ORIGINAL ARTICLE

ScienZTech

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND LIFE SCIENCES

Published by ScienzTech Publication Journal Home Page: www.scienztech.org/ijprls

Design, optimization and *invitro* evaluation of lovastatin nanostructures lipid carrier

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Article History:

Received on: 05 Nov 2018
Revised on: 04 Dec 2018
Accepted on: 15 Dec 2018
Published on: 28 Dec 2018

Volume: 6 Issue: 2

Keywords:

Nanostructured lipid carrier,
Invitro drug release,
peppas and Release kinetic studies,
Factorial design

ABSTRACT

The intention of this current study is to intensify the bioavailability of drugs which have lower bioavailability (<20 %) like Lovastatin in the form of NLC carrier and also to optimize the formulation to select perfect variables for the formulation. The Nanostructures lipid carrier was formulated using Hot Homogenization technique with some optimization by utilizing 2^3 factorial design with the heal of response like in-vitro drug release, % Entrapment Efficiency (EE%), % drug Content (%DC), Zeta potential (Zp), Polydispersity Index (PI) and Particle Size (PS) for 12 hours. The kinetic studies of in-vitro drug release was performed and the parameters of the drug in different kinetic models like higuchi kinetic, zero order, first order, peppas models were evaluated. Invitro release kinetics studies show that optimized formulation NLC (N3) obeys Super Case II kinetics transport mechanism i.e., release of drug through reduction of attractive forces between Lipid chains and Zero order release kinetics for controlled drug delivery. Hence Nanostructure lipid carrier shows a good control and predetermined rate of drug release of Lovastatin. From the obtained outcome, N3 formulation was concluded as an optimized formulation with selected formulation variables like Solid Lipid: Liquid Lipid ratio (6:4), Span 80 as Surfactant (1%) and process variables like homogenization Speed as 5000 Rotations per minute for 15 mins.

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DOI: https://doi.org/10.26452/ijprls.v6i2.1239

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INTRODUCTION

In this developing world, Nanoparticles were placing their own utility in the field of pharmacy. These are sub-micro level solid, colloidal polymeric drug carriers / systems. These nanoparticles can be used in cosmetic and tropical products by preparing Nano-capsules or Nano-spheres.

The encapsulation of a drug nanoparticle entails formation of 1 – 1000 nm diametric drug loaded particles. Compared to microparticles, the nanoparticles have more edge over them which are dictated by the size of the nanopaticle. The lesser the size of the nanoparticles, more value the nanoparticles have. submicron size of nanoparticles has numerous advantages over microparticles. Nanoparticle size of 100-400 nm showed 6 fold higher uptake when juxtaposed with 10μm microparticles in caco-2 cell line. The larger size (1-10μm) microparticles have lesser uptaking efficiency than that of smaller 100 nm size particles (15-250 folds greater).[1,2]

While collating the various studies, it is clear that the existing lipid particulate systems like Polymeric Nanoparticles and liposome have lesser potential

than lipid nanoparticles like NLC which. The next generation to the solid lipid nanoparticles (SLNs) is this novel NLCs. A NLC carrier consists of 2 phases: solid lipid and liquid lipid phase which are connected by the spatial arrangements. The ability of the drug load to avoid the crystalline character of lipid matrix by controlling conversion of amorphous form to crystals and enhanced drug loading efficiency is achieved by this alternative spatial arrangement. Hence, NLC acts as a good alternative carrier for conventional systems such as ointments, suspensions and solutions[3,4].

An idea NLC shows the following characteristics:

• Should be capable of using in the formulation of pulmonary, rectal, dermal, parenteral, ocular and oral drugs.

• Should be efficient controlled drug release carriers.

• Should have excellent drug loading capacity.

• Should maintain Good physical and chemical stability[5–7].

• feasibility of scaling-up to large scale.

• Good biocompatibility.

• Good physiochemical diversity.

• Good targeting ability by selective lymphatic uptake mechanism.

• High potential ability to enhance the bioavailability of poorly aqueous soluble drugs[8].

The intention of this current study is to intensify the bioavailability of drug which have lower bioavailability (<20 %) like Lovastatin in the form of NLC carrier and also to optimize the formulation to select perfect variables for the formulation. **Materials and Method**

Lovastatin got as a gift sample form Aurobindo pvt. Ltd. Witepsol, Oleic acid and other analytical chemicals are purchased from Himedia pvt. Ltd. Mumbai.

FTIR analysis

The chemical interaction between the exepients used like surfactants and lipids and the drug (Lovastatin) in the formulation can be determined undergoing the FTIR studies. Studies were carried out for Drug and lipid mixture, NLC dispersion by the potassium bromide (KBr) pelletization method and for pure Lovastatin, Witepsol, Span 80. Potassium bromide was mixed with 0.2% Lovastatin and passed into a mini KBr pellet press with 7 tons of pressure in it. The press handle was then moved for several times so that the mixture was pressed. By the mean while a Nanostructured lipid carrier was dried and this dispersion was stacked like a sandwich between a plane KBr pellets. This sample was then placed on sample stage of FTIR instrument (Bruker, Germany) with a resolution of four cm^{-1} and a wavelength of 4000 to 500 cm^{-1}.[9–11].

Formulation of Nanostructured lipid carrier:

Nanostructured lipid carrier formulation was prepared by using hot homogenization method. For finding out the ideal optimized formulation Eight different formulations were prepared by changing the process variables like Homogenization time and the conc. of formulation variables like surfactant (span 80), Combination of solid lipid and liquid lipid (Witepsol and Oleic acid) which are shown in Tables 1 and 2. The weighed quantity of lipid in the ratio[Drug:Lipid] as mentioned in the table was taken in a china dish according to the formulation. To get a clear viscous liquid, the lipid mixture was introduced into 75ºC and melted. To the clear viscous liquid 10 mg of Lovastatin was added with constant stirring. Thereby, a homogenous mixture was obtained. Simultaneously, 0.25-0.5% of Span 80 solution was taken in a beaker. To this beaker, the prepared homogenous mixture was added. Then the final mixture was subjected to homogenization under distinct homogenization time. A Nanostructured lipid carrier suspension was formed, which was milky white in colour[12–18].

The selected variables were fixed in 2^3 factorial design as shown in Table 1, was preferred by using Design Expert 9 Software, Stat-ease, Inc. USA, 8 factorial runs with17 formulation runs were generated. 8 formulation runs was used to determine the outcome of modifications in the dependent variables (PS nm, ZPmV and EE%) corresponding to the independent variables (Homogenization time, Surfactant concentration and Lipid concentration). In this optimization design, the application of first order response surface model and the illumination of the result were based on a 2^3 factorial design. Variables selected from pre-optimization parameters are given as X3 for different surfactant concentration (span 80) at 2-different levels code as low (-1) and high (+1); X2 for homogenization speed (5000 Revolutions per minute) with discreate time; X1 for solid lipid: liquid lipid ratio i.e., Witepsol : oleic acid proportion. The optimized NLC formulations were formulated using the previously designed variables and the dependent variables like Y3 - % entrapment efficiency, Y2 - zeta potential in mV, Y1 -particle size in mm were evaluated[12–18].

Evaluation procedures

Particle size distribution

Table 1: 2^3 factorialdesign for optimization of Lovastatin NLC

Formulatio	Independent variables					
	Sol.Lip:Liq.Lip in mg (Witepsol : Oleic acid)	Span 80 (Surfactant)(	Homogenizatio Speed (5000 Revolutions per minute) (minute)	Factor A:X1(mg)	Factor B:X2(Percenta	Factor C:X3 (min)
N1	1	-1	1	8:2	0.5	15
N2	-1	-1	-1	6:4	0.5	5
N3	-1	1	1	6:4	1.0	15
N4	-1	-1	1	6:4	0.5	15
N5	1	-1	1	8:2	0.5	15
N6	1	-1	-1	8:2	0.5	5
N7	-1	1	-1	6:4	1.0	5
N8	1	1	-1	8:2	1.0	5

Malvern Nanoparticle size analyzer was used for determining the particle size distribution parameters of the Nanostructured Lipid Carriers, which includes polydispersity index (PI), particle size (PS -Z). Before starting the analysis, the NLC was dispersed in the desired dilution which was deionised twice with distilled water and the final sample was prepared. Then the final sample was filtered using a 0.45μ membrane filter. Based on the viscosity of medium the DLS intensity was fixed by the instrument itself, i.e., for high viscous sample the instrument will fix 170º light scattering intensity and for low viscous samples the instrument will fix 90º light scattering intensity. All quantification were done in triplicate (n=3) and the final outcome should obey the ideal characteristics of a NLC

Particle size: 10- 1000 nm

PI should be : less than 0.3 [19–30].

Zeta Potential (ζ)

Malvern Nanoparticle size analyzer was used for the determination of Zeta Potential or surface charge potential of the Nanostructured lipid carrier. The prepared NLC was diluted and were injected into the probe in an electrophoretic cell through which an electric field (80 mV) was supplied [76]. All quantifications were carried out in triplicate at 25°C. By using the Smolochowski equation, the Zeta potential of NLC was determined directly [19–30].

$$\zeta = \epsilon\mu/\eta$$

In which, Is the viscosity of the liquid

ϵ- electric permittivity of the liquid

μ - Electrophoretic mobility

ζ - Zeta potential

Surface Morphology Studies - Scanning Electron Microscope (SEM) studies

N3 formulation of Lovastatin was selected as the optimized formulation. Then the surface morphology studies were done for this formulation using Scanning electron microscope (Hitachi S-3000N). Then the N3 formulation was dried. By using a sputter coater the dried powder samples were coated with platinum of 600 Å and examined through Scanning electron microscope. Coated NLC was placed on a sample holder and scanned through an electron beam. The electrons in the beam interact with the NLC particles and emit 2° electrons based on the nature of NLC surface, which gives the surface topography of the NLC. Then the particle size of the N3 formulation obtained by Malvern Nanoparticle size analyzer was juxtaposed with the particle size of the N3 formulation obtained by Scanning electron microscope [11–15].

Efficiency of encapsulation studies

centrifugation methoda centrifuge tube was priorly filled with 9 ml of phosphate buffer of pH 7.4. Simultaneously, 1 mLdispersion ofNanostructured lipid carrier Himedia dialysis bags and with a molecular weight of 12,000–14,000 DaltonIn order to extract the free drug from NLC carrierREMI centrifuge instrument revolutions per minutefor 1 hourphosphate buffer saline solution twas prepared by using the same technique with same ingredients but without the drugplaced under the UV Spectropho241 nmto determine the drug conc. from the withdrawn sample Lovastatin. The analysis was carried out in triplicate (n=3 [19–30].;

$$\%EE = \frac{Xs - Xt \ x\ 100}{Xs}$$

Where, **Xt** - Amount of drug in 5 ml saline

Xs - Total amount of drug used for formulation;

% EE- % Entrapment Efficiency

In-vitro drug release studies

The dialysis membrane method was carried out for determining the In-vitro drug release. This method traces out the amount of drug released from the dispersion of the Nanostructured Lipid Carrier. After closing or tying one end of the dialysis membrane, 1 ml dispersion of Nanostructured Lipid Carrier was filled into the dialysis membrane having pore size of 0.45 μm. Finally, the other side of the dialysis membrane was also closed to prevent leaking of the Nanostructured Lipid Carrier in it and this membrane act as a donor compartment. Then the prepared donor compartment was immersed into a 100 ml of pH 7.4 Phosphate Buffer Solution, stirred using a magnetic stirrer at 100 revolutions per minute and the phosphate buffer solution (PBS) was prepared. At a regular interval of 0, 1, 2, 4, 6, 8, 10, 12 hours 5ml of the sample was collected from this prepared PBS phase. Meanwhile, to maintain a sink condition 5 ml of freshly prepared phosphate buffer solution were replaced in the receptor compartment. Finally the samples were kept under the UV Spectrophotometer at a wavelength of 241nm and the absorbance of the Lovastatin released at each time interval was measured. The method was done in triplicate (n=3) [19–30].

In-vitro drug release kinetics

From the drug release data obtained from the above experiment, the type of drug release mechanism from Nanostructured Lipid Carrier was determined by fitting the obtained data into the different kinetic equations such as korsermeyer peppas, hixson crowell, higuchi square root, first order and zero order models. The righteousness of linear fit test was the major criteria used for the selection of the perfect model to determine their mechanism of drug release. [19–30].

RESULTS AND DISCUSSION

Compatibility Studies:

The Lovastatin and excipients compatibility studies were completed and the FTIR spectra results were shown as follows. The wave numbers of the main functional groups are

In the Lovastatin drug

-C-H bending: 990.20 cm^{-1}

-C-O stretching: 1118.85 cm^{-1}

-C=o stretching: 1723.73 cm^{-1}

–OH stretching: 3551.55 cm^{-1}, 2966.58 cm^{-1}, 2872.80 cm^{-1}; –OH stretching as 3340 cm^{-1}, 2944.50 cm^{-1}, 2832.87 cm^{-1}.Same functional groups are reproducible in Physical mixture which contains drugs, Witepsol, Oleic acid. The results are shown in Figures 1 and 2.

Optimization Formulation Process of Lovastatin Nanostructured lipid carrier

The optimized 2^3 factorial design are shown in Table 2 and Figure 3 disclosed about the effect of independent variables on dependent variables during the formulation of Lovastatin Nanostructured Lipid Carrier. The statistics that are finally recorded concludes that there was an indestructible connection between the lipid conc. and the particle size and this confirms that the increased size of particle increases the lipid conc. of the NLC as correlated in ANOVA ($p<0.0001$). While considering this criteria into the account, N3 formulation have a particle size of about 145.4± 3.16nm at low Solid lipid: Liquid lipid proportion(-1 level lipid).

Meanwhile, the decreased PS of NLC shows an increased ZP along with Increased surfactant conc. in the preparation of Lovastatin Nanostructured Lipid Carrier. The surfactant effect on variables was masked by the lipid effect with increase in lipid concentration, so that From this statistics we can conclude that the there is a proper stability of Nanostructured Lipid Carrier on its phase. The 'p' value was found to be less than 0.0001 while establishing it in ANOVA. Among all formulation (N1-N8), formulation N3 shows the ZP of -30.7± 2.06 at high +1 level with the surfactant conc. of 1.0 %. The Entrapment Efficiency % gets increased with increased homo. time and increased surfactant concentration. Out of the 8 formulations (N1-N8), N3 formulation have a high EE % of about 89.4 ± 2.24 at moderate 1 level homo. time. By considering all the datas obtained from the optimized formulation variables, N3 was selected as an optimized formulation. From the coefficient data from 2^3 factorial designs, polynomial equations were derived by considering Homogenization Time as C and Surfactant Concentration as B and Lipid Concentration as A are as follows:

Particle Size (nm) = 148.93 + 208.42 A + 202.586 A^2

EE (%) = 79.86 - 18.2834A + 0.878 C + 1.868 AC - 0.956 BC – 3.4248 A^2

ZP (mV) = – 27.24 - 9.0054 B

The Scanning Electron Microscopy studies (SEM) were done to analyze the Optimized Lovastatin Nanostructured Lipid Carrier N3 (Figure 3). In this SEM, the structure of Nanostructured Lipid Carrier

Table 2: Evaluation of the effect of variables on Lovastatin Nanostructured lipid carrier by 2^3 factorial design

Formula	Independent variables			Dependant variables			Other variables	
	X1 Sol.Lip:Lin mg(Witepsol : Oleic acid)	X2 Span 80(Surfa	X3 Homoge Speed(5(Revolutions per minute) (minute)	Y1 Particle size(nm)	Y2 Entrapm Efficiency%	Y3 Zeta potential(mv)	Poly Dispersity Index (PI)	% Drug Content	Invitro Drug release for 12 hrs
N 1	1	-1	1	294.8± 2.36	72.6± 2.68	-24.4± 2.06	0.644 ± 0.002	70.24 ± 1.48	74.82 ± 2.38
N 2	-1	-1	-1	875.9± 2.26	64.4± 2.10	-15.2± 1.08	0.524 ± 0.024	74.48 ± 2.02	62.54 ± 2.42
N 3	-1	1	1	145.4± 3.16	89.4± 2.24	-30.7± 2.06	0.443 ± 0.014	88.62 ± 2.24	84.92 ± 2.52
N 4	-1	-1	1	986± 2.06	54.6± 2.12	-12.9± 2.54	0.504 ± 0.012	67.34 ± 2.42	64.54 ± 2.36
N 5	1	-1	1	511.4± 2.24	68.8± 3.60	-237 ± 2.54	0.606 ± 0.012	66.24 ± 2.48	63.88 ± 2.66
N 6	1	-1	-1	292.6± 2.46	72.6± 2.86	-22.4± 2.06	0.658 ± 0.016	84.42 ± 2.86	74.22 ± 2.56
N 7	-1	1	-1	1125. 4± 2.66	58.7± 3.44	-13.1± 1.68	0.638 ± 0.014	56.56 ± 2.94	50.82 ± 2.82
N 8	1	1	-1	667± 3.26	58.9± 2.86	-22.4± 2.68	0.534 ± 0.014	66.54 ± 2.68	68.64 ± 2.64

*All values expressed as mean ± SD, n=3 , Note: +1: high level; -1: Low level

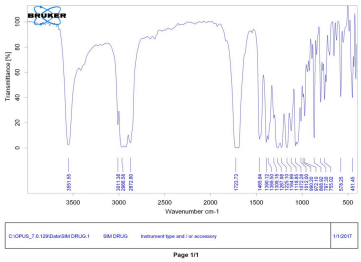

Figure 1: FTIR spectra of Lovastatin pure drug

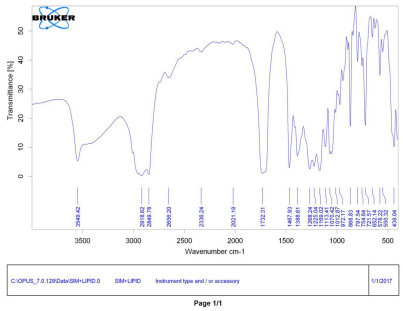

Figure 2: FTIR spectra of physical mixture of

was examined as blocks of various shapes which are linked together or a group of particles. This observation concluded as, the Nanostructured Lipid carrier of Lovastatin have high penetration rate and high drug loading efficiency through their physiological barriers; and the concentration of drug was uniformly distributed throughout the NLCs (Table 2). In-vitro drug release studies for Lovastatin Nanostructured Lipid Carrier (N3) uncloaked a finer controlled drug release of 84.92 ± 2.52% in 12 hours when juxtaposed with the available

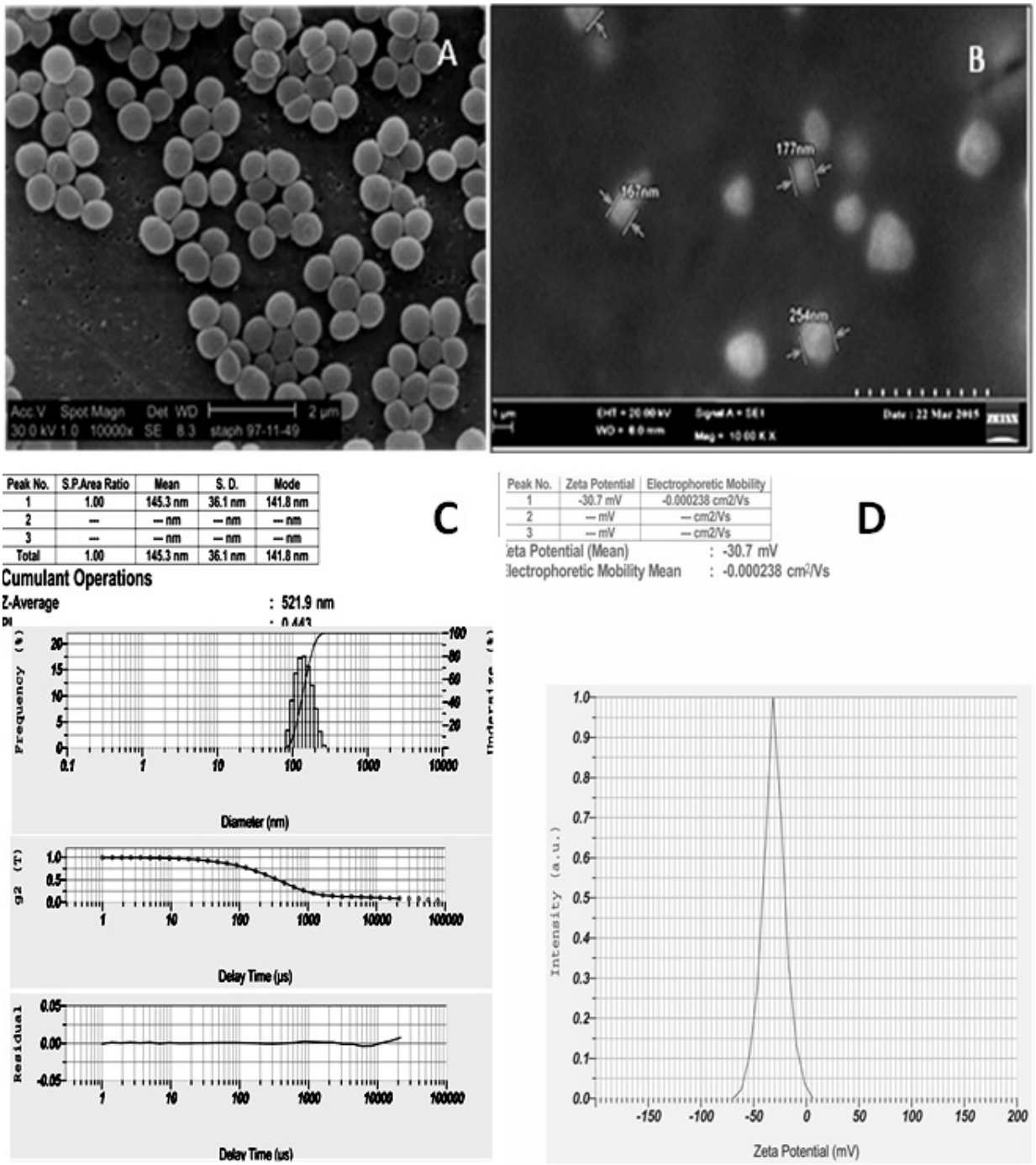

Figure 3: (Aand B) SEM Images; (c and D) PSand ZP of optimized NLC formulation (N3)

Lovastatin drugs that are available in the market (Figure 4). This concluded that desired amount of drug release was achieved in a controlled manner from the Nanostructured Lipid Carrier. The N3 Lovastatin Nanostructured Lipid Carrier formulation exhibited the maximum entrapment efficiency of 89.4± 2.24 % and a maximum drug content of 88.62 ± 2.24 %.

Invitro Drug Release Studies of Lovastatin NLC formulation

The Lovastatin Nanostructured Lipid Carrier in the pH of 7.4 have shown a sustained release pattern for 12 hrs and after 12hr the release of drug ranges from 50.24±2.56 to 84.92±2.86 % for formulations N1 to N8 Nanostructured Lipid Carrier respectively. The release is due to ionization and relaxation of Witepsol lipid which increased its solubility due to presence of surfactant and enhanced the drug release from Nanostructured lipid carrier in a cumulative manner. From the release data it shows that the formulation N3 the best formulation when compared

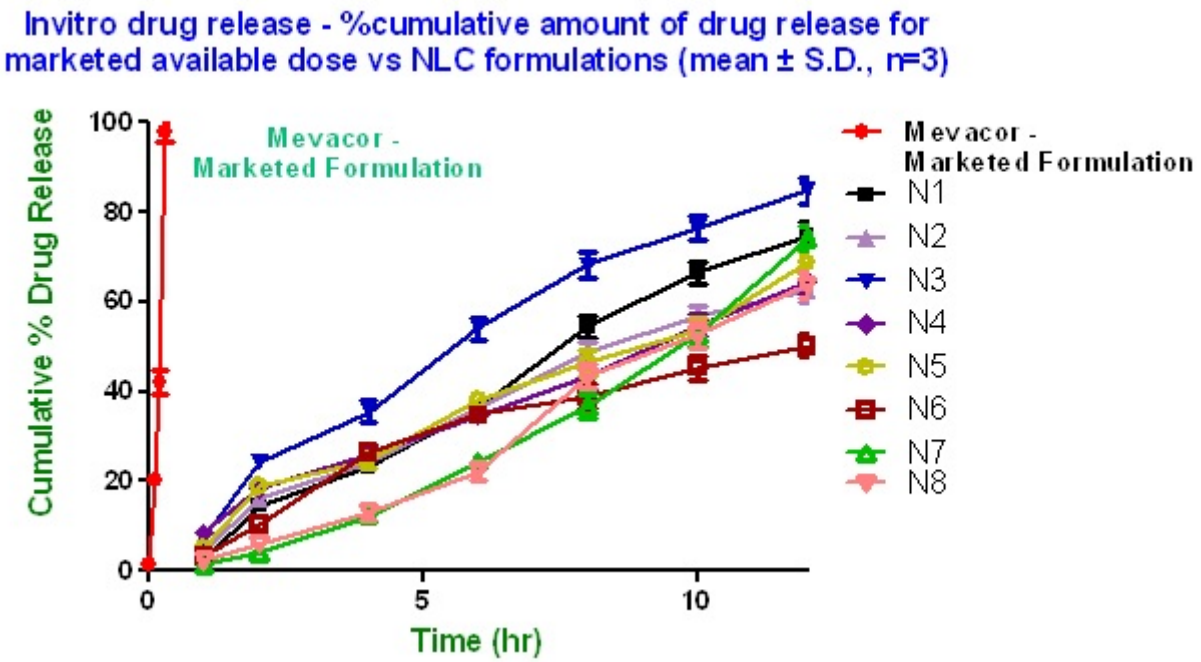

Figure 4: Comparison of Invitro Drug Release Studies of NLC Vs. Marketed dosage form (MavacorTablet)

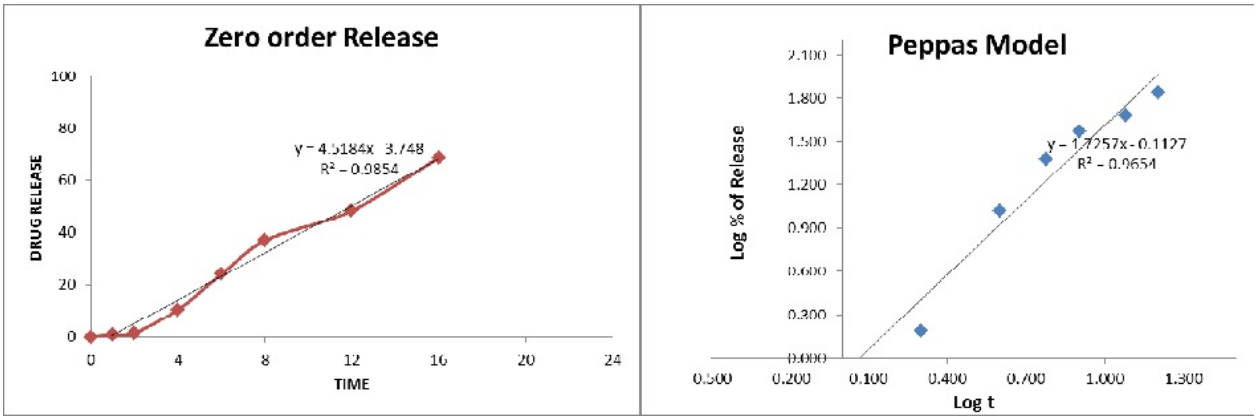

Figure 5: Graph shows (A) zero order release kinetic and (B) Peppas kinetic model of formulation N3

to all other formulation, because it shows a invitro drug release pattern in a cumulative manner i.e., 84.92 ± 2.52% for 12 hrs as shown in figure 4. N3 NLC shows a same release pattern of drug in a cumulative pattern throughout the time interval i.e. there is no any drug burst effect in-between time interval, it shows that the N3 NLC encapsulate the drug uniformly through the loaded concentration and also it have good drug content uniformity.

Invitro Release kinetics of optimized Lovastatin NLC formulation N3

The in-vitro drug release kinetic studies of optimized formulation N3 were assessed using different kinetic models like Higuchi, Korsmeyer-Peppas model, First order and Zero order. The formulations N3 release kinetic model was summarized in the figure 5. It was proved that Zero order model of N3 formulation have a good linearity than other models with the R^2 values of 0.9854. Hence we can conclude as the formulations N3 follows non linear release kinetics, where the rate of elimination is independent of conc. and the release of drug are at constant level per unit. Hence, this can be considered as an ideal method of drug release to attain a prolonged therapeutic outcome. The release exponent (n) value of N3 formulation was found to be 1.7257 respectively, the value n > 1 have been observed, which shows that the release of drug from lipid shows Super Case II kinetics transport mechanism. This was due to plasticization process in the Lipid layer appears from limiting of the attractive

forces within Lipid chains which enhance the mobility of Lovastatin from the core and lipid matrix to the external fluid.

CONCLUSION

The outcome of various studies conducted, gives a clear way to conclude that, for the preparation of a Nanostructured Lipid Carrier loaded Lovastatin, hot homogenization method with the process variable of homo. Speed as 5000 Revolutions Per Minute for 10 min. was carried out along with the designed formulation variables like Span 80 as Surfactant, oleic acid as Liquid Lipid and witepsol as Solid Lipid is the best formulation method. The NLC prepared from this methods shows Controlled & predetermined release pattern with zero order release kinetics and Super Case II kinetics transport mechanism i.e., Lovastatin drug release pattern shows limiting of the attractive forces within Lipid chains. Hence from this research the above discussed variables are suitable for formulation of low bioavailable drug like lovastatin by NLC formulation.

ACKNOWLEDGEMENT

The authors are thankful to all who have extended their constant support for the completion of the work.

Funding Support

None

Conflict of Interest

Authors declared no conflict of interest.

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Cite this article: Pawar Roshan K, S Kalaiselvan, K Balamurugan. **Design, optimization and *invitro* evaluation of lovastatin nanostructures lipid carrier**. Int. J Pharm. Res. Life Sci. 2018; 6(2): 24-33.