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Research Article

FORMULATION AND *IN VITRO* CHARACTERIZATION OF THE SOLID LIPID NANOPARTICLES OF NAFTOPIDIL FOR ENHANCING ORAL BIOAVAILABILITY

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ABSTRACT

Objective: Naftopidil (NAF) is a selective alpha1-adrenergic receptor antagonist with a nearly 20% bioavailability due to poor aqueous solubility, permeability, and extensive first-pass metabolism. To improve the bioavailability of the NAF, the solid lipid nanoparticles (SLN) of NAF were prepared.

Methods: SLNs NAF were prepared using the solvent emulsification/evaporation method with excipients Compritol 888 ATO and Poloxamer 188. Formulation F10 shows better entrapment efficiency (EE) as compare to other formulations so, it has selected to optimize the particle size, zeta potential, surface morphology, Fourier transform infrared spectroscopy (FTIR), and *in vitro* drug release and stability studies were assessed.

Results: The results showed that NAF was successfully incorporated in SLN. Having EE of all formulations ranged from 56% to 88%, drug loading ranged from 17% to 20%, drug content ranged from 77% to 98%, particle size and zeta potential of F10 were 270.2 nm and 21.7 mV, respectively, and FTIR revealed no interaction between drug and lipid in the formulation. The release of NAF-SLNs increased significantly, reaching a maximum of 4.547–82.418% in pH 6.8 buffer, the release data were fitted into the Korsmeyer-Peppas model yielding the highest correlation coefficient (R^2=0.916). The stability study revealed that the formulation stability and bioavailability might be improved.

Conclusion: It can be concluded that SLN could be effective nanoplatforms for increasing NAF oral bioavailability.

Keywords: Naftopidil, Solid lipid nanoparticles, Oral bioavailability, Entrapment efficiency.

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INTRODUCTION

Naftopidil (NAF) is a selective alpha1-adrenergic receptor antagonist used to treat benign prostatic obstruction and benign prostatic hyperplasia (BPH)-related lower urinary tract symptoms. It acts as an antihypertensive by blocking the 1-adrenergic receptor and causing vasodilation. NAF is a BCS Class IV drug with low aqueous solubility (0.11 mg/mL) and low permeability at intestinal pH (log P 3.77), resulting in 20% oral bioavailability in humans due to rate-limiting permeation in first-pass metabolism. As a result, low aqueous solubility, poor dissolution rate, low permeability, and high hepatic first-pass metabolism in the liver are thought to be the primary reasons for NAF low oral bioavailability. Because of these factors, the dosage of NAF is much higher than that of other pharmaceutical treatments for BPH [1]. To overcome the high dosing frequency, improve oral bioavailability, and control plasma drug levels, nanoparticles were prepared to reduce the dosage regimen's dosing frequency.

Nanoparticulate (NPs) drug delivery systems have a wide range of advantages because of their nano size, enhanced solubility, mucoadhesion, drug targeting, dual release behavior, and higher bioavailability. NPs delivery systems are colloidal formulations that are nanometric in size and can encapsulate both hydrophilic and lipophilic drugs. Researchers have shown a great deal of interest in the oral administration of solid lipid nanoparticles (SLNs) over the last three decades [2].

SLNs are new generation solid nanometer-scale delivery systems in which the oil phase has been replaced by a solid lipid. They are mostly made of triglycerides, partial glycerides, fatty acids, steroids and waxes that are biocompatible, biodegradable, with low toxicity [3]. SLNs have unique properties such as small particle size, large surface area, and phase interaction at interfaces, and are appealing for their ability to improve delivery materials [4]. SLNs have been proposed for different administration routes, such as oral, topical, ophthalmic, inhalation, and nasal administration as well as parenteral injection [5-7]. Studies have shown that encapsulating drugs in SLNs not only ensures controlled release, but also protects the incorporated drug from enzymatic degradation, resulting in improved absorption. SLNs improve drug bioavailability by extending retention and exposure durations at the targeted sites [8-10]. It is made up of lipids that are solid at both body and room temperature. It can improve drug solubility, stability, release, and drug load. Because NAF is a highly lipophilic drug, it is an excellent candidate for developing lipid-based nanoparticle systems [2].

Compritol 888 ATO (CMP) is an FDA-approved lipid composed of various esters of behenic acid and glycerol. CMP has a long behenic acid chain length, which can facilitate in drug intermolecular entrapment through inter-chain intercalation and hydrophobic interactions. Lipidic excipients used in the preparation of SLNs delivered through the oral route are susceptible to lipolysis by the intestinal lumen lipase/colipase enzyme system. This causes the drug to be released prematurely in the GIT, exposing it to the same problems as conventional drug delivery systems. Lipidic excipients with longer chain lengths, such as CMP, are more resistant than lipidic excipients with shorter chain lengths. Furthermore, CMP has been investigated as a matrix-forming agent for controlling drug release [11]. CMP is an excellent choice for developing NAF-loaded SLNs to improve oral bioavailability due to these properties.

To improve the oral absorption of NAF, researchers have tried various strategies such as solid dispersion [12-14], buccal film [15], tablets [16,17], and so on. As a result, the goal of this study is to improve the bioavailability of NAF by formulating it as SLN. Compritol 888 ATO (glyceryl behenate) was used as a lipid carrier and Poloxamer 188 as a stabilizer to make NAF-loaded SLN through the solvent emulsification/evaporation method. Surfactant concentration and homogenization speed were taken as optimizing parameters, and the prepared SLN was evaluated by particle size, zeta potential, entrapment efficiency (EE), surface morphology, and *in vitro* release behavior.

METHODS

Materials

NAF was provided as a gift sample by Intas Pharmaceuticals Pvt. Ltd., Gujarat, India. Compritol 888 ATO and Poloxamer 188 were obtained from Gattefosse (Saint-Priest, Cedex, France) and BASF Corporation, India, respectively. Water used in all experiments was distilled. All other chemicals and solvents were of analytical grade.

Preparation of SLN of NAF

Solvent emulsification/evaporation was used to prepare SLN of NAF. In brief, 50 mg of drug was dissolved in 1 mL chloroform, and different concentrations of lipid were dissolved in 2 mL chloroform separately; drug and lipid solution were mixed together. To remove the traces of organic solvent, the organic solvent mixture was completely dissolved and evaporated at 70°C using a rotary evaporator (Perfit, India). The drug-embedded lipid layer was then poured into 10 mL of aqueous solution containing surfactant at 70°C using a hot plate and homogenized for 10 min at various homogenization speeds using a high-speed homogenizer. After that, the suspension was allowed to cool at room temperature. SLN-NAF was lyophilized for 36 h at 60°C temperature and pressure <15 Pascal using a lyophilizer (SP Scientific Instruments, India).

The various NAF -loaded SLN formulations are prepared using the above-described method and have different compositions, as shown in Table 1. The composition was then optimized based on encapsulation efficiency, as described below.

Characterization of SLN of NAF

Visual appearance

Depending on the composition and particle size, SLN can range from translucent to milky.

Determination of EE and drug loading

An appropriate amount of dispersion was transferred in a centrifuge tube to determine the EE and drug loading of NAF in SLN s. The dispersion was centrifuged (Remi Scientific Instruments, Mumbai) for 15 min at 15000 rpm [18]. The supernatant was collected after centrifugation, and the percentage drug entrapment amount of free NAF was determined spectrophotometrically (λ-max=232 nm) [19]. The following equation was used to calculate the EE and drug loading:

$$EE\% = \frac{W_{(Added\ drug)} - W_{(Free\ drug)}}{W_{(Added\ drug)}} \times 100 \quad (1)$$

$$DL\% = \frac{W_{(Added\ drug)} - W_{(Free\ drug)}}{W_{(Total\ drug)}} \times 100 \quad (2)$$

Where, W (added drug) is the amount of drug added during the preparation of SLN, W (free drug) is the amount of free drug measured in the lower chamber of the centrifugal tube after centrifugation, and W (total drug) is the amount of both drug and excipients in the whole formulation.

Determination of drug content

By dissolving an accurately weighed 50 mg formulation in 10 mL methanol, the drug content of SLN can be determined. After dilution, absorbance can be measured using a UV- Spectrophotometer (Shimadzu, Japan) (λ-max=232 nm) [20].

Particle size and zeta potential analysis

The particle size diameter and zeta potential of the prepared SLNs were determined at room temperature using a Zeta Potential/Particle Sizer analyzer (Malvern). The sample (1 mL) was diluted with double distilled water and assesses for the different parameters [10,21].

Morphology studies

The morphological analysis of optimized formulation was conducted using transmission electron microscopy at 100 kV. Few drops of the sample were placed on a 300- mesh carbon-coated copper grid and dried at room temperature [22].

Fourier transform infrared spectroscopy (FTIR)

For structure analysis, FT-IR spectroscopy was used for the determination of drug interaction with excipients, an FT-IR spectrum (Bruker Alpha, Berlin, Germany) of NAF, drug plus excipients mixture, and formulation was recorded [23].

The spectrum was captured in the 4000–400 cm^{-1} wavelength range. An IR spectrum was recorded after a sample of NAF, drug plus excipients mixture, and formulation were filled into the die cavity of the sample holder.

In vitro drug release study

In vitro release study of SLN was determined in this work using dialysis method. In brief, SLN (1.0 mL) or drug solution with the equivalent drug concentration was enclosed in a dialysis bag and then placed in 100 mL of phosphate buffer saline pH 6.8 used as release media [24]. The entire system was kept at 37°C±0.5°C with continuous magnetic stirring. At selected time intervals (0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 h), 5 mL of solution was withdrawn from the release medium and replenished with the same volume of release medium. The collected samples were appropriately diluted before being analyzed with a UV-visible spectrophotometer at 232 nm. The amount of drug released was then measured by the cumulative percentage release. The kinetic equations used to determine the release kinetics were zero order (cumulative% release vs. time), first order (log% drug remaining vs. time), Higuchi's model (cumulative% drug release vs. square root of time), and Korsmeyer-Peppas model (log drug release vs. log time). The linear curve obtained by regression analysis of the plots was used to calculate the values of r^2 and k.

Table 1: Composition of NAF-loaded formulation using different types of lipids, homogenization speed, and different concentration of lipid and surfactant

Formulation batch	Naftopidil (mg)	Stearic acid (mg)	Compritol 888 (mg)	Precirol (mg)	Poloxamer 188 (mg)	Chloroform (mL)	Homogenization speed (rpm)
F1	50	10	-	-	100	3	6000
F2	50	-	10	-	100	3	6000
F3	50	-	-	10	100	3	6000
F4	50	-	10	-	150	3	6000
F5	50	-	10	-	200	3	6000
F6	50	-	5	-	150	3	6000
F7	50	-	15	-	150	3	8000
F8	50	-	20	-	150	3	6000
F9	50	-	15	-	150	3	6000
F10	50	-	15	-	150	3	10000

Stability studies

The stability studies of the best SLN formulation were performed by being stored at 4°C and 27±2°C/65%±5% relative humidity for 90 days and were examined at regular time intervals for changes in the EE of SLN [25].

RESULTS AND DISCUSSION

Preparation of SLN-NAF

The solvent emulsification/evaporation method for preparing NAF SLN was found to be a reliable, simple, and reproducible method. The prepared SLN was found to be free of foreign particles and homogeneous in appearance.

EE, drug loading and drug content

EE, drug loading, and drug content are an important parameter for characterizing SLN. Several factors were varied to achieve optimal encapsulation and drug loading, including the type and concentration of the lipids, surfactant concentration, and homogenization speed, as shown in (Table 1). All prepared formulations' EE, drug loading, and drug content are shown in (Table 2 and Fig. 1). The EE, drug loading, and

Table 2: Percentage entrapment efficiency, drug loading and drug content of different SLNs formulation containing Naftopidil

S. No.	Formulation code	Entrapment efficiency (%) (mean±SD)*	Drug loading (%) (mean±SD)*	Drug content (%) (mean±SD)*
1	F1	56.459±0.504	17.643±0.157	77.274±0.347
2	F2	71.690±0.417	22.403±0.130	80.748±0.306
3	F3	62.338±0.306	19.480±0.095	85.758±0.417
4	F4	85.886±0.030	20.449±0.007	79.211±0.504
5	F5	75.364±0.504	14.493±0.096	93.039±0.306
6	F6	79.847±0.040	19.475±0.009	87.428±0.504
7	F7	88.217±0.030	20.515±0.007	97.782±0.306
8	F8	84.243±0.050	19.146±0.011	89.298±0.400
9	F9	86.861±0.040	20.200±0.009	95.177±0.504
10	F10	88.818±0.041	20.655±0.009	98.784±0.809

*Each value is average of three independent determinations (n=3)

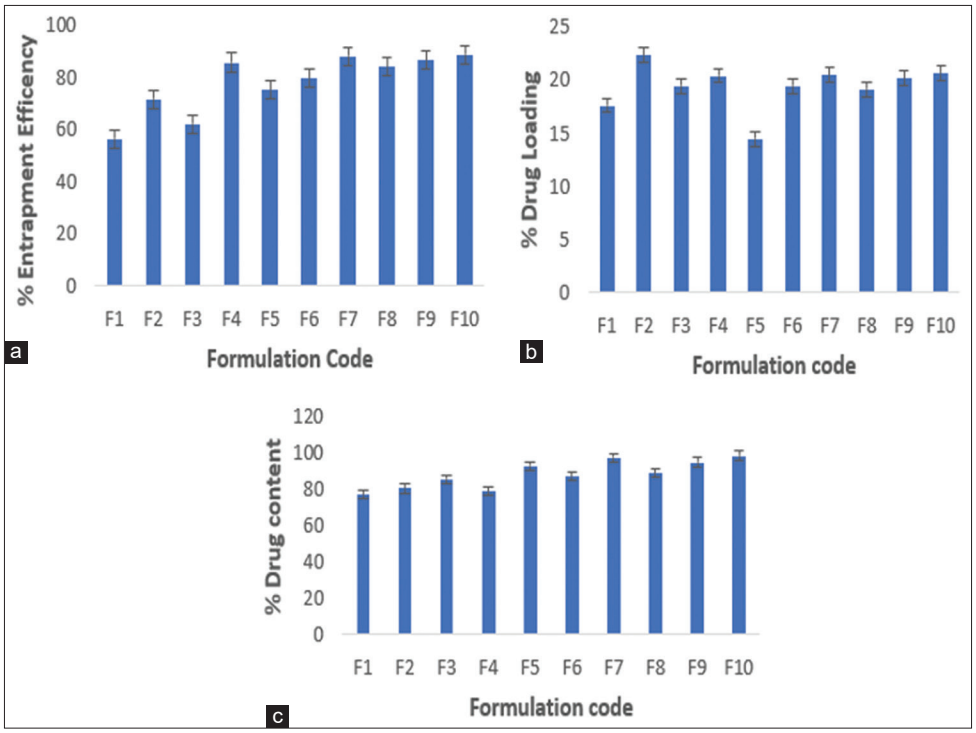

Fig. 1: Percentage (a) Entrapment efficiency, (b) Drug loading, and (c) Drug content of SLN formulations containing Naftopidil

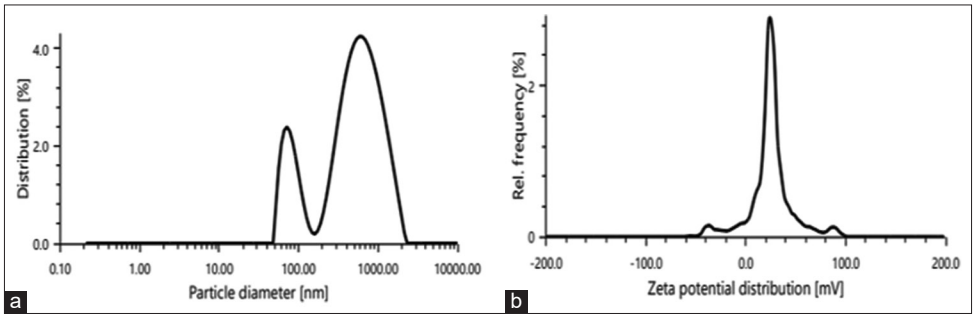

Fig. 2: (a) Particle size peak and (b) Zeta potential graph of SLN formulation (F10)

drug content of SLN were found to be 56.45–88.81%, 17.64–20.65%, and 77.274–98.784%, respectively.

Influence of different type of lipids and its concentration on EE

The effect of different types of lipids on EE was examined using three different lipids: stearic acid (F1), compritol 888 ATO in (F2), and precirol in (F3). It was observed that compritol 888 ATO (F2) has a higher EE (71.69%) than other lipids. Furthermore, the effect of lipid concentrations on %EE was investigated using four different concentrations of compritol 888 ATO, namely, 5 mg (F6), 10 mg (F4), 15 mg (F7), and 20 mg (F8). It was observed that concentration 15 mg (F7) has a higher EE (88.21%) than other lipid concentrations. Table 1 shows the different lipid concentrations, and Table 2 shows the (%EE).

Influence of surfactant concentration and homogenization speed on EE

The effect of surfactant concentrations on EE was examined using three different surfactant concentrations: 100 mg (F2), 150 mg (F4), and 200 mg (F5). It was observed that concentration 150 mg (F4) has a higher EE (85.88%) than other surfactant concentrations (Tables 1 and 2). Furthermore, the effect of homogenization speed on EE was investigated using three different homogenization speeds: 6000 rpm (F9), 8000 rpm (F7), and 10,000 rpm (F7) (F10). According to the findings, homogenization speed has a significant impact on EE. EE was found to increase with surfactant concentration (150 mg) was increased surface coverage of nanoparticles and thus prevents drug leaching from lipid matrix in all three batches of SLN formulations of different homogenization speeds (6000–10,000 rpm).

Based on the EE results, batch F10 was chosen for further research because it had a higher EE, 88.818±0.041%.

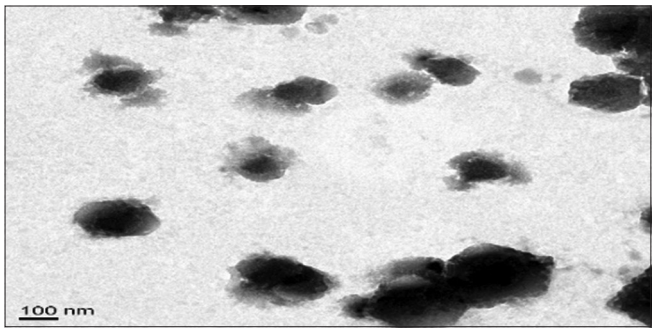

Fig. 3: TEM image of optimized SLN

Particle size distribution and zeta potential analysis

The PSD of the freshly prepared sample SLN-NAF confirmed the production of nanoparticles with unimodal and sharp distribution and a median particle size of 270.2 nm, as shown in (Fig. 2). The zeta potential (ZP) of +21.7 mV refers to nanoparticle surface charge and indicates the degree of repulsion between similarly charged nanoparticles. Because this repulsion prevents aggregation, ZP is considered as a predictor of long-term physical stability. The stabilization of SLN in the colloidal system, given by poloxamer 188, is mainly driven by steric action. ZP greater than (±) 20 mV is considered sufficient when the mechanism of stabilization is a steric and electrostatic combination. Therefore, the PSD of the produced SLN was expected to be stable over time.

Surface morphology

TEM images were used to demonstrate the morphology of the SLNs, as shown in Fig. 3. These TEM images revealed the colloidal sizes and spherical structure of all dispersions. Furthermore, TEM micrographs

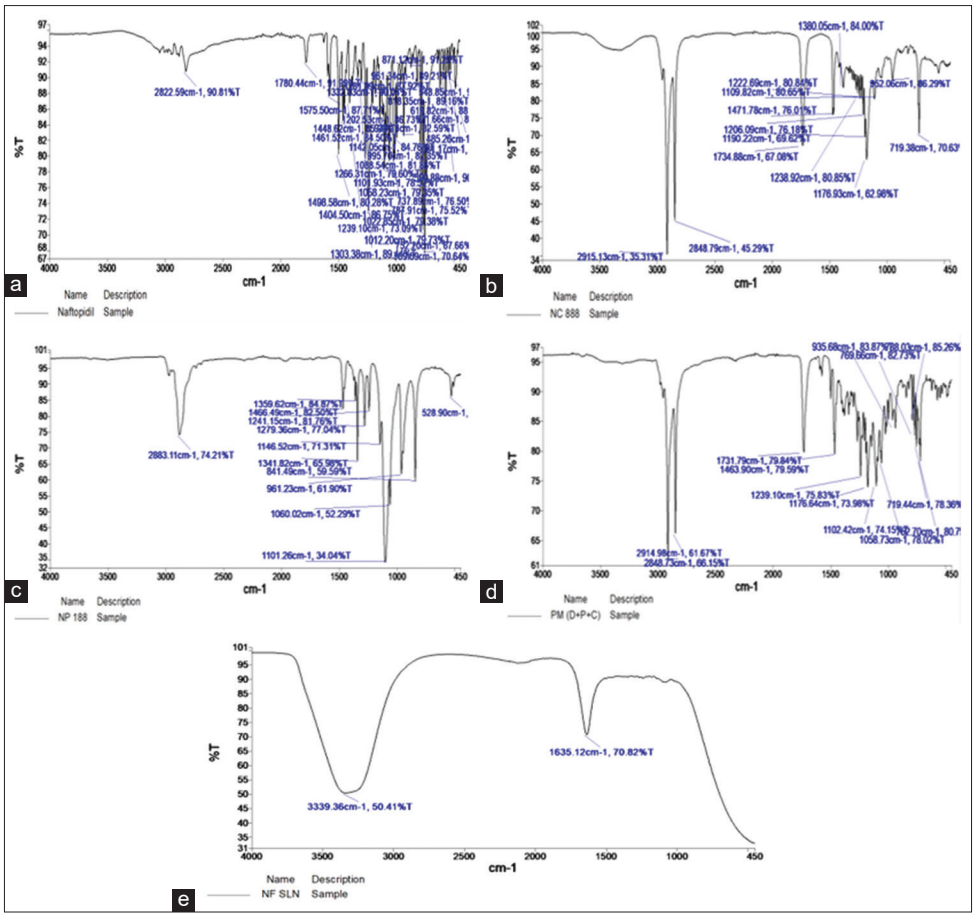

Fig. 4: FTIR spectra of (a) Pure drug, (b) Compritol 888, (c) Poloxamer 188, (d) Physical mixture (A+B+C), and (E) SLN-NAF formulation (F10)

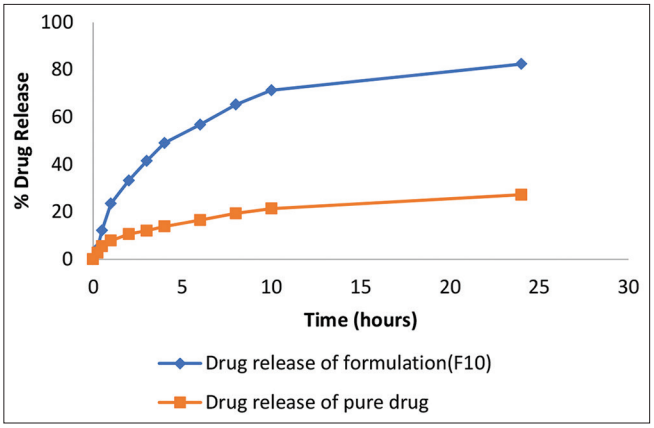

Fig. 5: *In vitro* drug release of F10 formulation and pure drug

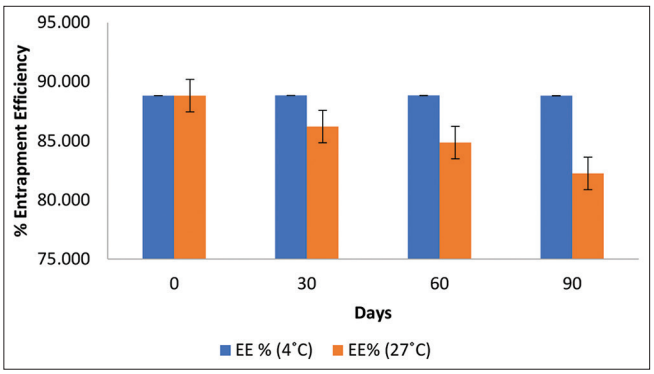

Fig. 6: Effect of storage temperature (at 4°C and 27°C) on Entrapment Efficiency of F10

Table 3: Effect of storage temperature (at 4°C and 27°C) on Entrapment Efficiency of F10

Sr. No.	Days	Entrapment efficiency (%) (at 4˚C) (mean±SD) *	Entrapment efficiency (%) (at 27˚C) (mean±SD) *
1	0	88.818±0.042	88.818±0.042
2	30	88.839±0.031	86.213±0.031
3	60	88.832±0.046	84.857±0.040
4	90	88.812±0.012	82.239±0.050

*Each value is average of three independent determinations (n=3)

confirm the presence of a NAF coat on the surface of SLNs, where a grey shell was observed.

FTIR

An FT-IR analysis was performed to evaluate the chemical interaction between NAF, excipients, physical mixture, and formulation (Fig. 4). The main peaks of NAF at 2822.59 cm^{-1} (CHstretching), 1575.5 cm^{-1} (C=Cstretching), 1266.31 and 1239.10 cm^{-1} (CN and CO stretching), 1332.83 cm^{-1} (CH bending), 1780.44 cm^{-1} (C=O stretching), and 1181.09 cm^{-1} (C–O–C stretching), were all observed in the spectra of NAF. As well as excipients like Compritol 888 ATO show at 2915.13 cm^{-1} (C–H stretching band of long fatty acid chain), 1734.88 cm^{-1} (Carbonyl stretching band in the fatty acid ester), and 1342 cm^{-1} (C–H bending); and Poloxamer 188 show at 2883.11 cm^{-1} (C–H stretching band of long fatty acid chain), 1341.82 cm^{-1} (O–H bending), and 1101.26 cm^{-1} (C-O stretching). Some of these diagnostic bands of physical mixture like 2914.98 and 2848.73 cm^{-1} (CHstretching), 1239.10 cm^{-1} (CO stretching), 1176.64 cm^{-1} (C–O–C stretching), 1731.79 and 1102.42 cm^{-1} (C=O stretching); 1635.12 cm^{-1} (C=O stretching) of formulation F10 were found with smaller intensity due to less concentration of NAF in the formulation compared to pure NAF.

The presence of NAF in the formulation induced changes in the spectrum profile of SLN with additional peak at 3339.36 cm^{-1}, attributed to primary amines and alcohols, respectively, of Compritol 888 and NAF; the stretch of C=O at 1635.12 cm^{-1}. Peak changes are an indication of interactions in the system, again suggesting that NAF was indeed loaded within lipid matrices of SLN.

***In vitro* drug release study**

Fig. 5 depicts the release profiles of the best formulation when compared to pure drug solution. The pure drug solution, 5.523% NAF, was released within 30 min, followed by 27.508% within 24 h. NAF-SLNs revealed a biphasic release pattern. Significant release was observed in 2 h, followed by sustained release for up to 24 h. The initial rapid release was observed due to the faster dissolution of NAF adsorbed on the surface of the SLNs. The NAF entrapped in the inner portion of the lipid matrix of SLNs, which releases NAF slowly by diffusion, resulted in a sustained release of NAF after 2 h. The lipid matrix behavior was responsible for the prolonged release of NAF-SLNs. It could be due to the drug's resistance to desorption and diffusion. Within 24 h of the study, the release of NAF-SLNs increased significantly, reaching a maximum of 4.547–82.418% in pH 6.8 buffer medium. NAF is a drug that is insoluble in water, which limits its dissolution and bioavailability. NPs delivery systems have been shown to improve the solubility and dissolution of poorly soluble drugs. To investigate the mechanism, the release data were fitted into various kinetics models, with the Korsmeyer-Peppas model yielding the highest correlation coefficient (R^2) (R^2=0.916), implying that the mechanism of NAF release from NAF-SLNs was in controlled manner.

Stability studies

The stability study of batch F10 was carried out at stored at 4°C and 27°±2°C/65%±5% relative humidity for 90 days. After 90 days, there was a slight change in the EE of SLN at 27°C as compared to 4°C. As shown in Table 3 and Fig. 6, this was due to increased drug exposure from lipid matrices at higher temperatures.

The results confirmed that the SLN formulation had long-term stability; this could be attributed to higher drug solubility in the lipid matrix due to poloxamer 188, and because of its nonionic nature, it decreases electrostatic repulsions between the particles, thus stabilizing the nanoparticles by forming a coat around their surfaces.

CONCLUSION

The SLNs of NAF were prepared by the solvent emulsification/evaporation method. This was a useful method for the successful incorporation of the poor water-soluble drug NAF and the production of NAF-SLN with a minimum particle size and maximum EE%. There were no significant changes in the physical stability of the optimized NAF-SLN after 3 months of storage at 4°C. As a result, bioavailability may be improved. As a result, we can conclude that SLNs of NAF provide controlled drug release, and these systems are used as drug carriers for lipophilic drugs, to improve the bioavailability of poorly water-soluble drugs through nanoparticles, and as a drug delivery system.

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AUTHORS CONTRIBUTION

Both the authors contributed to design and implementation of the research, to analysis of the results, and to writing of the manuscript.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest to be disclosed.

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