	Particle size (ηm)
OT1	87.12	19.32	234.49
OT2	93.23	10.50	*
OT3	92.42	11.37	502.18
OT4	89.16	16.26	*
OT5	90.26	14.61	186.29
OT6	92.24	11.64	*
OT7	**91.31**	**13.03**	**175.84**
OT8	88.43	17.35	*
OT9	89.41	15.88	*
OT10	92.18	11.73	*
OT11	92.31	11.53	*
OT12	91.23	13.15	380.98
OT13	83.52	24.72	*
OT14	88.27	17.59	*
OT15	91.32	13.02	*

* Batch was not stable and hence particle size was not performed.

From the above observation batch OT7 was taken as optimized batch for Irbesartan for further studies.

3.6 Evaluation Of Optimized IBR-NLC

3.6.1 Particle size

Particle size for optimized IBR-NLC was found to be 175.84 ηm with a polydispersity index 0.452. This reveals that the size distribution of the particles was quite narrow and they had a uniform size as shown in figure 12.

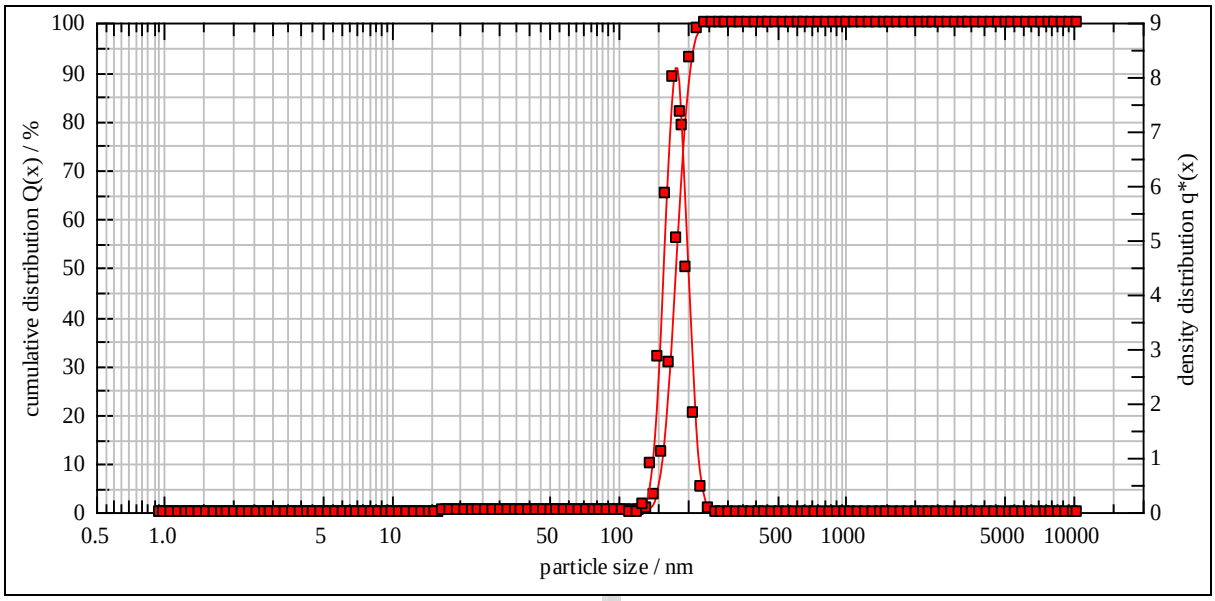

Figure 12: Particle size for optimized IBR-NLC

3.6.2 Drug Entrapment Efficiency (% EE) and Drug Loading (% DL):

Entrapment efficacy and drug loading for optimized IBR-NLC was found to be 91.31% and 13.03%.

3.6.3 Morphology of particles:

In order to give information on the morphology and size of the optimized OLM-NLC and IBR-NLC, SEM was used to take images of the optimized NLCs. Figure: 13 show the images of surface morphology and internal structure of IBR-NLC after freeze-drying. The results indicated that the particles were round and homogeneous with a smooth surface. There was no drug crystal or aggregation of particles visible.

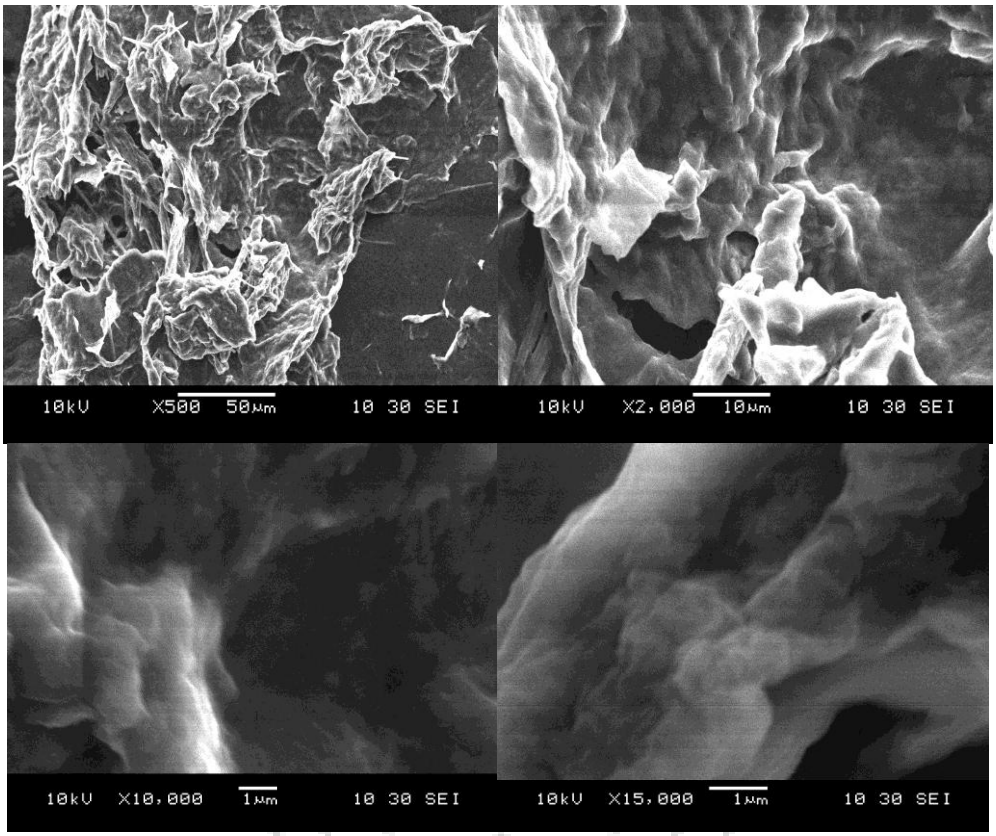

Figure 13: SEM morphology of IBR-NLC showing the surface structure of the lyophilized powder of IBR-NLC at 500, 2000, 10000, 15000 resolution

3.6.4 *In vitro* drug release studies:

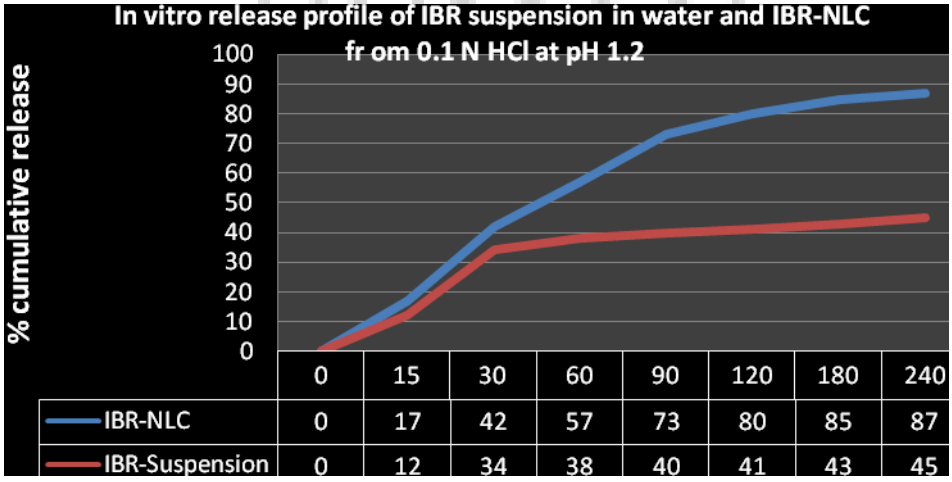

Figure 14: *In vitro* drug release profile of IBR-NLC and IBR suspension in water from 0.1 N HCl at pH 1.2

As shown in figure 14 IBR-NLCs showed no burst release at initial stage in dissolution medium, which was evidence that there was no unencapsulated drug attaching to the surface of the particles. IBR-NLC show somewhat same release as the IBR-Suspension initially. IRB continued to release from NLC over a period of 4 hrs, which gives a sustain release profile. A maximum of 87% of the drug was released from NLC as compared to 45% from drug suspension in water, over a period of 4 hrs in the acidic pH i.e stomach condition which is also an absorption site of the drug. Thus drug is released from the NLC at its desirable site of absorption and over a larger period of time.

4 CONCLUSION

In this study, IBR-NLC for oral administration was successfully prepared by a high shear homogenization method. Glycerol monostearate, Capryol 90 and Cremophore EL with transcutol P were selected as the solid lipid (V_1), liquid lipid (V_2) and surfactant with co-surfactant combination (V_3) respectively for IBR-NLC.

The rate of release of Irbesartan from NLC formulation was found to be significantly higher than the pure drug suspension. IBR-NLC showed 87% drug release which was higher than the pure drug in 0.1N HCl at pH 1.2. This shows that drug was dissolved to larger extent than the pure drug at stomach condition which is the site of absorption for IBR. Thus, NLC prepared offer a potential approach to enhance the oral bioavailability of poorly water soluble drugs. Based on these findings further studies can be done to determine the precise and specific mechanisms for improvement of oral absorption of poorly water soluble drugs in NLC formulations

5 Acknowledgements:

Authors are thankful to AICTE (RPS) for funding the research project. Authors are also thankful to Zydus Cadila Healthcare Pvt. Ltd. Mumbai, India for providing us with the gift sample of the drug Irbesartan.

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