

Preparation, Characterization and *in vivo* Evaluation of Felodipine Solid-Lipid Nanoparticles for Improved Oral Bioavailability

Usha Kiranmai Gondrala, Narendar Dudhipala and Veerabrahma Kishan*

*Nanotechnology Laboratory, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal- 506009, Telangana, India.

Received July 21, 2015; accepted August 15, 2015

ABSTRACT

Felodipine is an antihypertensive drug with poor oral bioavailability due to the first pass metabolism. For improving the oral bioavailability, felodipine loaded solid lipid nanoparticles (SLNs) were developed using trimyristin, tripalmitin and glyceryl monostearate. Poloxamer 188 was used as surfactant. Lipid excipient compatibilities were confirmed by differential scanning calorimetry. SLN dispersions were prepared by hot homogenization of molten lipids and aqueous phase followed by

ultrasonication at a temperature, above the melting point. SLNs were characterized for particle size, zeta potential, drug content, entrapment efficiency and crystallinity of lipid and drug. *In vitro* release studies were performed in 0.1N HCl and phosphate buffer of pH 6.8 using dialysis method. Pharmacokinetics of felodipine-SLNs after oral administration in male Wistar rats was studied. The bioavailability of felodipine was increased by 1.75 fold when compared to that of a felodipine suspension.

KEYWORDS: Solid-lipid nanoparticles; felodipine; lipophilic; bioavailability; pharmacokinetics.

Introduction

Felodipine (FD) is a calcium channel blocker, and used as an antihypertensive drug. It is practically insoluble in water and has poor bioavailability (15%) because of extensive hepatic first pass metabolism (Capewell et al., 1998). Possible methods to avoid first pass metabolism include: transdermal, buccal, rectal and parenteral routes of administration.

Oral route is the most commonly used and preferred route for the delivery of drugs, although several factors like pH of GIT, residence time and solubility can affect this route. Lymphatic delivery is an alternative choice to avoid first pass metabolism in peroral drug delivery (Driscoll, 2002). Enhanced lymphatic transport of drugs reduces the hepatic first-pass metabolism and improves oral bioavailability, because intestinal lymph vessels drain directly into thoracic duct, further in to the venous blood, thus bypassing the portal circulation (Cavalli et al., 2003). The main function of the lymphatic system is to facilitate absorption of long chain fatty acids via chylomicron formation. Two different lipid based approaches are known to enhance the lymphatic transport, which include construction of a highly lipophilic prodrug and incorporation of drug in a lipid carrier (Charman and Porter, 1996).

Solid lipid nanoparticles (SLNs) are one of the carrier systems having more advantages than other colloidal delivery systems with regard to biocompatibility and

scale up (Müller et al., 2000). Various methods, such as high-pressure homogenization, solvent emulsification/ evaporation were reported in literature for preparing SLNs (Mehnert and Mäder, 2001).

Previously, the dissolution rate and oral bioavailability of FD was improved by nanosuspension technique (Bhanuand Malay, 2014). Improvement in the solubility of FD was reported by self-nanoemulsifying system approach (Pradeep et al., 2009). The bioavailability of felodipine was enhanced by targeting the M cells of Peyer's patches using PLGA nanoparticles (Shah et al., 2014). But, solid lipid nanoparticles of FD were not reported till now.

The aim of the present work was to study the improvement of bioavailability by incorporating felodipine in SLNs prepared with different lipids such as tripalmitin (TP), trimyristin (TM) and glyceryl monostearate (GMS). The SLNs were prepared by hot homogenization followed by ultra-sonication method. Drug excipient compatibility was assessed by DSC. The SLNs were characterized for particle size, zeta potential and *in vitro* release. Bioavailability study in rats was performed and was compared with that of felodipine suspension.

Materials and Methods

Materials: TP, Tripalmitin (glyceryl tripalmitate; Dynasan-116), TM, trimyristin (glyceryl trimyristate; Dynasan-114) were obtained from Sasol, Witten,

Germany. Poloxamer 188 was obtained from Sigma (St. Louis, MO, USA). GMS, Monostearin (glyceryl monostearate) was from S.D. Fine-Chem Ltd, India. Felodipine was a gift from M/s. Aurobindo Labs., Hyderabad, India. Nitrendipine was a gift from M/s. Everlight Chemicals, India. Centrisart filters (molecular weight cut off 20,000) were purchased from Sartorius, Goettingen, Germany. Chloroform, methanol, acetonitrile and dichloromethane were of HPLC grade (Merck, India).

Preparation of felodipine loaded SLNs

Felodipine loaded SLNs were prepared by hot homogenization followed by ultrasonication method (Manjunath and Venkateswarlu, 2005). Felodipine (10 mg) and lipid (100-300 mg) were dissolved in 10 mL of a mixture of chloroform and methanol (1:1). The compositions are given in Table 1. The organic solvent mixture was completely evaporated at 70 °C using rotaevaporator (Heidolph, Laborota 4000, Germany). Drug embedded lipid was molten by heating to 5 °C above the melting point of lipid. The aqueous phase was prepared by dissolving Poloxamer 188 (150 mg) in double distilled water (Millipore, India) sufficient to produce 10 mL and heated to same temperature as that of molten lipid phase. Hot aqueous solution was added to molten lipid phase and homogenized (DIAX 900, Heidolph, Germany) for 4 min at 11,000 rpm. The temperature was maintained at 5 °C above the melting point of lipid throughout the homogenization process. The coarse hot o/w emulsion thus obtained was sonicated using a probe sonicator - 12T (Vibracell, USA) for 15 min. The obtained nanoemulsions were cooled to room temperature to obtain SLNs.

TABLE 1

Compositions of felodipine loaded solid lipid nanoparticles and suspension.

Ingredients (mg)	Formulation Code			
	F-TP	F-GMS	F-TM	F-Susp
Felodipine	10	10	10	10
Dynasan-116 (Tripalmitin)	100	-	-	-
Glyceryl monostearate	-	200	-	-
Dynasan-114 (Trimyristin)	-	-	100	-
Poloxamer-188	150	150	150	-
Sodium carboxy methyl cellulose	-	-	-	50
Egg lecithin	100	100	100	-
Double distilled water (mL)	10	10	10	10

Measurement of Size, PDI and ZP of SLNs

Size and zeta potential of all drug loaded SLN samples were measured by using Zetasizer (Nano ZS 90, Malvern Instruments, UK). All the samples were diluted with aqueous phase of the formulation to get optimum measurements. Average particle size in nanometers, polydispersity index and zeta potential were measured.

Analytical methods

Estimation of felodipine in serum samples was conducted by HPLC (Shimadzu 10, Japan). The analysis was performed at 240 nm with a SPD-10AV UV-Visible detector, pump LC-10AT, reversed-phase column C₁₈, 25 cm × 4.5 mm, 5 μm column maintained at 25 °C employing a mobile phase of acetonitrile (66%) and water (34%) delivered at a flow-rate of 1 mL/min. The retention time of the drug was found to be 10.71 min. The calibration curve was linear in the concentration range of 0.1–10 μg/mL ($r^2 = 0.99$) in rat serum.

Determination of drug content

Felodipine loaded SLN (0.1 mL) was diluted to 1 mL with chloroform/methanol mixture (1:1) and final dilution was made with mobile phase and total content was determined by HPLC (Shimadzu, Japan) method as described above.

Determination of entrapment efficiency

Entrapment efficiency (EE) was determined by measuring the concentration of free drug (unentrapped) in aqueous medium as reported previously (Venkateswarlu and Manjunath, 2004). The aqueous medium was separated by ultra-filtration using centrisart tubes (Sartorius, USA), which consisted of a filter membrane with M.Wt. cut off 20,000 Da. About 1 mL of the formulation was placed in the outer chamber and sample recovery chamber was placed on top of the sample and centrifuged at 4000 rpm for 15 min (Biofuge, Heraeus). The SLN along with encapsulated drug remained in the outer chamber and aqueous phase moved into the sample recovery chamber through filter membrane. The amount of felodipine in the aqueous phase was estimated by HPLC method as described above and the EE was calculated by the following equation:

$$EE = \frac{W_{total} - W_{free}}{W_{total}} \times 100$$

where, W_{total} was the weight of drug added in the system and W_{free} weight of the free drug in aqueous system.

Physical stability studies

FD loaded solid lipid nanoparticles stored at room temperature and refrigerated temperature for two months. The average size, PDI and ZP were determined periodically after 1st day, one month and two months.

Drug excipient compatibility study by differential scanning calorimetry (DSC)

The pure drug and lipid excipients used in the study were felodipine, tripalmitin, trimyristin, glyceryl monostearin. DSCs were also obtained at 1:1 ratio of physical mixtures consisting of drug: tripalmitin/trimyristin and drug: glyceryl monostearin, using a differential scanning calorimeter Mettler-Toledo DSC 821e (Columbus, OH). A heating rate of 10 °C/min was employed in the range of 27 °C to 240 °C. Analysis was performed under nitrogen purge. Standard aluminum pans were used containing 10 mg of samples (Suvarna et al., 2015).

***In vitro* release studies of felodipine from SLNs**

In vitro release studies were performed using dialysis method. Dialysis membrane having a pore size 2.4 nm, with molecular weight cut off 12,000–14,000 was used. Membrane was soaked in double-distilled water for overnight. A volume of 2 mL of felodipine loaded SLN formulation was placed in the dialysis bag and the receptor compartment was filled with 100 mL of buffer medium consisting of 0.1N HCl or phosphate buffer pH 6.8. An aliquot of 5 mL of sample was withdrawn from receiver compartment at time intervals of 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hr. Fresh medium was replaced each time to maintain constant volume (Narendar and Kishan, 2014). Samples were analyzed by UV Visible spectrometer.

Animal study protocol

Male Wistar rats were obtained from M/s. Mahaveer enterprises, Hyderabad. The animals were quarantined in the animal house. Rats had free access to food and water *ad libitum*. The study protocol was approved by the Institutional Animal Ethics Committee of University College of pharmaceutical sciences, Kakatiya University, Warangal. Twenty-four male Wistar rats weighing 200-230 g were kept for overnight fasting with free access to water. The animals were divided into four groups of six animals each and SLN formulations, F-TP, F-TM, F-GMS and felodipine suspension were administered by oral route.

Oral administration

Three groups of rats were administered with their respective formulations using oral feeding needle based on body weight at 10 mg/kg. For comparison, felodipine was administered as sodium carboxy methylcellulose suspension to fourth group. Rats were anaesthetized and blood samples (0.3 mL) were collected from the retro-orbital venous puncture at 0.5, 1, 2, 4, 6, 8, 10 and 12 hr after drug administration. The blood samples were centrifuged (5000 rpm, 15 min) and serum was collected and stored at -20°C until analysis.

Serum drug analysis by HPLC

For determination of felodipine, to 100 μL of serum, 25 μL of methanol and to this 25 μL of internal standard (nitrendipine, 150 ng/mL) was added and vortexed for 2 min. The samples were made alkaline by addition of 100 μL of 1N NaOH and vortexed for 3 min. To this sample, 750 μL of dichloromethane was added and vortexed for 5 min and then centrifuged at 4000 rpm for 15 min. The organic layer was separated and evaporated. The residue was reconstituted with mobile phase and a volume of 20 μL of sample was injected into HPLC (LC 10AT, Shimadzu, Japan) with UV-detector at 240 nm (SPD 10AV, Shimadzu, Japan) using Lichrospher C₁₈ (250 mm \times 4.6 mm i.d., 5 μm particle size) analytical column for analysis. Acetonitrile: water at a ratio 66:34 v/v was used as mobile phase with a flow rate of 1 mL/min. Retention time of 10.9 min for felodipine and 7.2 min for internal standard, nitrendipine were obtained

(Figure 1). The standard graph was plotted in the linearity range of 0.1-10 $\mu\text{g/mL}$ concentration with $r^2 > 0.995$.

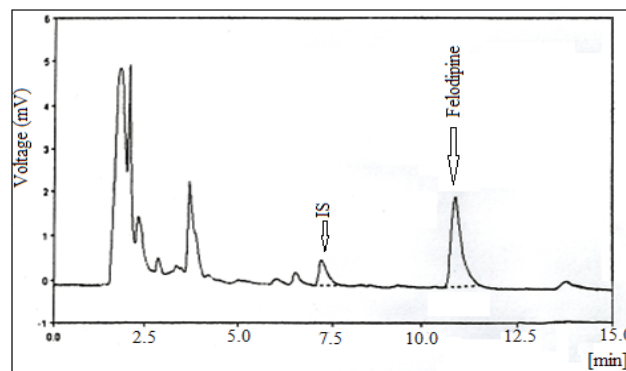


Fig. 1. Representative chromatogram showing retention times of felodipine (10.9 min) and nitrendipine, an internal standard (7.2 min) in serum drug analysis.

Calculation of pharmacokinetic parameters and statistical significance

Pharmacokinetic parameters such as C_{max} , T_{max} , AUC, $t_{1/2}$ and MRT were calculated by using Kinetica software (version 5.0). The statistical significance of observed differences in C_{max} , AUC, $t_{1/2}$ and MRT of different groups were assessed by ANOVA test by using Graph pad Prism software. All data were expressed as mean \pm S.D. *P*-value below 0.05 was considered to be statistically significant.

Results and Discussion

Preparation of felodipine loaded SLNs

Hot homogenization followed by ultra-sonication is a reliable, simple and reproducible method for preparing SLN (Venkateswarlu and Manjunath, 2004). Initially, homogenization of the lipid phase with hot aqueous poloxamer solution for 4 min was used to produce a coarse emulsion followed by sonication resulting in average particle size between 90 and 140 nm. A further increase in homogenization time showed increase in particle size to a greater extent. Thus, 4 min homogenization time was selected for all the formulations and further reduction of size was attained with sonication. Sonicating the coarse emulsion for 15 min resulted in particles between 94 and 135 nm with narrow size distribution. In order to optimize the lipid to drug ratio, different amounts of all three lipids (100, 200 and 300 mg) were tried with fixed amount of drug (10 mg). Lipid content 100 mg for triglycerides (TP & TM) and 200 mg for monoglyceride (GMS), helped in the good encapsulation efficiency (Table 2). Based on these results, the lipid to drug ratio of 100:10 for TP & TM and 200:10 for GMS were used for further studies.

Optimization of size

To obtain stable and smaller SLNs, poloxamer concentration was varied from 0.5% to 2% and their

effect on particle size was measured. A poloxamer concentration of 1.5% was effective in producing smaller size SLN in case of all the three lipids (94.49 ± 10.79 nm for F-TP, 113.46 ± 9.71 nm for F-GMS and 135.2 ± 4.26 nm for F-TM). These results clearly suggested that an optimum concentration of 1.5% poloxamer was sufficient to get nanoparticles effectively and prevented agglomeration during the homogenization process. High concentration of surfactant (2%) was avoided to prevent decrease in the entrapment efficiency and also toxic effects associated with surfactants (Müller et al., 2000). Among the glycerides used, TP produced least size SLN when compared with GMS. Similar trend was reported for the etoposide loaded SLN (Reddy and Murthy, 2005).

Total content and Entrapment Efficiency

The drug content of the SLN was highest for the formulation F-TP (9.7 ± 0.12) followed by F-TM (9.64 ± 0.67) and least for F-GMS (8.7 ± 0.34). Entrapment efficiencies (EE) of F-TP, F-TM and F-GMS are shown in Table 2. SLN formulation of F-GMS prepared with glyceryl monostearate showed less drug-loading capacity when compared with that of F-TP and F-TM respectively ($p < 0.05$). The EE of the SLN for felodipine was in the order of F-TP > F-TM > F-GMS. The higher drug content and EE with TP was attributed to the high hydrophobicity due to the long chain fatty acids attached to the triglyceride resulting in increased accommodation of lipophilic drugs (Jenning and Gohla, 2000).

Stability studies

When all SLN formulations were stored at 4°C & 25°C resulted in increased particle size. Increase in size

was from 103.28 nm to 129.3 nm with F-TP, from 91.64 nm to 111.61 nm with F-GMS and from 111.58 nm to 138.4 nm with F-TM (Table 3). Lipids of less ordered crystal lattices such as GMS, though favored drug inclusion, and were unstable due to the presence of monoglycerides (Heitai et al., 1998).

There was some difference found in sizes (10-15% at 4°C & while at RT about 20-25%) and the zeta potentials also changed to some extent with exception of F-TM SLN formulation during two months study at room temperature and also at 4°C.

Drug excipient compatibility study by differential scanning calorimetry

DSC thermograms of pure samples of felodipine, Dynasan -116, glyceryl monostearate and Dynasan-114 and along with their physical mixtures of felodipine and lipids are shown in Figure 2. Sharp endothermic peaks were observed for pure felodipine at 148.56°C, Dynasan 116 at 72.57°C, GMS at 71.33°C and Dynasan 114 at 70°C. In case of physical mixtures, felodipine and Dynasan-116 mixture showed broader endothermic peak at 138°C, and a sharper peak at 68.51°C. Similarly, felodipine and Dynasan-114 mixture showed a broader peak at 138°C and sharper one at 65.00°C. Further, felodipine and GMS mixture showed a broader peak at 138°C and sharper peak at 50.77°C. In general, drug and lipid peaks were retained but shifted towards left side and indicated the loss of purity of individual components due to intimate mixing process. Thus, DSC analysis indicated that there was no interaction between felodipine and lipids used for the development of SLNs.

TABLE 2

Physical characters - Particle size, zeta potential and entrapment efficiency of different lipid SLN formulations (mean \pm S.D., $n = 3$).

Formulation	Size (nm)	PDI	ZP (mV)	EE (%)	Total drug content (mg)
F-TP	94.49 ± 10.79	0.232 ± 0.10	-21.1 ± 7.01	95.77 ± 0.31	9.7 ± 0.12
F-GMS	$113.46 \pm 9.71^*$	0.302 ± 0.06	-28.96 ± 4.29	87.53 ± 1.27	8.7 ± 0.34
F-TM	$135.2 \pm 4.26^§$	0.275 ± 0.03	-26.7 ± 2.91	94.46 ± 0.65	9.64 ± 0.67

*Statistical significance with F-TP and F-TM ($p < 0.05$).

§Statistical significance with F-TP ($p < 0.05$).

TABLE 3

Effect of storage at refrigerated temperature and room temperature on Size, PDI and ZP of optimized SLN formulations (mean \pm SD, $n = 3$).

Condition	Day	Size (nm)			PDI			Zeta Potential (mv)		
		F - TP	F - GMS	F - TM	F - TP	F - GMS	F - TM	F - TP	F - GMS	F - TM
25°C	1	103.2 ± 2.0	91.6 ± 1.9	111.5 ± 4.9	0.29 ± 0.08	0.37 ± 0.07	0.29 ± 0.09	-19.9 ± 2.4	-32.9 ± 11.4	-25.5 ± 5.6
	30	118.1 ± 6.3	104.1 ± 9.8	123.2 ± 2.2	0.32 ± 0.06	0.28 ± 0.03	0.28 ± 0.01	-27.0 ± 1.4	-27 ± 9.8	-26.5 ± 2.2
	60	129.3 ± 7.5	111.6 ± 1.5	138.4 ± 1.5	0.27 ± 0.04	0.33 ± 0.01	0.26 ± 0.04	-29.6 ± 5.4	-26.0 ± 4.0	-28.1 ± 3.6
4°C	1	103.2 ± 2.0	91.6 ± 1.9	111.5 ± 4.9	0.29 ± 0.08	0.37 ± 0.07	0.29 ± 0.09	-19.9 ± 2.4	-32.9 ± 11.4	-25.5 ± 5.6
	30	111.5 ± 1.4	102.2 ± 1.8	118.5 ± 1.1	0.22 ± 0.09	0.19 ± 0.02	0.22 ± 0.03	-24.2 ± 7.5	-23.6 ± 3.9	-27.6 ± 3.4
	60	117.9 ± 1.4	104.9 ± 1.7	127.1 ± 1.4	0.31 ± 0.01	0.22 ± 0.03	0.31 ± 0.05	-25.3 ± 4.8	-22.7 ± 4.2	-26.2 ± 4.3

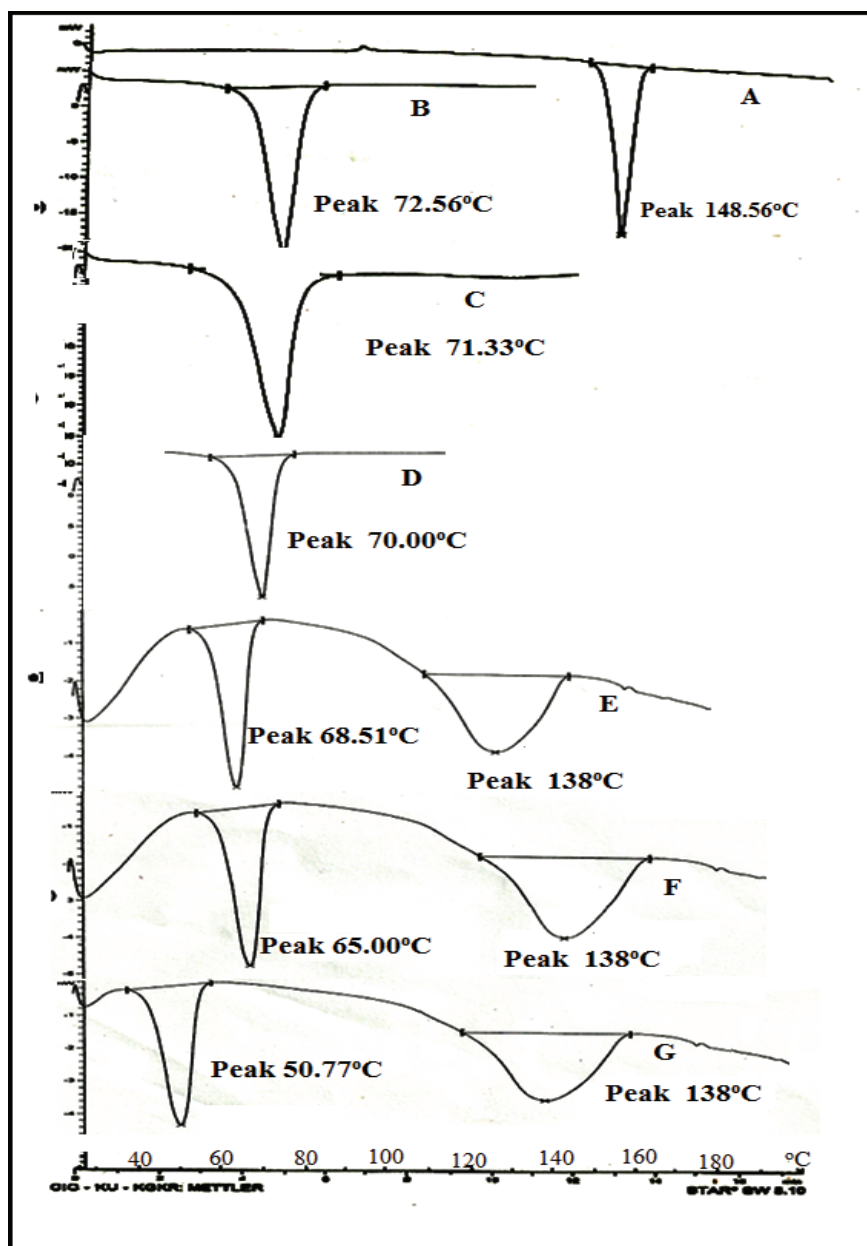


Fig. 2. DSC thermograms of (A) drug, (B) Dynasan-116, (C) Dynasan-114, (D) glyceryl monostearate, (E) physical mixture (Dynasan-116:drug), (F) physical mixture (Dynasan-114:drug) and (G) physical mixture (glyceryl monostearate:drug).

In vitro drug release of SLNs and suspension by dialysis method

The drug release was observed over a period of 24 h. The cumulative percentage drug release was calculated. The release profiles are shown in Figures 3 and 4. The drug release was observed over a period of 24 h. At pH 1.2, the cumulative amount of felodipine released from formulation F-susp was 20.09%, whereas for formulations F-TP, F-GMS and F-TM were 33.49%, 25.47% and 35.18% respectively. At pH 6.8, the cumulative amount of drug released from formulation F-susp was 34.59%, whereas for formulations F-TP, F-GMS and F-TM were 48.23%, 46.27% and 49.77% respectively. In the above two cases the cumulative percentage drug release was increased from all formulations (F-TP,

F-GMS, F-TM and F-Susp) when compared to suspension either in pH 1.2 or pH 6.8 medium. In general, the decreasing order of % cumulative drug release from formulations at 24 hr is F-susp < F-GMS < F-TP < F-TM in both media. However, the drug release from F-GMS, F-TP and F-TM formulations was not significantly different. This is probably due to packing of the drug molecules in lipid mixture of SLN formulations when compared to suspension, and thus these SLNs released drug faster. The individual profiles are different for first 12 hr. From F-TM, relatively faster drug release was noticed over the others. Subsequently, in next 12 hr period from all the formulations, release was increased. But from none of the formulations, 50% drug was released. This could be due to less solubility of drug in 0.1N HCl and pH 6.8 phosphate buffer.

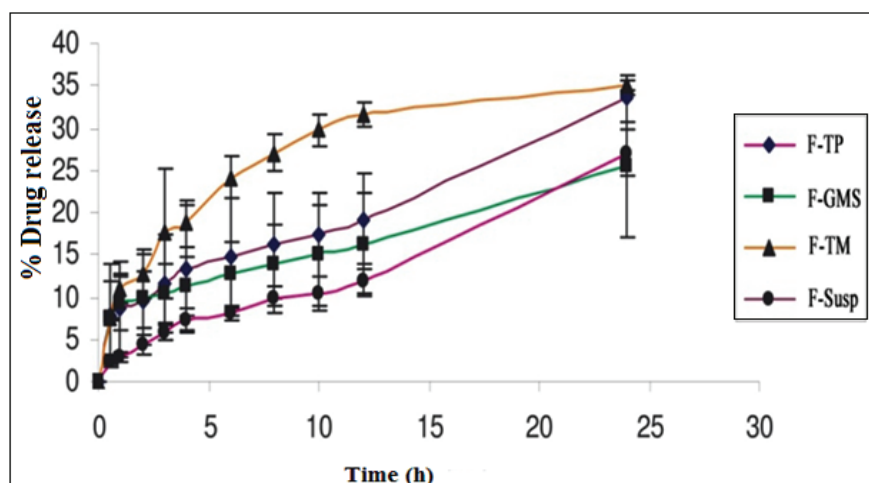


Fig. 3. *In-vitro* release of FD from FD-SLN_s in 0.1N HCl (mean±SD, n=3).

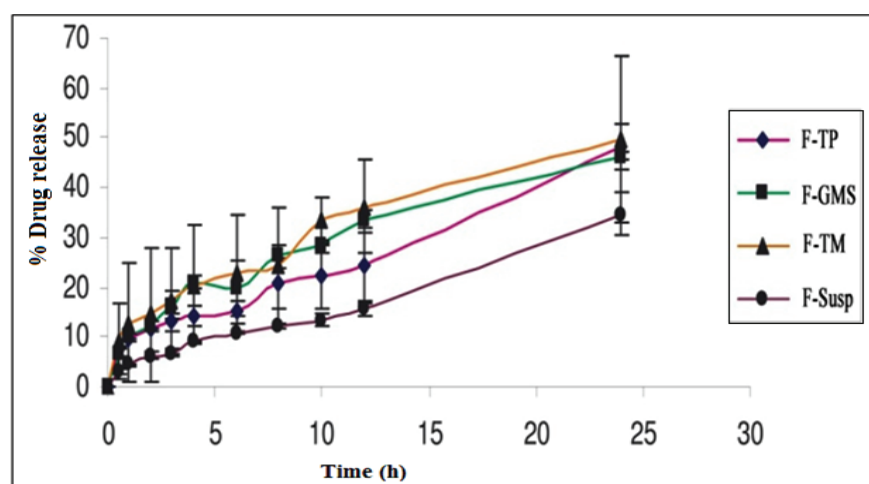


Fig. 4. *In-vitro* release of FD from FD-SLN_s in pH 6.8 phosphate buffer (mean±SD, n=3).

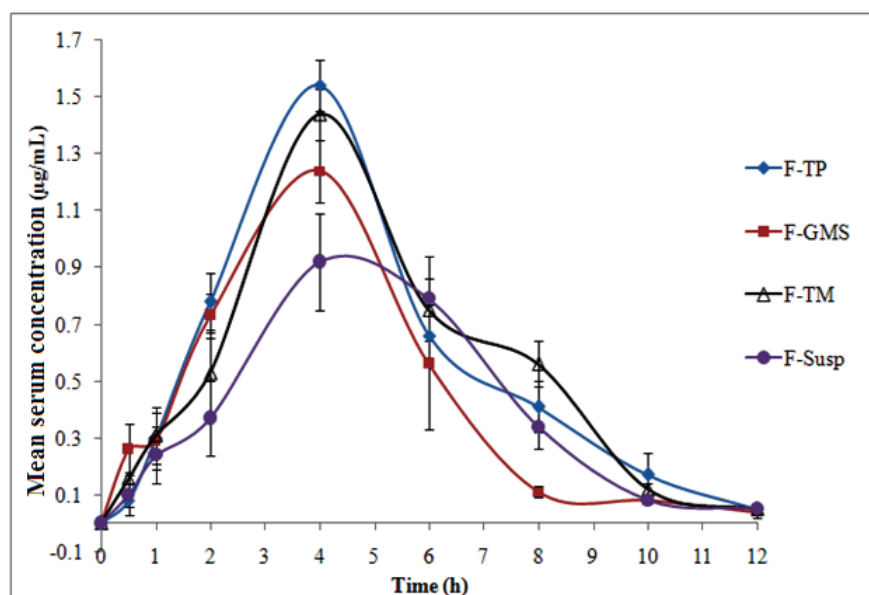


Fig. 5. Serum concentration Vs time profiles of felodipine upon oral administration of F-Susp, F-TP, F-GMS and F-TM to male wistar rats (mean±SD, n=6).

Pharmacokinetic parameters

In this study, three different formulations and drug suspension (F-TP, F-TM, F-GMS and F-Susp) were given to rats by oral administration. Serum concentration–time

curves of felodipine after oral administration are shown in Figure 5. Peak serum concentration (C_{max}) for felodipine suspension observed was $0.92 \pm 0.43 \mu\text{g/mL}$ at 4 h (t_{max}). All SLN formulations of felodipine displayed

significantly ($p < 0.05$) higher values of C_{max} when compared to that of suspension formulation. Peak plasma concentrations were in the following order: F-TP > F-TM > F-GMS > suspension. Increase in $AUC_{(0-\infty)}$ suggested that SLNs of felodipine were taken up by Peyer's patch of intestine (Mansbach and Nevin, 1998; Porter and Charman, 2001). Lipid nature, fatty acid chain length and hydrophobicity would influence the lymphatic uptake (Nordskog et al., 2001; Ros, 2000; Holm et al., 2001). *In vitro* release data of felodipine loaded SLN formulations also showed more release with F-TP than other two SLN formulations. Mean residence time (MRT) was not statistically significant when compared with control suspension Table 4.

TABLE 4

Pharmacokinetic parameters of FD after oral administration of SLN formulations and suspension (mean \pm SD, n = 6).

Parameter	F-TP	F-GMS	F-TM	F-Susp
C_{max} ($\mu\text{g/mL}$)	1.59 \pm 0.36*	1.25 \pm 0.21*	1.32 \pm 0.64*	0.92 \pm 0.43
t_{max} (h)	4 \pm 0.00	4 \pm 0.00	4 \pm 0.00	4 \pm 0.00
$AUC_{(0-\infty)}$ ($\mu\text{g/mL}\cdot\text{h}$)	6.82 \pm 1.30*	4.29 \pm 1.05	5.96 \pm 2.13	4.19 \pm 1.26
$t_{1/2}$ (h)	1.27 \pm 0.20	1.46 \pm 0.27	1.42 \pm 0.28*	1.24 \pm 0.28
MRT (h)	5.00 \pm 0.60	4.16 \pm 0.31	4.80 \pm 0.62	5.01 \pm 0.28

* Statistical significance with F - Susp, ($p < 0.05$).

The decreasing order of $AUC_{(0-\infty)}$ values for formulation F-TP > F-TM > F-GMS > F-Susp. All the SLNs formulations yielded increased bioavailability over suspension. However, F-TP formulation improved maximum oral bioavailability when compared to suspension (F-Susp). Comparison of prepared SLNs by One way ANOVA analysis showed that the C_{max} , $AUC_{(0-12)}$, $t_{1/2}$ and Mean residence time (MRT) were statistically significant.

Conclusion

In the present study, felodipine loaded SLN were prepared by hot homogenization followed by ultrasonication method using different lipids. Lipid-drug excipient compatibility was confirmed by DSC studies. The method resulted in consistent production of smaller size nanoparticles in the range of 90-140nm with narrow size distribution and good entrapment efficiency. The surfactant (poloxamer) concentration was optimized at 1.5% based on the particle size and EE. The stability data and *in vitro* release profile indicated controlled release of the drug and excellent physical stability for short-period. An HPLC method for serum drug analysis was developed. The pharmacokinetic studies showed an increased $AUC_{(0-\infty)}$ for triglyceride SLNs (TP and TM), followed by monoglyceride SLN (GMS). Enhanced oral bioavailability of felodipine (up to 1.75 times) was observed with F-TP SLN formulation when compared to a suspension. The current investigation illustrates the effect of lipid nature on the EE (%), *in vitro* release and bioavailability of lipophilic drug.

Acknowledgements

We thank Prof. Y. Madhusudan Rao, University college of Pharmaceutical Sciences, Kakatiya University, for his help during this work. Prof. E. Ram Reddy and Mr. Gopal Kishan Rao of Central Instrumentation Centre, Kakatiya University for their help in getting DSC curves. Ms. Usha Kiranmai thanks the UGC, New Delhi for scholarship.

Declaration of interest: The authors report no conflicts of interest.

References

- Bhanu PS and Malay KD (2014). Nanosuspension for enhancement of oral bioavailability of felodipine. *Appl Nanosci* **4**: 189-197.
- Capewell S, Freestone S, Critchlev JA, Pottage A and Prescott LF (1988). Reduced felodipine bioavailability in patients taking anticonvulsants, Department of clinical pharmacology, Royal Infirmary, Edinburgh. *Lancet*, **27** (2): 480-2.
- Cavalli R, Bargoni A, Podio V and Muntoni E (2003). Duodenal administration of solid lipid nanoparticles loaded with different percentages of tobramycin. *J Pharm Sci* **92**(5): 1085-1094.
- Charman WN and Porter CJH (1996). Lipophilic prodrugs designed for intestinal lymphatic transport. *Adv Drug Deliv Rev* **19**(2): 149-169.
- Driscoll MC (2002). Lipid-based formulations for intestinal lymphatic delivery. *Eur J Pharm Sci* **15**: 405-415.
- Harivardhan Reddy L and Murthy RSR (2005). Etoposide loaded nanoparticles made from glyceride lipids: formulation, characterization, in vitro drug release and stability evaluation. *AAPS Pharm Sci Tech* **6**(2): E158-E166.
- Heitai H, Tawashi R and Philips NC (1998). Drug retention and stability of solidlipid nanoparticles containing azidothymidine palmitate after autoclaving, storage and lyophilization. *J Microencapsul* **15**(2): 173-84.
- Holm R, Mullertz A, Pedersen GP and Christensen HG (2001). Comparison of the lymphatic transport of halofantrine administered in disperse systems containing three different unsaturated fatty acids. *Pharm Res* **18**(9): 1299-1304.
- Jenning V and Gohla S (2000). Comparison of wax and glycerides solid lipid nanoparticles. *Int J Pharm* **196**(2): 219-222.
- Manjunath K and Venkateswarlu V (2005). Pharmacokinetics, tissue distribution and bioavailability of clozapine solid lipid nanoparticles after intravenous and intraduodenal administration. *J Contr Rel* **107**: 215-228.
- Mansbach CM and Nevin P (1998). Intracellular movement of triacylglycerols in intestine. *J Lipid Res* **39**(5): 963-968.
- Mehnert W and Mäder K (2001). Solid lipid nanoparticles production, characterization and applications. *Adv Drug Deliv Rev* **47**: 165-196.
- Müller RH, Mäder K and Gohla S (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art *Eur J Pharm Biopharm* **50**: 161-177.
- Narendar D and Kishan V (2014). Candesartan cilexetil loaded solid lipid nanoparticles for oral delivery: characterization, pharmacokinetic and pharmacodynamic evaluation. *Drug Delivery Early Online*: 1-10. DOI: 10.3109/10717544.2014.914986.
- Nordskog BK, Phan CT, Nutting DF and Tso P (2001). An examination of the factors affecting intestinal lymphatic transport of dietary lipids. *Adv Drug Deliv Rev* **50**(1-2): 21-44.
- Porter CJH and Charman WN (2001). Intestinal lymphatic drug uptake: an update. *Adv Drug Deliv Rev* **60**(6): 61-80.
- Pradeep RP, Shailesh VB and Anant RP (2009). Extended release felodipine self-nanoemulsifying system. *AAPS Pharm Sci Tech* **10**(2): 515-23.

- Ros E (2000). Intestinal absorption of triglyceride and cholesterol, dietary and pharmacological inhibition to reduce cardiovascular risk. *Atherosclerosis* **151(2)**:357-379.
- Shah U, Joshi G and Sawant K (2014). Improvement in antihypertensive and antianginal effects of felodipine by enhanced absorption from PLGA nanoparticles optimized by factorial design. *Mater Sci Eng C Mater Biol Appl* **35(1)**:153-63.
- Suvarna G, Narender D and Kishan V (2015). Preparation, Characterization and *In vivo* Evaluation of Rosuvastatin Calcium Loaded Solid Lipid Nanoparticles. *Int J Pharm Sci Nanotech* **8(1)**: 2779-2785.
- Venkateswarlu V and Manjunath K (2004). Preparation characterization and *in vitro* release kinetics of clozapine solid lipid nanoparticles, *J Contr Rel* **95(3)**: 627–638.

Address correspondence to: Prof. V. Kishan, Department of Pharmaceutics, University college of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana - 506009, India.

Ph: 0870-2446259; E-mail: vbkishan@yahoo.com
