Original Article

Nanostructured Lipid Carrier: A Potential System for Enhanced Oral Bioavailability of Felodipine

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ABSTRACT

Background: Felodipine is BCS class II drug with poor and variable bioavailability due to its insolubility in water (19mg/L) and extensive metabolism in liver and gut. Thus, in the study Nanostructured lipid carriers (NLCs) of Felodipine were formulated to improve its solubility and bioavailability. **Methods:** NLCs loaded with Felodipine were prepared by high shear homogenization with ultrasonication. The NLCs were characterized for particle size, polydispersity index, entrapment efficiency, content of drug, *in vitro* drug release studies, stability studies and *in vivo* bioavailability studies. **Results:** The mean particle size and polydispersity index for optimized formulation F2 was found to be 187.0 ± 0.06 and 0.259 ± 0.002 respectively. The drug content achieved was between the ranges of 51.15 ± 0.01 to 69.14 ± 003% for F1 to F5 formulations. The zeta potential of optimized formulation was found to be -38.2 mV, which showed good stability. Formulation F2 showed highest percentage entrapment efficiency of 75.15 ± 0.003. *In vitro* drug release studies showed sustained release pattern with maximum drug release of 72.82% by F2 formulation at the end of 12h. The bioavailability studies demonstrated significant enhancement in bioavailability of Felodipine NLCs in comparison to marketed product. Stability studies carried out for optimized formulation F2 showed that the NLCs are more stable at 4 ± 2°C. **Conclusion:** Nanostructured lipid carriers loaded with Felodipine were able enhance the bioavailability of drug by 2.0 folds in comparison to marketed product and also demonstrated sustained drug release pattern for longer period of time.

Key words: Felodipine, Oleic acid, Compritol ATO 888, High shear homogenizer, Oral bioavailability.

INTRODUCTION

Hypertension is defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic pressure ≥ 90 mmHg, is one of the most common chronic disease.[1] Calcium channel blockers are primarily utilised for the therapy of systemic arterial hypertension. A dihydropyridine calcium channel blocker Felodipine, has been extensively used in the treatment of hypertension.[2] Felodipine is BCS class II drug and is practically insoluble in water (19mg/L). It is extensively metabolized in liver and gut as well as entirely excreted as metabolites. Felodipine has poor and variable bioavailability (15-20%).[3] Various studies were conducted by researchers to increase the solubility and oral bioavailability of Felodipine. For instance, Dong HW *et al.,* prepared solid dispersions(SD)ofFelodipinebysupercritical anti-solvent precipitation method which showed higher dissolution rate of drug over 90 % in 2 h.[4] Cong L *et al.,* prepared nanocrystals of Felodipine resulting in an increased dissolution rate with AUC_0-t value of 1.6-fold higher than that of the commercial tablets.[5] Sahu *et al.,* prepared and evaluated Felodipine nanosuspensions showing up to 79.67 % release in 4 h.[6] Grandhi S *et al.,* formulated matrix tablet from solid dispersions of Felodipine

Submission Date: 14-12-2020;
Revision Date: 06-04-2021;
Accepted Date: 28-07-2021.

DOI: 10.5530/ijper.56.1.10

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by wet granulation technique. These tablets showed extended drug release of 87.84 % in 8 h.[7] Anusha A, developed self micro emulsifying drug delivery system (SMEDDS) of Felodipine, where the dissolution from liquid SMEDDS and solid SMEDDS was significantly high (P<0.0001) compared to drug suspension.[8] Many solid dispersions of Felodipine with varying polymers or methods of preparations were also tried to increase the solubility of drug.

Pharmaceutical nanotechnology has taken the advantage of the advent of nanotechnology; new pharmaceutical dosage forms are under development to deliver many pharmaceutical drug molecules.[9] Poor intrinsic dissolution rate and aqueous solubility of drug greatly influence the oral drug delivery. Recently, NLCs have been widely attracting researchers for the oral delivery of lipophilic drugs.[10] NLCs with unique characteristics can be formulated by combining solid and liquid lipids which provide firm loading of drug molecule inside the matrix during the shelf life.[11] Solubility of drug is higher in liquid lipid as compared solid lipid. Due to this, NLCs can achieve high drug loading and slow drug release thereby, avoids drug loss prior to the solid lipid decomposition.[12] By review of literature, it was understood that high shear homogenization is the simple, rapid and easy method to prepare NLCs. Thus, the present study attempts to design and evaluate Nanostructured lipid carrier of Felodipine with an aim to enhance its solubility and oral bioavailability.

MATERIALS AND METHODS

Materials

Felodipine pure drug was obtained as a free gift sample from Cipla Pvt. Ltd. Bangalore, India. Compritol ATO 888 was obtained by Gattefosse, France. Oleic acid was purchased from S.D Fine Chemicals, Mumbai, India. Poloxamer 188 was purchased from Ozone International, Mumbai, India. Dialysis membrane with molecular weight cut off of 12000-14000 Dalton was purchased from Hi Media Laboratories Pvt. Ltd. Mumbai, India. All the other chemicals used were of analytical grade.

Methods

Preliminary Lipid Screening

Selection of the suitable lipids to develop lipid nanoparticles is one of the crucial parameter. Thus, Felodipine solubility was determined in various solid and liquid lipids, to select the suitable lipid to encapsulate the large quantity of drug. Lipid screening was done by dissolving drug with increasing quantity in different melted solid lipids (Approximately 100mg) and determined the maximum amount of drug dissolved in every lipid.

Optimization of Process Parameters

For process optimization, homogenization speed, homogenization time, ultrasonication time and surfactant concentrations were varied (Table 1) and evaluated for particle size and size distribution.

Preparation of NLCs by High Shear Homogenization Followed by Ultrasonication Method

NLCs were prepared by high shear homogenisation and ultrasonication method.[13] In the method, lipids were melted (10 °C above their melting point) and to the melted mass drug was added slowly. The dispersion was kept at the same temperature until it becomes optically clear. The aqueous phase of surfactant solution was prepared separately by dissolving Poloxamer 188 with distilled water and heated to the same temperature as that of lipid solution. Hot solution of surfactant was added in to the lipid phase dropwise with continuous stirring on magnetic stirrer for 10 min. The mixing was further continued with high shear homogenizer at 12000 rpm for about 30 min following ultrasonication for 15 min. The prepared formulation was then stored at 4°C. The composition of NLCs formulations F1 to F5 is given in Table 2 as well as the method is depicted with schematic representation in Figure 1.

Evaluation of Felodipine NLCs Formulations

Determination of Particle Size, PDI and Zeta Potential

The size distribution of the formulations was measured by Dynamic Light Scattering Particle Size Analyzer (Nanotrac Particle Size Analyzer). The zeta potential

Table 1: Formulation Design of Felodipine NLCs Using Solid/ Liquid Lipids and Surfactant.

Formulation code	Drug: lipid ratio	Drug (mg)	Compritol ATO 888 (mg)	Oleic acid (mg)	Poloxamer 188 (%)
F1	1:1	10	10	10	1.0
F2	1:1.5	10	15	15	1.0
F3	1:2	10	20	20	1.0
F4	1:2.5	10	25	25	1.0
F5	1:3	10	30	30	1.0

Drug: Felodipine, Solid lipid: Compritol ATO 888, liquid lipid: Oleic acid, surfactant: Poloxamer 188

Table 2: Optimization of Process Parameters.

Parameters	Speed	Particle size	PDI
Homogenization speed (rpm)	9000	968.25	1.95
	12000	729.36	1.25
	14000	310.18	0.43
Homogenization time (mins)	10	754.63	0.48
	20	567.27	0.36
	30	420.32	0.28
Ultrasonication time (mins)	5	432.4	0.46
	10	329.8	0.32
	15	221.4	0.21
Surfactant concentration (%w/v)	0.5	233.5	0.94
	1	229.6	0.41
	1.5	342.2	0.89
	2	386.7	0.97

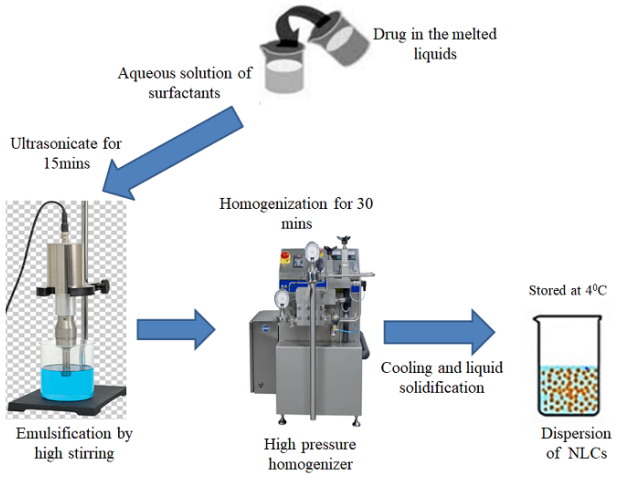

Figure 1: Representation of NLC's preparation by high shear homogenisation followed by ultrasonication method.

was determined by Malvern Zetasizer and the average values of triplicates were taken.[14]

Drug Content

NLCs loaded with 1mg equivalent amount of Felodipine was added to 10ml of methanol: phosphate buffer pH 6.8 (1:10) with continuous stirring for 2hr. Obtained colloidal suspension was subjected to ultracentrifugation at 10,000 rpm for 30 min. Then, supernatant was collected, suitably diluted and further analyzed for drug content spectrophotometrically at 363 nm.[15]

Entrapment Efficiency

The entrapment efficiency of NLCs was determined by ultracentrifugation method. The obtained supernatant after ultracentrifugation of NLCs (30,000 rpm at 25°C) for 30 min was suitably diluted with pH 6.8 phosphate buffer and analysed for unassociated drug spectrophotometrically at 363 nm.[16] The Felodipine encapsulation efficiency of the nanoparticles was calculated as follows:

$$\% \text{ Efficiency} = \frac{\text{Total amount of drug} - \text{Total amount of unbounded drug}}{\text{Total amount of drug}} \times 100$$

Transmission Electron Microscopy (TEM)

External morphology of prepared nanosuspension was determined by using transmission electron microscopy. Samples of the nanosuspension were prepared by placing a drop onto copper grid. Digital Micrograph and Soft Imaging Viewer software were used to perform the image capture and analysis, including particle sizing.

In vitro Drug Release

Suspension of NLCs equivalent to 10mg of Felodipine was transferred to a dialysis bag (mol. weight cut off 12,000–14,000 Dalton) and sealed. The bag was then immersed for 2hrs in dissolution apparatus containing 900 ml of 0.1 N HCl pH 1.2 buffer followed by pH 6.8 phosphate buffer for about 12hr with a constant speed of 50 rpm at 37°C± 0.5°C. Required quantities of test samples were withdrawn at regular intervals and the same quantities were replaced with fresh solution of buffers. The samples were suitably diluted and analyzed spectrophotometrically at 363 nm.[17,18]

Kinetics of Drug Release

To study the release mechanism and release rate kinetics of NLCs, the obtained data was fitted in to Zero order, First order, Higuchi matrix, Hixson Crowell and Korsmeyer- Peppas model. On the basis of R^2 values obtained, the best fit model was chosen by using Microsoft excel Windows version 7.

In vivo Bioavailability Studies

Ethical approval was received from the Institutional Animal Ethics Committee prior to the beginning of research work. The animals were procured from *in vivo* Biosciences, Bengaluru by Institutional Animal Ethics Committee and provided for the study. Healthy male Wistar rats weighing 150-200gms were housed in polypropylene cages and maintained at room temperature under 12 h dark/light cycles. They were fed with standard pelleted diet and water. The animals were acclimatized for one week under laboratory conditions before experiments on the animals. The animals were fasted overnight and had free access to water throughout the experimental period. Twelve healthy male wistar rats were selected and divided into 2 groups each group

containing 6 rats. Group 1 received marketed product of Felodipine 0.108 mg in normal saline by oral route. Group 2 received NLCs containing equivalent to 0.108mg of Felodipine for 6 animals in normal saline through oral route. After 0.5, 2, 4, 6, 8, 10, 12 and 24 hr, 0.5ml of blood was collected from eye by retro-orbital puncture into eppendorf tube with 10µl of EDTA. The samples were centrifuged at 5000 rpm for 20min. Supernatant plasma was taken and filtered through 0.45µm membrane into clean vials and then analyzed in UV Spectrophotometry.[19]

Short Term Stability Studies

The stability studies were conducted according to ICH guidelines. Samples were stored in glass vials for 60 days at 4°C and at room temperature (25 ± 2°C). After 30, 60 and 90 days samples were evaluated for % entrapment efficiency and *in vitro* drug release studies.[20]

Statistics

The data as described in the experimental sections was statistically analysed by performing two-way analysis of variance (ANOVA) using GraphPad Prism 7.0 software; a value of $P<0.05$ were found to be statistically significant in all the cases.

RESULTS

Preliminary Lipid Screening

For solid lipid, Felodipine has shown maximum solubility in Compritol ATO 888 and solubility was in an order of Compritol ATO 888>stearic acid > Glyceryl monostearate. For liquid lipid Felodipine has shown maximum solubility in oleic acid and solubility was in an order of Oleic acid> Ethyl Oleate> Olive oil.

Optimization of Process Parameters

Optimization of process parameters was done by varying homogenization speed, homogenization time, ultrasonication time and surfactant concentration as shown in Table 1. Based on desired particle size, PDI and reproducible results the optimized parameters selected were as follows; homogenization speed-1400rpm, homogenization time-30 min, ultrasonication time -15 min and surfactant concentration-1.0%. The results are shown in Table 2.

Evaluation of Felodipine NLCs Formulations

Particle size and size distribution

The mean particle size for formulation F1 to F5 varied in the range of 187.0±0.06 nm to 321.9±0.01 nm. The NLCs mean particle size was found to be reduced with increasing the concentration of lipid up to certain range. Further increase in lipid concentration showed an increase in the mean particle size of NLCs. The mean Polydispersity index of NLCs loaded with drug (F1 to F5) varied between the ranges of 0.259±0.002 to 0.382±0.004 as tabulated in Table 3.

Zeta Potential

It has been reported that the value of zeta potential less than -30 mV or higher than +30 mV predicts good physical stability of nanoparticles dispersion. Zeta potential of F1-F5 are given in Table 3 which are in the range of -22.9 to 38.2 mV and Figure 2 shows the zeta potential of F2 formulation.

Drug Content and Entrapment Efficiency

The percent drug content and encapsulation efficiency for formulations F1 to F5 were ranged between 51.15% to 69.13% and 53.33% to 80.15% respectively (Table 3).

SEM and TEM Analysis

SEM and TEM images of optimized NLCs formulation F2 indicated that, the prepared NLCs were in nano size range. SEM and TEM images of the optimized NLCs formulation F2 is shown in the Figure 3 A and Figure 3 B respectively.

In vitro Drug Release

The drug release at the end of 2h for F1-F5 was found to be in the range of 17.69% -20.01%, this release is due to the drug present on the surface of nanoparticles. At the end of 12h the mean cumulative release of drug from

Table 3: Particle Size and Polydispersity Index, %Drug Content, % Entrapment Efficiency and Zeta Potential.

Formulation	Particle size*	PDI*	Percent Drug content*	Percent Entrapment efficiency*	Zeta potential (mV)
F1	203.0±0.06	0.282±0.032	51.15± 001	53.33±0.004	-24.1
F2	187.0±0.01	0.259±0.002	69.14± 003	80.15±0.003	-38.2
F3	192.3±0.004	0.274±0.005	66.12± 002	74.0±0.005	-22.9
F4	253.5±0.02	0.349±0.003	55.24±007	62.27±0.003	-22.5
F5	321.9±0.01	0.382±0.004	54.13±004	58.33±0.006	-24.0

*Results are expressed as mean ± standard deviation (mean±SD) $n=3$

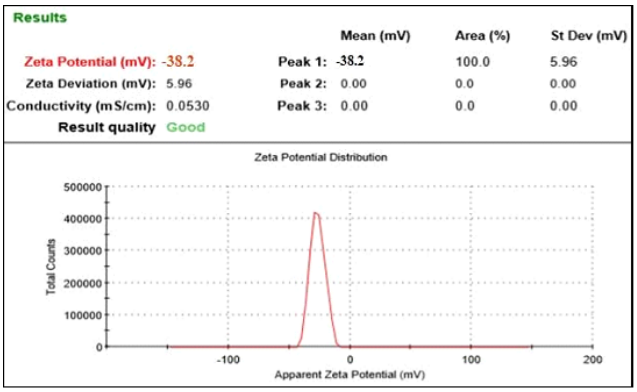

Figure 2: Zeta potential of formulation F2.

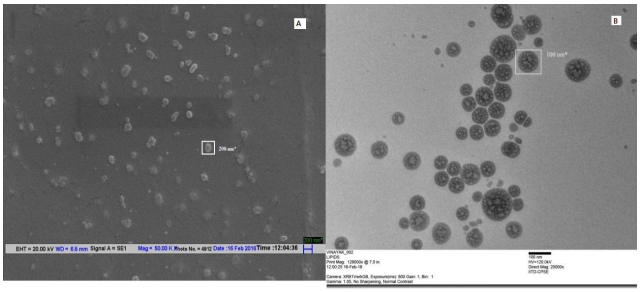

Figure 3: A) Scanning Electron Microscopy B) Transmission Electron Microscopy of optimized formulation F2.

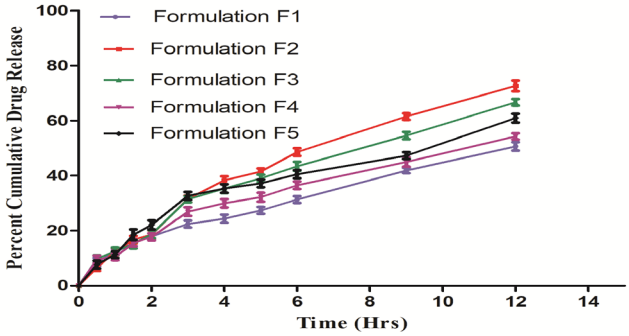

Figure 4: In *vitro* dissolution profile of the formulations F1 to F5.

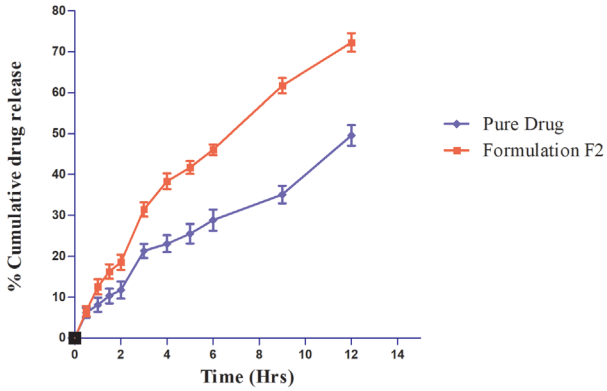

Figure 5: Comparative *in vitro* drug release profile of optimized formulation F2 and pure drug.

F1-F5 was found to be in the range of 50.60-72.82%. The *in-vitro* release profiles of formulations F1-F5 are shown in Figure 4 and the release profile of optimized F2 formulation and pure drug is compared in Figure 5. All formulations F1 to F5 showed biphasic drug release profile, with beginning burst release of drug which was due to surface drug adsorption, this phase is followed by a phase of slower drug release. In the second phase, the mechanism of drug release is diffusion of entrapped drug from inside the NLCs in to the release medium. Pure drug release profile showed ~50% drug release in 12hrs, whereas the optimized NLCs formulation F2 showed drug release of about 72.82% up to 12hrs which indicates increase in bioavailability of nano formulation (shown in Figure 4).

In-vitro Kinetics of Drug Release

The release data obtained was fitted in to different kinetic models to determine the release constant as well as regression coefficient (R^2). Based on the obtained regression coefficients, the drug release profile of NLCs formulations (F1-F5) were best fitted with Higuchi Matrix model.

In vivo Studies

The study was carried out on male Wistar rats for the comparison of plasma drug concentration of optimized NLCs formulation F2 with the marketed product which were given orally with normal saline. Comparative graph of plasma concentration v/s time of optimized formulation F2 and marketed product was plotted (Figure 6). AUC of Marketed product was found to be 81.1 µg/ml. h, C_{max} of 4.569 µg/ml and T_{max} of 4 h when given orally, whereas optimized formulation F2 showed AUC of 222.7 µg/ml. h, C_{max} of 13.040 µg/ml and T_{max} of 8 h, which was calculated by Trapezoidal method. AUC_{0-t} of Marketed product 81.1 µg/ml. h was increased up to 222.7 µg/ml. h for optimized formulation F2 when given through oral route.

Statistical Correlation

For the statistical correlation of *in-vivo* bioavailability, the number of animals in each group (n) = 6 were taken. Two-way ANOVA was applied for the statistical comparison of data. Degree of freedom was taken 5%. $^{*}p<0.05$ and $^{***}p<0.001$ compared to marketed formulation. If the hypothesis is 95% of confidence then degree of freedom is 5% ($p\leq0.05$). If the hypothesis is 99% of confidence then the degree of freedom 1%

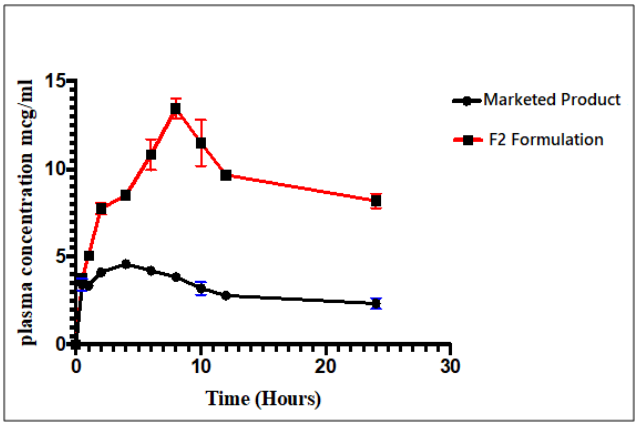

Figure 6: Comparative *in-vivo* release profile of Optimized formulation F2 and marketed product by oral administration.

($p \leq 0.01$). Here null hypothesis is not working so that alternative hypothesis comes into existence.

Short Term Stability Studies

The results of stability studies show no significant difference with respect to entrapment efficiency and cumulative percentage drug release of F2 formulation stored at 4 ± 2°C/65 ± 5% RH compared to that stored at room temperature. Thus, formulation stored at 4±2°C/65±5% RH showed better stability as compared to the formulation stored at 25±2°C/65 ± 5% RH.

DISCUSSION

A new form of NLCs comprising of lipid matrix and having a unique nanostructure have been developed. These carriers enhance drug loading as well as incorporate drug firmly during its storage. Solid-lipid nanoparticles (SLN) can be exploited as efficient delivery systems in commercial production but these show certain limitations like, higher water content in the nanolipid and possibility of drug expulsion during storage.[21] Mainly to avoid drug expulsion, combination of lipids that does not form highly ordered crystalline arrangements is required. Thus, NLCs come in to existence as they consist of combination of solid and liquid lipids, which results in matrix with higher imperfections to accommodate higher drug molecule than SLN.

Around 40% of the APIs face solubility problems which lead to their low oral bioavailability. Felodipine, an antihypertensive drug that belongs to BCS Class II i.e. low solubility and high permeability and have oral bioavailability of only 15%. In order to overcome this problem, Felodipine loaded nanostructured lipid carrier was formulated so as to reduce the particle size of the drug, thereby increasing the dissolution rate and hence the oral bioavailability. It was also aimed to provide sustained manner of drug release for prolonged period of time, thus reducing the dosing frequency.

Preliminary lipid screening was performed with different solid and liquid lipids to select a suitable lipids in the formulation of NLCs. Felodipine has shown maximum solubility in Compritol ATO 888 and Oleic acid, this might be due to structural convenience between Compritol ATO 888, Oleic acid and Felodipine. On the basis of Lipid screening Compritol ATO 888 and Oleic acid were selected for formulation of NLCs. Also, for better and reproduceable results, process parameters such as homogenization speed, homogenization time, and ultrasonication time and surfactant concentration were optimized in the preliminary study.

A total five formulations (F1-F5) were formulated by using solid lipid Compritol ATO 888, liquid lipid oleic acid and a surfactant poloxamer 188 with the use of high shear homogenization followed by ultrasonication method and evaluated. Among all formulations of NLCs, F2 formulation with drug: lipid ratio of 1:1.5 shows lower particle size (nano range) of 187.0 ± 0.06 nm. Polydispersity index suggests the width of particle size distribution that ranges between 0 to 1. If a PDI value is neared to 0 indicates the monodispersion of sample. However, PDI< 0.2 is considered as narrow size distribution whereas a PDI>0.5 indicates a very broad distribution. Therefore, PDI measurement was essential to confirm the size distribution of the particles and F2 NLCs formulation showed lower PDI indicating homodispersion. Zeta potential is used to demonstrate the charge stability of dispersed systems. Zeta potential of NLCs F2 was found to be -38.2 mV which indicates good stability of formulation. This is due to surfactant that reduces the electrostatic repulsion among the particles and sterically stabilizes the particles by forming a coat around their surface. Formulation F2 demonstrated maximum drug content as well as entrapment efficiency of 69.14±003% and 80.15± 0.003% respectively. Also, formulation F2 which has a lowest mean particle size has resulted in maximum percent release of drug (72.82%) at the end of 12h. This is because, smaller the particle size greater will be the surface area compared to their volume, thus, almost all drug will be at or near the particle surface which can be easily released. In contrary, larger particles possess large cores which leads to more drug encapsulation but slowly diffuses out. Based on these all findings of NLCs evaluation, F2 formulation can be considered as optimized formulation.

Encapsulation efficiency and drug content were enhanced with increasing concentration of solid lipid (up to 15 mg), further increase in concentration of solid lipid (up to 30 mg) leads to decrease in the entrapment efficiency. This is because, in NLCs molecules of lipid (solid and liquid) distributed in lipid matrix and an imperfect structured nanoparticle were formed, that enhances drug entrapment in structure. At higher contents of lipids, increasing drug to lipid ratio reduces entrapment efficiency due to reduced drug- lipid miscibility.[22,23]

The *in vivo* study was performed on male Wistar rats and plasma drug concentration of optimized F2 formulation of NLCs was compared with that of marketed product plasma drug concentration. As the $AUC_{0\text{-}t}$ obtained for marketed product was 81.1 µg/ml. h and that of optimized formulation F2 was 222.7 µg/ml. h (calculated by Trapezoidal method), the NLCs of Felodipine were capable of enhancing the bioavailability by 2.0 folds when compared to the bioavailability of marketed product and efficiently sustain the release of drug for prolonged time period. Thus, from the present study it can be concluded that NLCs prepared with proper process and formulation optimization could significantly enhance the bioavailability of poorly water-soluble drug Felodipine.

CONCLUSION

Five formulations of Felodipine loaded Nanostructured lipid carriers were successfully prepared with high shear homogenization and ultrasonication method. Based on evaluation results of NLCs, F2 formulation was considered as optimized formulation for further evaluation. SEM and TEM images suggested that the particle size of F2 formulation were in nano range. Zeta potential was found to be between -22.5 to -38.2 which predict good physical stability of nanoparticles dispersion. The dissolution rate depends upon the mean particle size. Therefore, F2 formulation showed maximum release i.e. 72.82±0.002%. For *in vivo* bioavailability study male Wistar rats were subjected to the pharmacokinetic study. Stability studies carried out for optimized formulation F2 showed that the NLCs were more stable at 4±2°C. In conclusion, Nanostructured lipid carriers loaded with Felodipine were capable of enhancing the bioavailability of drug by 2.0 folds in comparison to marketed product and also demonstrated sustained drug release pattern for longer period of time.

Ethical approval

Ethical approval was obtained from Institutional Animal Ethics Committee prior to the beginning of research work. (Resolution No: KLECOP/CPCSEA/Re.no.221/PO/RE/S/2000/CPCSEARes.25-09/09/2017). In this study, all the procedures using Wistar rats, weighed 150–200 g, male, 6–8 weeks of age, were provided by the Institutional Animal Ethics Committee of KLE College of Pharmacy, Belagavi, Karnataka, India and was performed out in accordance with the guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

ACKNOWLEDGEMENT

Authors are thankful to their regards to Dr. Prabhakar Kore Basic Science Research Centre, KLE Academy of Higher Education and Research Belagavi, for providing their amenities to carry out this work. The authors are also thankful to Cipla Pvt. Ltd. Bangalore, India, for providing Felodipine pure drug as gift sample. The authors are thankful to Kesar Control System, AICTE-MODROB 2017-2018 for providing stability chamber to carry out the stability studies in research work. Authors are also thankful AICTE-MODROBE for providing Ultrasonic probe sonicator VC750.

CONFLICT OF INTEREST

The authors declare that they have no any conflict of interests.

ABBREVIATIONS

BCS: Biopharmaceutical Classification System; **NLCs:** Nanostructured lipid carriers; **TEM:** Transmission Electron Microscope; **SEM:** Scanning Electron Microscope; **SD:** solid dispersions; **SMEDDS:** Self Micro Emulsifying Drug Delivery System; **PDI:** Polydispersity Index; **AUC:** Area Under Curve.

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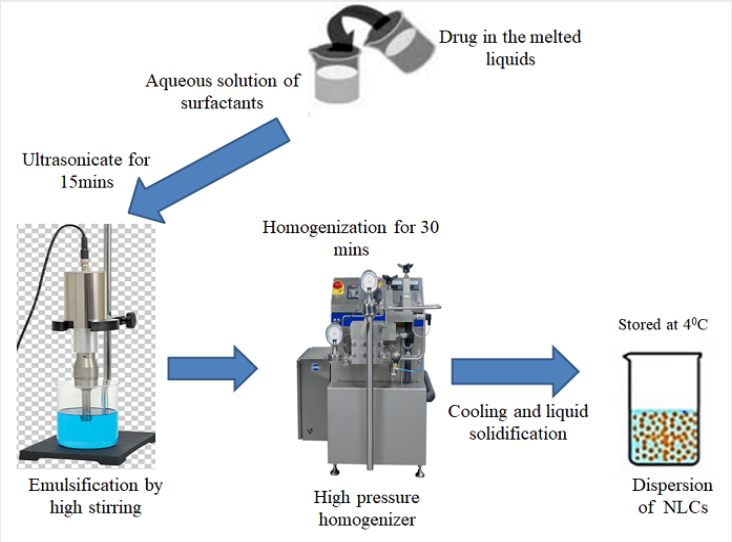
SUMMARY

- Nanostructured lipid carriers of Felodipine were successfully prepared by using high shear homogenization and ultrasonication teqniques.
- Preformulation study to determine drug-excipient compatibility was carried out by FTIR and DSC, which revealed that, the drug sample was pure and the lipids and surfactant used were compatible with Felodipine.
- A total five formulations (F1-F5) were prepared by using Compritol ATO 888 as solid lipid, oleic acid as liquid lipid and poloxamer 188 as a surfactant.
- Felodipine loaded NLCs were characterised for their particle size, polydispersity index, % drug content, % entrapment efficiency, zeta potential , surface morphology, *in-vitro* drug release studies, *in-vivo* bioavailability and stability studies.
- Based on evaluation results of NLCs, F2 formulation was considered as optimized formulation for further evaluation.
- Zeta potential of optimized formulation F2 was -38.2 showed good stability.
- *In vitro* drug release study showed initial burst effect, this may be due to drug present on the surface of NLC followed by sustained release.
- Developed UV method was used for determination of Felodipine in rat plasma for bioavailability and pharmacokinetic evaluation.
- The relative bioavailability of NLC formulation showed an enhanced bioavailability of 2.0 times greater than that of Marketed product.

PICTORIAL ABSTRACT



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Cite this article: Patil AS, Jaknoor V, Gadad AP, Masareddy RS, Dandagi PM, Bolmal U. Nanostructured Lipid Carrier: A Potential System for Enhanced Oral Bioavailability of Felodipine. Indian J of Pharmaceutical Education and Research. 2022;56(1):77-85.