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Original Article

FORMULATION AND EVALUATION OF NANOPARTICLE DRUG DELIVERY SYSTEM FOR TREATMENT OF HYPERTENSION

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ABSTRACT

Objective: The aim of the current research is to formulate and evaluate Trandolapril loaded solid lipid nanoparticles (SLNs) for the management of high blood pressure.

Methods: SLNs were formulated using Glyceryl monostearate and poloxamer 188 by hot homogenisation and ultrasonication method. Different concentrations of lipid and surfactant were used for the preparation adopting 3^2 full factorial design. The prepared formulations were initially evaluated for particle size, PDI, zeta potential and entrapment efficiency to obtain the optimised formulation.

Results: The optimised formulation TF 6 reported the particle size of 212.6±5.39 nm and entrapment efficiency of 91.02±0.57%; this was further characterised for FT-IR, DSC and scanning electron microscopy. The *in vitro* release of drug for the prepared formulations was performed for 24 h and the optimised formulation showed better-controlled drug release compared to other formulations.

Conclusion: The pure Trandolapril solution was collated with the optimised formulation TF 6 and the result concluded that the formulation showed controlled drug release compared to pure drug. This study proves that Trandolapril SLNs can be prepared for increasing the release of drug for prolonged period.

Keywords: Trandolapril, Solid lipid nanoparticles, Hypertension, Hot homogenisation and ultrasonication

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INTRODUCTION

Hypertension is a chronic disorder and is also a risk factor for many other diseases like cardiovascular disease, ischemic heart disease, stroke etc., and is affected globally [1]. High blood pressure is one of the most serious and preventable risk to the health of individual as well as to the society [2]. The most convenient method of administration of antihypertensive drugs is oral delivery. Poor oral bioavailability prevents several medications from achieving the minimal effective concentration necessary for therapeutic action [3]. Many of the antihypertensives are poorly water soluble, which leads to reduction in oral bioavailability.

Trandolapril is a nonsulfhydryl ACE inhibitor used to treat heart failure and elevated blood pressure. It belongs to BCS class II classification of drugs having a poor water solubility and oral bioavailability of around 4%-9% and a half-life of about 6 h [4, 5].

An increase in a drug's water solubility can be achieved in a number of ways. The most recent technologies to improve a medicinal molecule's solubility is nanocarriers [6]. Few significant nanocarriers include lipid-based nanocarriers, polymeric nanoparticles, dendrimers, carbon nanotubes, liposomes, polymeric micelles, quantum dots and magnetic nanoparticles [7].

Drug delivery methods using lipids may incorporate different type of oils, surfactants, and co-solvents. They are one of the most often used methods for overcoming absorption barriers and improving the bioavailability of poorly water-soluble medicines. Solid lipid nanoparticles have been used for regulated medication delivery and selective targeting since they are biologically compatible and biodegradable molecules. The lipophilic drugs are dissolved in lipid which safeguard the drug from enzymatic degradation and promote the drug transport through the lymphatic route, hence avoids the hepatic first-pass metabolism.

The lipid matrix that makes up these colloidal carriers holds to be solid at body temperature as well as ambient temperature and also has an average diameter of particles ranging between 50 nm-1000 nm. The cells of the Reticulo Endothelial System (RES) do not readily accept up these smaller particles, allowing the particles to pass through liver and spleen filtration [8]. They are having the ability to carry both hydrophilic and lipophilic drugs. Major advantages of formulating oral SLNs are due to the particles size, it passes first pass metabolism when it is taken orally. Lowers the risk of acute and chronic toxicity. It is more stable compared to liposomes. Improved drug stability. This makes SLNs a better colloidal carrier system compared to other colloidal carrier system [9]. Smaller particle size promotes higher surface area, thereby leading to higher drug release. Homogeneous dispersion of the drug in the lipid matrix causes slow release of the drug [10].

Therefore, this study is focused on designing using full factorial design and optimizing the best formulation for the trandolapril loaded solid lipid nanoparticle. As the drug is lipophilic in nature only reduction in particle size does not increase the aqueous solubility so it is incorporated in solid lipid nanoparticle. *In vitro* dissolution study is performed to obtain the result of increase in aqueous solubility of the drug. The novelty of the present work lies in formulating and evaluating the Trandolapril in a colloidal system where the solubility is enhanced with the controlled drug release behaviour.

MATERIALS AND METHODS

Materials

Trandolapril was acquired from PVR Life Sciences Hyderabad. Poloxamer 188 was procured from Yarrow chemicals. Glyceryl monostearate was provided by KLE College of Pharmacy Bengaluru. Dialysis membrane was purchased from Hi-Media pharmaceuticals. Other compounds used were in analytical range.

Methods

Formulation optimization

Trandolapril loaded SLNs were statistically optimized by using three factors two levels full factorial design. The optimization was performed using Minitab®21 software using the independent variables lipids as X_1 (3%-4% w/v), poloxamer 188 as X_2 (1%-2% w/v). Particle size Y_1 and entrapment efficiency Y_2 were found to be

affected by independent factors X_1 and X_2. This design depicted 9 experimental runs. Based on smaller particle size and greater entrapment efficiency, the optimal formulation was selected. Late the statistical analysis was evaluated to examine the effect of used variables (X_1, X_2) and factors (Y_1, Y_2) [11, 12].

Formulation of SLNs

Formulation of Trandolapril loaded solid lipid nanoparticles was prepared by hot homogenisation and ultrasonication method. Glyceryl monostearate (GMS) was dissolved in the solvent mixture of chloroform and methanol of ratio 1:1. to this solvent mixture the drug was added and completely dissolved. This solution was maintained at a temperature that is 5 °C over the lipid melting point, this is considered as oil phase. To obtain the aqueous phase, poloxamer 188 was added to distilled water and completely dissolved. The temperatures of oil phase and aqueous phase are kept constant. Both the oil phase and aqueous phase were mixed using magnetic stirrer at 1200 rpm keeping temperature as constant. This solution was homogenised at 9000 rpm for 10 min using IKA ® T18 ultra turrax homogeniser and the solution was sonicated using Labman™ probe sonicator for 15 min and the resultant SLN dispersion was lyophilised using mannitol 2% as cryoprotectant to yield a dry powder of Trandolapril loaded solid lipid nanoparticles [13, 14]. The prepared formulations were further characterized.

Table 1: 3^2 factorial design formulation table of trandolapril loaded SLNs

Formulation code	Independent variables	
	X_1 (GMS)	X_2 (Poloxamer 188)
TF1	3%	1%
TF2	3%	1.5%
TF3	3%	2%
TF4	4%	1%
TF5	4%	1.5%
TF6	4%	2%
TF7	5%	1%
TF8	5%	1.5%
TF9	5%	2%

Characterizations

Measurement of particle size (ps), pdi and zeta potential (zp)

The prepared formulations were evaluated for PS, polydispersity index and ZP, the mean of all these parameters is reported further. The equipment used for the nanoscale analysis was Malvern zetasizer NS [15].

Measurement of entrapment efficiency

Entrapment efficiency was evaluated by the method named cold centrifugation using Eltek® refrigerated micro centrifuge. The SLN dispersion containing 2 mg equivalent weight was used and centrifugation performed for 20 min at 10000 rpm. After centrifugation the supernatant liquid was observed. This liquid was pipetted followed by dilution with phosphate buffer pH 6.8 upto 10 ml. The absorbance of the sample was captured using SHIMADZU UV spectrophotometer at the wavelength of 207 nm [16, 17]. This formula was used to determine the entrapment efficiency:

$$\%EE = \frac{Total\ amount\ of\ drug - Unloaded\ SLN}{Total\ amount\ of\ drug} \text{ X } 100$$

Differential scanning calorimetry (DSC)

Thermal attributes of drug and excipients was characterized by DSC to recognize the physical form of the drug, physical mixture and optimized formulation. DSC thermograms of drug and optimized formulation were obtained [18].

Fourier transform infrared spectroscopy (FT-IR)

The interaction between the excipients and the drug was been determined by the FTIR study. The major peaks of drug followed by excipients, mixture of drug and excipients and the optimised formulation was carried out to fig. out the compatibility of the formulation composition. The spectra were obtained by JASCO FT-IR 460 plus spectrophotometer in the spectral range of 4000-400 cm^{-1} [19].

Surface morphology

Scanning electron microscopy was evaluated to study the size range along with morphological attributes of the formulation. To obtain the surface characteristics of the formulation [20].

***In vitro* dissolution estimation**

In vitro dissolution of drug was carried out by the method with Dialysis bag. Dialysis membrane was used for the release study. Dialysis membrane was soaked in distilled water 24 h before the release studies. 2 mg equivalent weight of the trandolapril loaded SLNs was incorporated into the dialysis that is tied at the two ends. 50 ml of phosphate buffer pH 6.8 was added to a beaker and the dialysis membrane was fixed in it, where the solution was stirred using magnetic stirrer at 50 rpm and the temperature was maintained at 37±0.5 °C, at the time intervals of 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h the sample of 1 ml was taken and same volume was added to the beaker to maintain the sync condition. Concentration of drug release from the Trandolapril loaded SLNs was calculated using UV spectrophotometer at 207 nm [21].

RESULTS AND DISCUSSION

Design optimization

Design of the formulation

3^2 factorial design was used for optimizing the formulation of Trandolapril-loaded solid lipid nanoparticles. The concentrations of lipid and surfactant were kept as independent factors (X_1 and X_2). The dependent factors or responses were particle size (Y_1) and entrapment efficiency (Y_2). The formulation was optimized using the result of response parameters.

Table 2: Responses observed in dependent variables by independent variables, All data showed as mean±SD (n=3); where n is the number of observations

Formulation code	Dependent variables	
	Y_1	Y_2
TF1	242.8±6.42 nm	83.18±0.69%
TF2	235.4±7.64 nm	84.86±0.73%
TF3	221.1±4.11 nm	86.47±1.04%
TF4	269.4±8.26 nm	84.27±0.84%
TF5	243.2±3.27 nm	87.91±0.33%
TF6	212.6±5.39 nm	91.02±0.57%
TF7	321.8±4.52 nm	86.97±0.96%
TF8	289.3±6.88 nm	88.72±0.58%
TF9	278.4±5.48 nm	90.83±0.46%

Measurement of PS, PDI and zeta potential

The analysis of particle size, PDI and zeta potential was performed using Malvern equipment. The prepared formulation's particle size was measured, and it proved that they all fell within the range of 200-330 nm with narrow size distribution with PDI of 0.238–0.303 and the zeta potential was found to be in the range of-17.5 to-21.9 mV. With an increase in the lipid content, there was a noticeable rise in particle size.

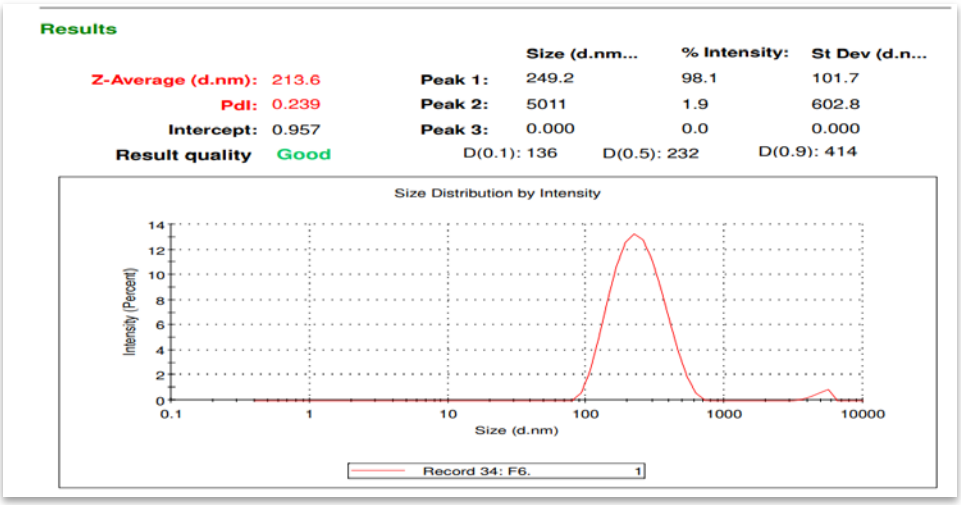

Fig. 1: Particle size of formulation TF6

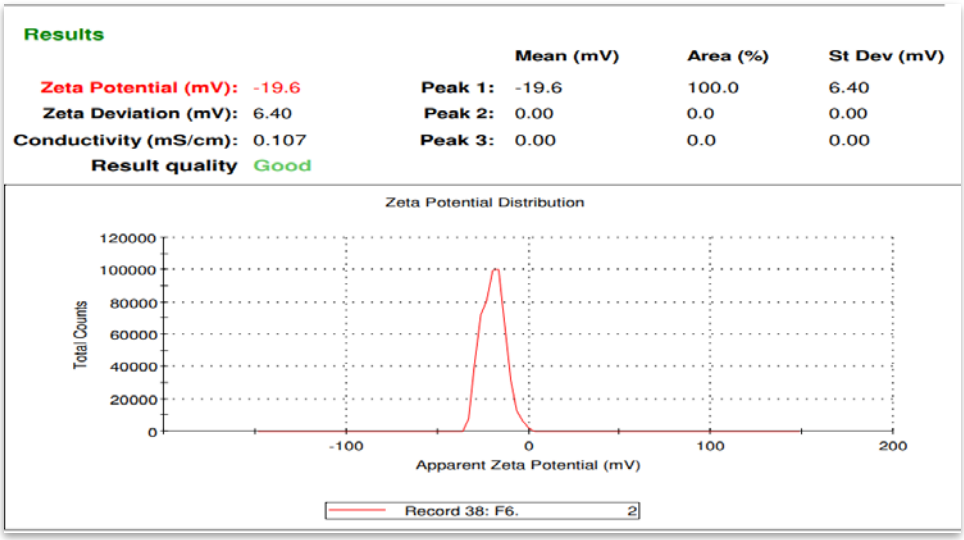

Fig. 4: Zeta potential of formulation TF6

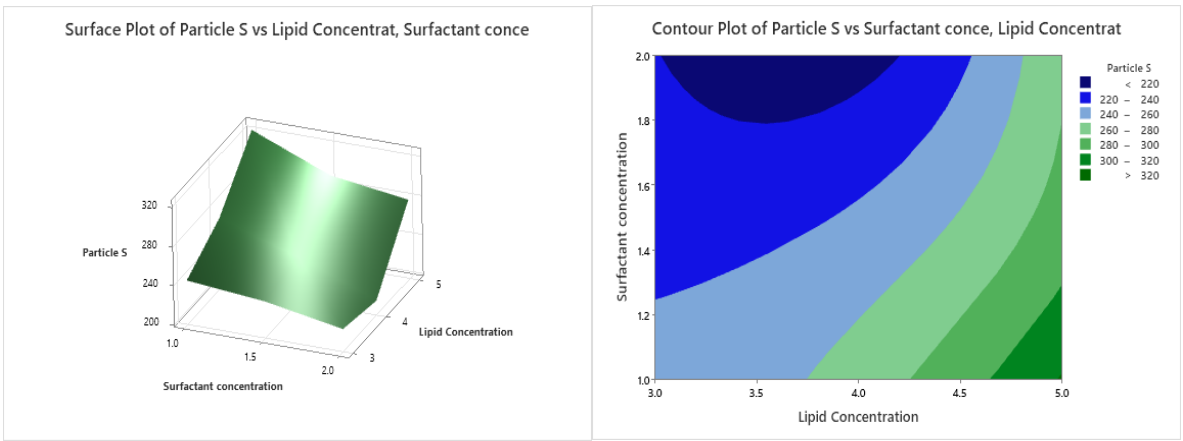

Fig. 3: Response surface plot of particle size v/s lipid concentration, surfactant concentration

Influence of lipid and surfactant concentration on particle size

The effect of lipid concentration was observed in the response particle size (Y_1). It was observed that the rise in concentration of lipid increased the particle size of the particles. As the concentration increased from 3%-5% the particle size gradually increased, the R^2value was found to be 90.49% and p value was found out to be 0.025 which is<0.05 which reports it was statistically significant. The increase in the particle size is maybe due to the aggregation of lipid particles. But with respect to surfactant concentration from 1%-2%, as the concentration increased the particle size was decreased due to the surface tension between the particles which obstruct the particle agglomeration. Response of the dependent variables with independent variables is observed in the surface plot and contour plot [22].

Regression equation for particle size

257.11-24.01 Lipid Concentration_3-15.38 Lipid Concentration_4+39.39 Lipid Concentration_5+20.89 Surfactant concentration_1.0-1.14 Surfactant concentration_1.5-19.74 Surfactant concentration_2.0

Entrapment efficiency (%EE)

For the prepared formulation the entrapment efficiency of the drug was observed between 83-91% as represented in fig. 5. Due to high lipophilicity of Trandolapril, the entrapment efficiency was found to be high. As the entrapment efficiency of the TF6 formulation with 4% lipid concentration and 2% of surfactant concentration observed to be better formulation compared to other formulations. As the concentration of lipid with surfactant increased, entrapment efficiency increased likewise. But at 5% of lipid concentration, all the different concentrations of surfactant found out be lesser than that of TF6 formulation (4% GMS and 2% poloxamer 188). The formulation TF 6 was further carried out for other evaluation parameters.

Influence of lipid concentration and surfactant concentration on EE

The entrapment of the drug in the lipid matrix is increased with the increase in concentration of the lipid. The increased concentration of lipid has the larger capacity to encapsulate the drug inside the lipid matrix. Surfactant concentration also increases the entrapment efficiency. But at the concentration of 5% of lipid the entrapment was decreased compared to 4% lipid concentration that is because the 2% concentration of surfactant for 5% lipid may not be sufficient to produce the surface tension that is required to increase the entrapment efficiency [23]. The R^2 value of model was 94.59% and p value<0.05 was observed, concluding that the responses were statistically significant. The response of entrapment efficiency v/s lipid concentration and surfactant concentration is explained in the given fig. 4 below.

Regression equation for entrapment efficiency

87.137-2.300 Lipid Concentration_3+0.597 Lipid Concentration_4+1.703 Lipid Concentration_5-2.330 Surfactant concentration_1.0+0.027 Surfactant concentration_1.5+2.303 Surfactant concentration_2.0

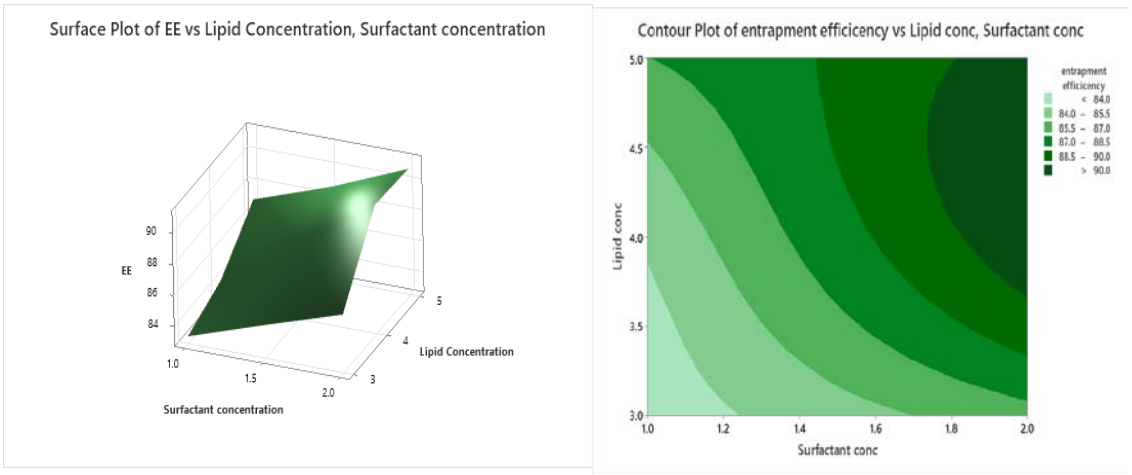

Fig. 4: Response surface plot of entrapment efficiency v/s lipid concentration, surfactant concentration

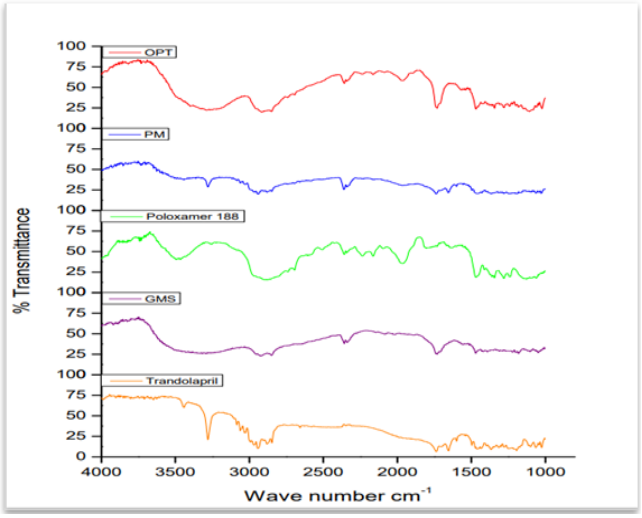

Fig. 5: FT-IR peaks of trandolapril, GMS, poloxamer 188, physical mixture (PM) and optimised formulation (opt)

Fourier transform infrared spectroscopy

The analysis of compatibility and identification was studied using FT-IR spectroscopy, this study showed the peaks of functional groups with respect to Trandolapril at the wavenumber of 3280.32 cm^{-1}, 2943.8 cm^{-1}, 1193.72 cm^{-1} and 1737.55 cm^{-1} for the functional groups NH, CH, C-O-C, and C-O for the optimised formulation. Slight shifts in the peaks and reduction in the intensity of the peaks represented that the Trandolapril was completely entrapped in the lipid matrix. The major functional groups observed for the optimised formulation at the wavenumber 3290.93 cm^{-1}, 2915.84 cm^{-1}, 1107.9 cm^{-1} and 1730.8 cm^{-1} for the functional groups NH, CH, C-O-C, and C-O. There were no new peaks observed in the optimised formulation TF 6; this shows the drug and excipients were compatible with each other as represented in fig. 5.

Differential scanning calorimetry

To analyse the thermal attributes of Trandolapril, physical mixture and optimised formulation DSC was carried out. The endothermic sharp peak for Trandolapril was observed at 130 °C, which was unaffected in the physical mixture. The physical mixture showed 2 peaks. The peak at 58 °C represents the melting point of lipid and the drug peak is also observed. In the formulation, the peak of the drug was disappeared stating that the drug was in amorphous in nature and the drug was uniformly distributed in the lipid matrix, as shown in fig. 6 [24].

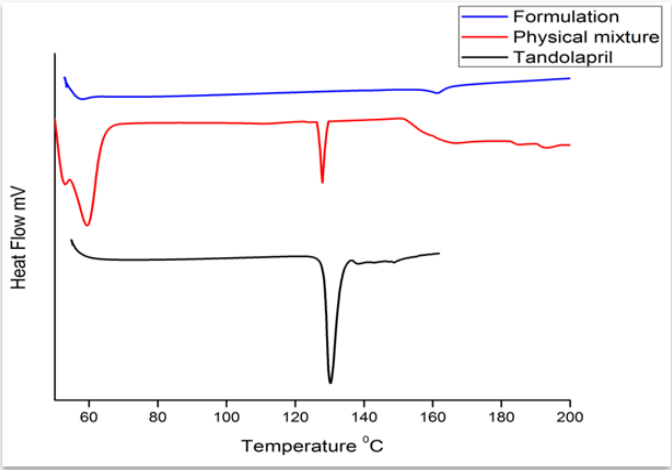

Fig. 6: DSC thermograms of trandolapril, physical mixture and optimised formulation

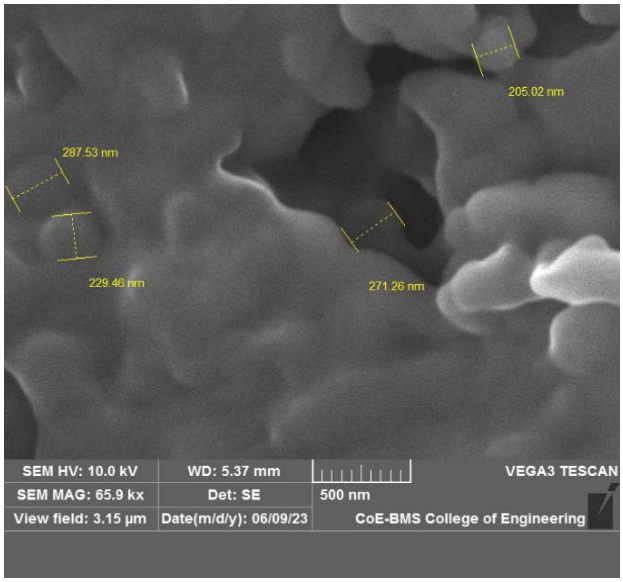

Fig. 7: SEM image of optimised formulation TF6

Surface morphology

SEM results of the optimized formulation showed that the particles are in the spherical shape and having the smooth surface and it also confirmed the particles were under the nano range diameter as shown in fig. 7 [25].

***In vitro* drug dissolution study**

The release profile of drug from the processed 9 formulations was performed using dialysis membrane for 24 h. After calculating the drug release of 9 formulations for 24 h, TF6 was found to be having good slow drug release compared to other formulations. Initially, for 2 h there was a burst release of drug that is because of biphasic release pattern [26]. The formulation TF5 and TF6 are having the highest entrapment showed highest drug release. The formulation TF 6 showed better drug release compared to other formulation because of the smaller particle size and higher entrapment efficiency. As the release of drug from TF6 formulation observed to be controlled in compliance with other formulations, so it was considered as the best formulation, as represented in fig. 8.

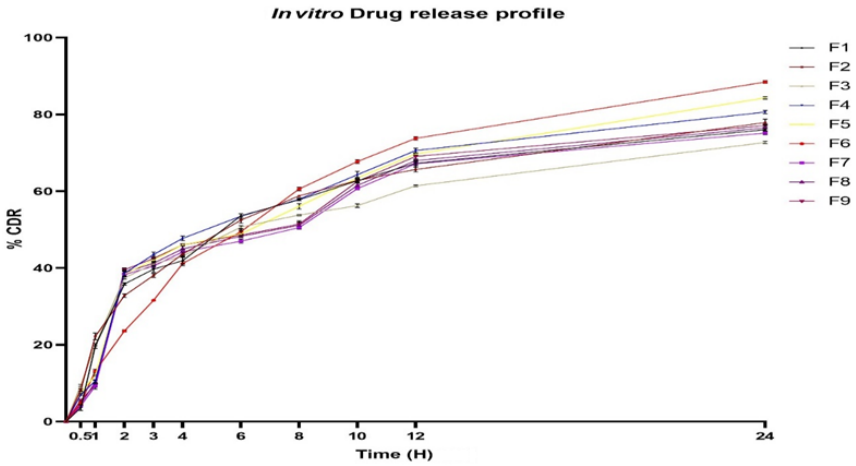

Fig. 8: *In vitro* drug dissolution study of the prepared formulations for 24 h. All data showed as mean±SD (n=3); where n is the number of observations

Release kinetics

The drug release kinetics of the formulation is identified by the kinetic models like zero order, first order, Higuchi release. First-order kinetics is the rate of drug release is directly proportional to the amount of drug remaining in the formulation. The optimised formulation was best fitted in first-order kinetics with the R^2value of 0.9923, which shows that the data where the amount of drug release is dependent on the amount of drug remained in the lipid matrix [27]. The release kinetics for different models is mentioned below in the table 3.

Table 3: Release kinetics of the formulation TF 6 in different kinetic models

Formulation	Kinetic models				
	Zero order	First order	Higuchi	Korsemeyer peppas	Hixon-crowell
TF 6	0.6205	0.9923	0.9650	0.9501	0.9722

Comparative *in vitro* dissolution study

The *in vitro* dissolution of the drug solution was accomplished with the dialysis membrane as performed for the prepared formulation. The drug release was found to be 97.72% for 8 h. The formulation TF 6 which showed the highest drug release at 24th hour was compared with the pure drug solution, as shown in fig. 10 [13].

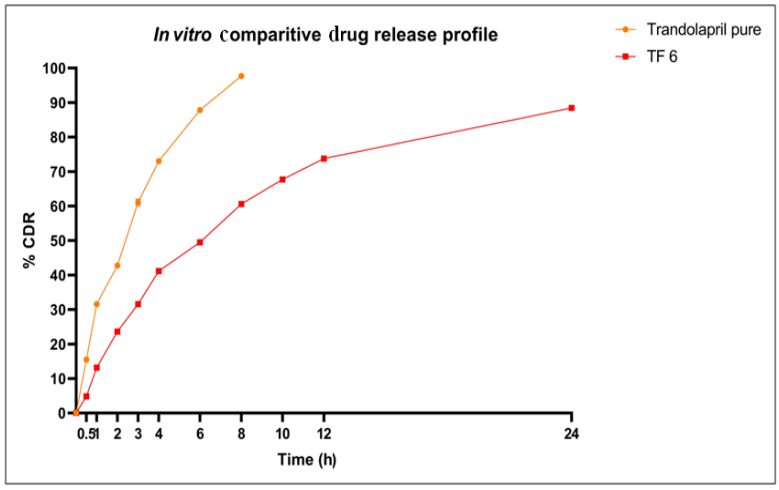

Fig. 10: Comparative drug dissolution studies between the pure drug and formulation TF6. All data showed as mean±SD (n=3); where n is the number of observations

Table 4: Accelerated stability studies according to ICH guidelines. All data showed as mean±SD (n=3), where n is the number of observations

Condition/Response	4±2 °C	25±2 °C/60±5% RH	40±2 °C/75±5%
Particle Size	224.5±12.7 nm	216.3±4.4 nm	229.6±6.7 nm
Zeta Potential	-18.9±1.2 mV	-18.1±1.9 mV	-17.4±1.1 mV
Entrapment Efficiency	88.91±0.4 %	89.16±0.14 %	87.91±0.32 %

Stability study

Stability study for the optimised formulation TF 6 was carried out according to ICH guidelines under three conditions, Accelerated temperature (40±2 °C/75±5%) room temperature (25±2 °C/60±5% RH) and refrigerated temperature (4±2 °C) for 90 d. There was no significant change in the particle size, PDI, zeta potential and entrapment efficiency in the formulation at room and refrigerated temperature, which reported that the formulation was stable for 90 d.

CONCLUSION

The trandolapril-loaded solid lipid nanoparticles formulated were found to be in the nano range as the particle size is reduced to nanometer range the solubility of the drug was also increased. The diameter of the particles was found in between the limits of 200–330 nm, zeta potential of the range-17.5 to-21.9 mV. An excellent entrapment efficiency was observed (83%). One formulation was optimised by considering the factors like PS, entrapment efficiency, PDI and zeta potential, and the optimised formulation was analysed for further studies like DSC, SEM and FT-IR. Thermal analysis of the drug and optimised formulation was analysed, the morphological studies showed that the crystalline drug was transformed into amorphous nature. The components used in the formulation of trandolapril-loaded solid lipid nanoparticles were discovered to be compatible and the formulation showed sustained drug release. The trandolapril-loaded SLNs was compared with the pure drug, which concluded that the optimised formulation showed controlled drug release. Collectively data shown a promising drug delivery system for Trandolapril. Therefore, from the above study, we can conclude that poorly water-soluble drug can be incorporated successfully in the SLNs and the solubility can be increased.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

No conflict of interest

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