RESEARCH ARTICLE

Simvastatin-loaded PLGA nanoparticles for improved oral bioavailability and sustained release: Effect of formulation variables

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The objective of this study was to prepare a nanoparticulate formulation of simvastatin (SV) for improving oral bioavailability and sustaining the drug release while investigating the effect of various formulation parameters on characteristics of nanoparticles. Nanoparticles containing SV were prepared by a modified emulsification solvent evaporation technique using a biodegradable polymer, poly(d,l-lactide-*co*glycolide) (PLGA) as a sustained release carrier. The effect of various formulation parameters such as drug polymer ratios (SV:PLGA, 1:4 to 1:1), organic solvents (methanol/dichloromethane), and surfactants (PVA/polysorbate-80) in a fixed concentration (0.5%, w/v) were studied for particle size, drug loading, and entrapment efficiency. Nanoparticles were characterized by differential scanning calorimetry (DSC) and their shapes were observed by scanning electron microscopy (SEM). An aqueous solubility study indicated that the dissolution rates were remarkably increased for nanoparticles compared with the drug alone. The *in vitro* drug release study of the nanoparticles showed a biphasic release pattern: one initial burst release of 40.56% in the first 4 h which can be helpful to improve the penetration of drug followed by a second slow-release phase (extended release) consistent with a Higuchi diffusion mechanism. The hypolipidemic activity of nanoparticles was determined in comparison with SV in male Wistar rats for changes in total cholesterol (CH) and triglyceride (TG) levels in blood. Nanoparticles showed a significantly better *in vivo* performance than SV in reducing total CH and TG levels which is primarily attributed to the improved solubility and dissolution of nanoparticles. Together, these results indicate that nanoparticulate formulations are ideal carriers for oral administration of SV having great potential to improve the oral bioavailability and sustain the drug release, thereby minimizing the dose-dependent adverse effects and maximizing the patient's compliance.

Key words: *Emulsification solvent evaporation technique, nanoparticles, Poly (d,l-lactide-coglycolide), simvastatin*

INTRODUCTION

The oral delivery route is commonly recognized as the most preferred and convenient route for the administration of drug formulations. In order for a drug to be absorbed into the systemic circulation following oral administration, it must be dissolved in gastrointestinal fluids. For hydrophobic drugs belonging to Class II of the biopharmaceutical classification system, it is this dissolution process which acts as the rate controlling step and, therefore, determines the rate and degree of absorption.[1,2] Approximately, 30% of selling medicines and 40% of new chemical entities entering development programs had too low aqueous solubility or oral bioavailability to bring about satisfactory therapeutic efficacy.[3] Thus, one of the major current challenges facing the pharmaceutical industry involves the development of strategies to improve the aqueous solubility and dissolution rate of drugs.[4-6] Drug solubility can be enhanced using traditional approaches such as designing prodrug,[7] reducing particle size by micronization,[8] co-solubilization by micellization and complexation,[9] solid dispersions,[10] and use of solubilizing excipients.[11] Recently, major research efforts have been focused on the development of nanotechnology-based drug delivery systems including biodegradable polymeric

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nanoparticles,[12] smart polymeric micelles,[13] nanocrystals[14] or nanosuspension,[15] and nanoemulsion[16] to enhance the dissolution rate of poorly soluble drugs and improve oral bioavailability.

Simvastatin (SV) is a cholesterol-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus* and widely used to treat hypercholesterolemia.[17] When given orally, SV (a lactone) is readily hydrolyzed *in vivo* to the corresponding β, δ-dihydroxy acid form, a potent competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA)-the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.[18] However, it has a short half-life and is practically insoluble in water. It is also generally considered that compounds with poor water solubility will show dissolution rate-limited absorption *in vivo* and hence poor absorption, distribution, and site-specific delivery.[19,20] Therefore, it is very important to introduce effective methods to enhance the solubility and dissolution rate of drug, substantially leading to its improved oral bioavailability. Sustained release formulation, nanoparticles, are reported to solve these problems due to the alteration of its tissue distribution, improving the drug efficacy, reducing the drug toxicity, and prolonging the half-lives in blood.[21,22]

MATERIALS AND METHODS

Materials

Simvastatin (SV) was provided as a gift sample from Biocon Ltd, Bangalore, India. Poly(d,l-lactide-*co*glycolide) (PLGA, Av. Mw 15,000 Da) with a lactide/glycolide ratio of 50:50 was kindly provided from Sun Pharma Advanced Research Centre Ltd, Vadodara, India. Polyvinyl alcohol (PVA) and tween-80 were purchased from Qualigens Fine Chemicals, Mumbai and Himedia Lab. Pvt. Ltd, Mumbai, India, respectively. Dichloromethane and methanol were obtained from S.D. Fine Chemicals Ltd, Mumbai, India. All other materials used were of analytical reagent grade.

Drug polymer interaction study

A drug–polymer interaction study was carried out by IR spectroscopy (Thermo Fisher Scientific, Nicolet x 700 FT-IR Spectrometer, Rigas Labs S.A., Greece). The IR spectra of SV and its physical mixture with polymer PLGA were studied over a frequency range of 4000 to 650 cm^{-1}.

Formulation optimization and preparation of nanoparticles

An attempt has been made to optimize the nanoparticle formulation using various formulation parameters like drug polymer ratios (SV:PLGA, 1:4, 1:3, 1:2, 1:1), different organic solvents (methanol/dichloromethane), and different surfactants (PVA/tween-80) in a fixed concentration (0.5%, w/v) to prepare nanoparticles by a modified emulsification solvent evaporation technique.[23] Typically, different ratios of drug and polymer (keeping drug constant at 20 mg and varying polymer concentration; [Table 1] were dissolved in 20 ml of solvent to form a homogeneous solution. This homogeneous solution was added slowly to 120 ml of 0.5% (w/v) aqueous surfactant solution using high pressure homogenizer (REMI, India) to prepare the emulsion. The emulsion formed was stirred on laboratory magnetic stirrer for 2 h at 25°C followed by centrifugation (SIGMA, Germany) for 30 mins at 15,000 × g. After centrifugation, the supernatant was discharged and the pallets obtained were washed by using the same volume of distilled water as of the supernatant and again centrifuged at 15,000 × g for 10 mins. The washing process was repeated three times and the washed nanoparticles were subjected to freeze drying (Christ Alpha 2-4 LD, Freeze Drying Solutions, UK).

Characterization of nanoparticles

Particle size

The mean particle size of the nanoparticles were measured by laser dynamic light scattering (NPA150, Microtrac, USA). The analysis was performed at a measuring angle of 180° and at a temperature of 25°C using samples appropriately diluted with filtered water (0.22 μm filter). For each sample, the mean diameter ± standard deviations of five determinations were calculated applying multimodal analysis. Values reported are the mean diameter ± standard deviation for three replicate samples.

Entrapment efficiency and drug content

Accurately weighed 10 mg of freeze dried nanoparticles and dissolved in 10 ml of methanol and after suitable dilution analyzed by the UV spectrophotometer (Shimadzu, Pharmaspec-1700) at the wavelength of 238 nm. SV contents were determined from standard curve. SV entrapment efficiency (%) and SV contents in nanoparticles (% w/w) were calculated by equations (1) and (2), respectively.

$$\text{Simvastatin content in nanoparticles (\% w/w)} = \frac{\text{Mass of simvastatin in nanoparticles}}{\text{Mass of nanoparticles}} \times 100 \quad (1)$$

$$\text{Simvastatin entrapment efficiency (\%)} = \frac{\text{Mass of simvastatin in nanoparticles}}{\text{Mass of simvastatin added during nanoparticle preparation}} \times 100 \quad (2)$$

Table 1: Characteristics of SV-loaded PLGA nanoparticle formulations

Formulation	Drug: polymer ratio	SV entrapment (%)	SV content (%)	Particle size (nm)
F1	1:4	87.54±0.88	38.55±1.96	288.67±17.75
F2	1:3	81.89±1.41	34.93±1.33	246.57±10.67
F3	1:2	78.03±0.99	31.45±1.40	224.20±16.48
F4	1:1	67.83±1.09	22.75±1.53	209.63±13.58

Values given are mean ± SD (*n*=3)

Surface charge

Nanoparticles were characterized with respect to zeta potential (NPA152-31A Zetatrac, Microtrac, USA) by using dynamic light scattering technology joined with the interaction of random Brownian motion with driven electric field motion of particle suspensions. All analyses were performed on samples appropriately diluted with filtered water (0.22 μm filter). For each sample, the mean diameter ± standard deviations of five determinations were calculated applying multimodal analysis. Values reported are the mean value ± standard deviation for three replicate samples.

Scanning electron microscopy

The morphology of SV and SV-loaded PLGA nanoparticles was observed using a scanning electron microscope (SEM) (Hitachi SU 1500, Japan). The samples were sputter coated with a gold palladium layer using an ion sputter (JFC-1100, JEOL Ltd, Japan) for 5 mins at 20 mA. Observation was performed at an accelerating voltage of 5 kV and at a working distance of 10 mm.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) analyses of samples were carried out on DSC-60 (Shimadzu, Japan). Temperature and enthalpy were calibrated with the standard materials indium (melting point=156.6°C) and zinc (melting point=419.5°C) at a heating rate of 5°C/mins. Sample powders (3-4 mg) were crimped in aluminum pans and heated at a scanning rate of 10°C/mins from 20 to 160°C under a nitrogen purge.

Solubility study

The solubility of SV was determined in triplicate by adding an excess amount of SV and SV-loaded PLGA nanoparticles in 10 ml of phosphate buffer solution (pH 6.8) in screw capped vials. The resulting mixtures were vortexed and then placed in a constant temperature shaking bath maintained at 25°C until equilibrium was reached (for 48 h). Suitable aliquots were centrifuged at 12,000 rpm for 15 mins. The supernatant layer was removed, suitably diluted with methanol and then the concentration of SV was determined by UV-spectrophotometry (Shimadzu, Pharmaspec-1700) at the wavelength of 238 nm.

In vitro drug release studies

The *in vitro* drug release studies were performed by using a dialysis bag diffusion technique.[24] Briefly, SV-loaded PLGA nanoparticles (equivalent to 20 mg of SV) were dispersed in 5 ml of phosphate buffer (pH 6.8) and then put in the dialysis bags (Himedia Laboratories, Mumbai, India) with a molecular weight cut-off of 12,000–14,000 Da. The bags were hermetically sealed and immersed in a beaker containing 100 ml of phosphate buffer of pH 6.8. The contents were stirred continuously with a magnetic stirrer at 50 rpm with temperature adjusted to 37°C. At predetermined time intervals, 1 ml of dispersion was removed and analyzed for drug content by UV-spectrophotometry at 238 nm. The removed volume of dispersion medium was replaced with fresh buffer. Drug release studies for pure drug (SV) were also carried out and compared with the developed nanoparticles.

In vivo studies in rats

The hypolipidemic activity of SV-loaded PLGA nanoparticles was determined in comparison with SV in male Wistar rats (Sri Venkateshwara Enterprises, Bangalore, India), weighing between 150 and 180 g. The rats were housed in a cage and maintained on a 12 h light/dark cycle at room temperature (25°C) and relative humidity of 55±10%. Animals had free access to food and water. The study protocol was approved by the Institutional Animal Ethics Committee of KLEU's College of Pharmacy, Belgaum, India. The animals were divided into three groups of three animals each, namely test group, reference group, and control treatment group. The treatment was given for 14 days. Each group daily received 2 ml of coconut oil orally using gavage feeding needles in the morning throughout 14 days. After the feeding of coconut oil, reference and test groups were administered orally 1 ml of 2% w/v gum acacia aqueous suspensions containing SV and SV-loaded PLGA nanoparticles (equivalent to 10 mg/kg body weight), respectively. Also, the control group received daily 1 ml of 2% w/v gum acacia solution via oral administration. Blood samples were collected under light ether anesthesia by retroorbital puncture; initially, after 7 days and after 14 days. The serum samples were analyzed for total cholesterol (CH), triglycerides (TG) by the *in vitro* diagnostic kit (Erba Mannheim, Germany). Briefly, fixed volumes of sample and standard were mixed with the working reagent separately, followed by incubation at 37°C for 10 mins. The absorbance of the developed color was read at 505 nm for CH and at 546 nm for TG determination.

Statistical analysis

The results were presented as mean ± standard deviation (SD). Statistical analysis of data was performed by using Student's *t*-test. The differences in lipid profiles were statistically analyzed by using one-way analysis of variance (ANOVA) followed by Tukey's test. Probability values of $P<0.05$ were considered to be statistically significant.

RESULTS AND DISCUSSION

Compatibility study

For studying the probable interaction between drug and polymer, the IR spectroscopy was done. The spectra of SV showed the presence of following peaks: 3553 cm^{-1} (O–H stretching vibration), 3011, 2959, and 2872 cm^{-1} (C–H stretching vibration), 1714 cm^{-1} (stretching vibration of ester and lactone carbonyl functional group). Similar peaks were seen in physical mixture of SV and PLGA. Therefore, the study indicates no interaction between drug and polymer.

Formulation optimization and preparation of nanoparticles

The formulation was optimized for further studies, on the basis of good morphology (in terms of particle size and surface properties), high entrapment efficiency, and high drug content. Structurally, SV as a complex chemical structure consists of two specific components, a dihydroxyheptanoic acid unit and partially reduced naphthylene ring imparting lipophilic characters. Thus, SV shows solubility in various organic solvents such as methanol and dichloromethane and very less solubility in water. Initially two organic solvent methanol and dichloromethane were tried for preparation of SV-loaded PLGA nanoparticles. When methanol was used in preparation of nanoparticles, a very low drug entrapment (31.34±1.76%) and drug content (10.43±1.15%) were obtained with a drug polymer ratio 1:2; this was mainly due to more hydrophilic nature of the methanol. On the other hand, with dichloromethane sufficient SV entrapment and SV content were obtained. This was probably due to its hydrophobic nature which enabled SV to retain in the hydrophobic nanoparticle matrix. Hence, dichloromethane was used as an organic phase to prepare nanoparticles using an emulsification solvent evaporation technique. Different SV:PLGA ratios varied from 1:4, 1:3, 1:2, and 1:1 (formulations F1, F2, F3, and F4) were used in the study. The results [Table 1] showed that formulation number F1–F4, an increase in the concentration of PLGA lead to an increase in SV entrapment, SV loading and mean particle size. This was probably caused by the increasing viscosity of organic phase (polymer solution), which increases the diffusional resistance to drug molecules from organic phase to the aqueous phase, thereby entrapping more drug in the polymer nanoparticles.[25] Increasing polymer concentration also increases particle size due to poorer dispersability of the PLGA solution into the aqueous phase. Moreover, an increase in the viscous forces resist the droplet breakdown by opposing the shear stresses in the organic phase and the final size and size distribution of particles depends on the net shear stress available for droplet breakdown.[26] The formulation F3 renders 78.03±0.99% SV entrapment and 31.45±1.40% SV content with 224.20±16.48 nm particle size showing comparatively lower particle size as compared to F2 and F1. Two non-ionic surfactants PVA (formulation A) and tween-80 (formulation B) in fixed concentration (0.5% w/v) were incorporated to further optimize the formulation. Similarly formulation without any surfactant (formulation C) was also prepared for comparing the effect of surfactant on entrapment efficiency, drug content, and particle size. Formulations A and B showed a remarkable increase in entrapment efficiency and drug content and significantly smaller particle size as compared to formulation C [Table 2]. Observations reveal that PVA (0.5%, w/v) is a better surfactant as compared to tween-80 (0.5%, w/v) in terms of entrapment efficiency, drug content, and particle size. Enhanced entrapment efficiency and drug content in formulation A may be attributed to the adequacy of the stabilizer's protection against agglomeration of particles. PVA has a greater tendency to migrate to the surface of PLGA nanoparticles than tween-80. PVA stabilizes the nanoparticles surface more effectively and hence a lower particle size is attained.

Table 2: Effect of surfactants on the characteristics of SV-loaded PLGA nanoparticles prepared by 1:2 drug polymer ratio

Formulation	SV entrapment (%)	SV content (%)	Particle size (nm)	Zeta potential (mV)
A	78.03±0.99	31.45±1.40	224.20±16.48	-24.63±0.76
B	72.21±1.05	27.53±0.90	392.33±20.03	-22.76±0.68
C	27.03±1.09	10.43±1.31	1131.33±31.20	-32.18±0.74

Values given are mean ± SD (*n*=3)

Characteristics of nanoparticles

Particle size

The mean diameter of all the nanoparticles formulations were determined and are listed in Tables 1-2. The formulation F3 prepared by using dichloromethane as an organic solvent, drug polymer ratio 1:2, and PVA as stabilizer, had 224.20±16.48 nm sizes [Figure 1] with optimum entrapment efficiency and considered as the best optimized nanoparticle formulation for further study.

Zeta potential

Zeta potential can greatly influence the stability of nanoparticles. Extremely positive or negative zeta potential values cause larger repulsive forces, whereas repulsion between particles with similar electric charge prevents aggregation of the particles and thus ensures easy redispersion.[27,28] In the case of a combined electrostatic and steric stabilization, a minimum zeta potential of ± 20 mV is desirable.[29] Formulations A and B prepared using two different non-ionic surfactants PVA and tween-80 showed nearly similar zeta potential of –24.63 mV and –22.76 mV respectively which indicates good physical stability of nanoparticles. Whereas formulation C prepared without using any surfactant showed higher zeta potential of –32.18 mV which may be attributed due to the presence of carboxyl groups on the polymeric chain extremities of pure PLGA nanoparticles.

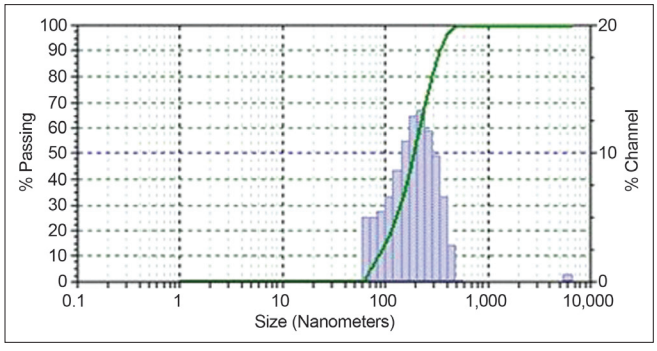

Figure 1: Laser light scattering the particle size histogram of optimized SV-loaded PLGA nanoparticles prepared by using dichloromethane as an organic solvent, drug polymer ratio 1:2, and PVA as a stabilizer

Surface morphology

The SEM images of SV and SV-loaded PLGA nanoparticles are shown in Figure 2. It can be revealed from the Figure 2a that SV consisted of a mixture of large crystals, indicating its crystalline nature. However, the prepared SV-loaded PLGA nanoparticles [Figure 2b] had a nearly spherical shape with a relatively uniform size of about 200 nm in diameter and no drug crystals were present.

Differential scanning calorimetry

The DSC thermograms of SV, PLGA, SV/PLGA, and SV-loaded PLGA nanoparticles are shown in Figure 3. SV was characterized by a single, sharp melting endothermic peak at 141.87°C, which corresponded to its intrinsic melting point indicating its crystalline nature (the endothermic value was 71.14 J/g). PLGA exhibited a glass transition peak at 34.91°C and no melting endothermic peak was observed, because PLGA appears amorphous in nature. The DSC curve of SV/PLGA physical mixture showed a glass transition peak at 33.83°C corresponding to the PLGA, followed by the endothermal melting peak at 134.02°C characteristic of SV. However,

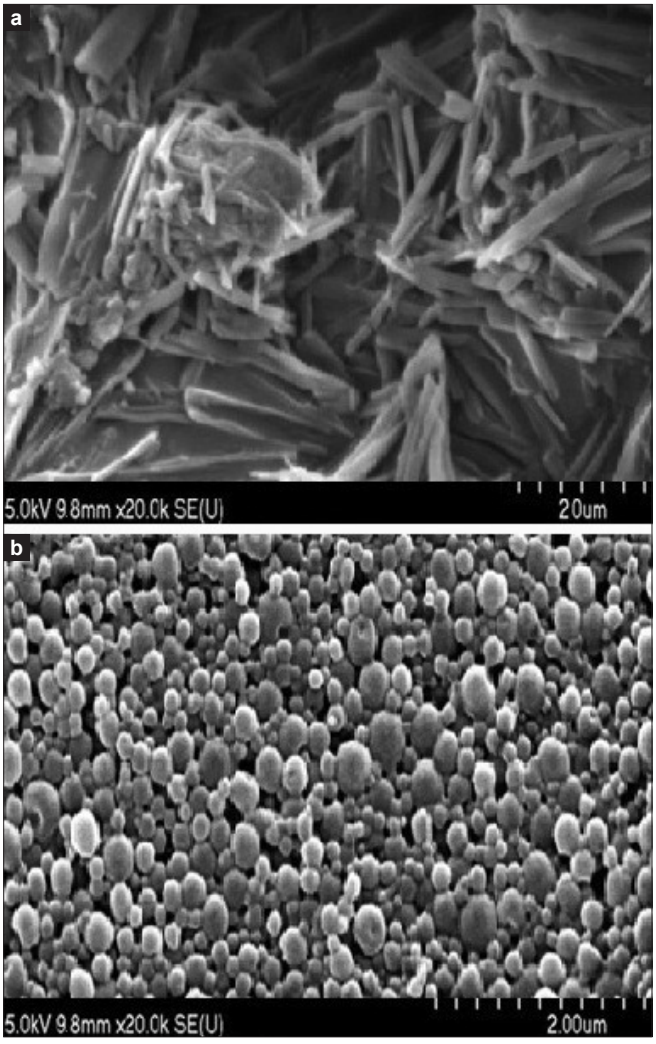

Figure 2: Scanning electron microscopy images of (a) SV and (b) SV-loaded PLGA nanoparticles

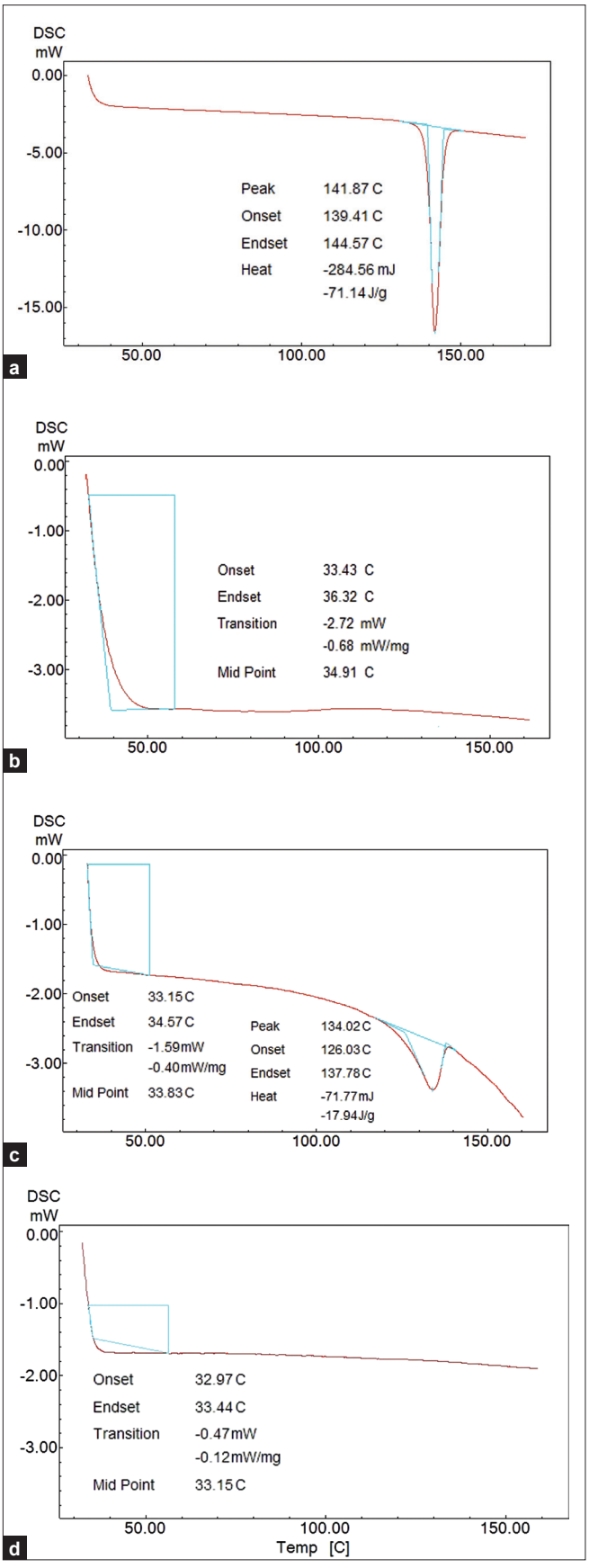

Figure 3: DSC thermogram of (a) SV, (b) PLGA, (c) SV/PLGA physical mixture, and (d) SV-loaded PLGA nanoparticles

no characteristic melting peak of SV was identified in the DSC curve obtained from SV-loaded PLGA nanoparticles suggesting that SV in nanoparticles was molecularly dispersed as an amorphous form.

Solubility study

The solubility testing showed increased solubility for an amorphous state of SV-loaded PLGA nanoparticles compared to SV. The solubility of SV was 15.65±0.44 μg/ml, which agreed well with the literature.[30] SV-loaded nanoparticles resulted in an approximately 4.8-fold increase in solubility after 48 h (74.20±1.1 μg/ml) in comparison with SV.

In vitro drug release studies

The *in vitro* release profiles of SV-loaded PLGA nanoparticles and pure drug are shown in Figure 4. The nanoparticles show a biphasic release pattern: one initial burst release followed by a second slow-release phase (extended release). The release of SV had a first burst release of 40.56% in the first 4 h, which may be probably due to the drug that was adsorbed or close to the surface of the nanoparticles. Moreover, the smaller particle size of nanoparticles is associated with smaller diffusion path, so drug accessible to the solid/dissolution medium interface can diffuse easily to the medium. Thereafter, the release rate decreased that reflects the release of drug entrapped in the polymer and would mainly depend on the drug diffusion and the degradation of the bulk polymer. The initial burst release can be helpful to improve the penetration of drug, whereas sustained release delivers the drug over a prolonged period of time. SV-loaded PLGA nanoparticles released 54.77% of the accumulative amount of SV in 24 h compared with 37.82% in 24 h of the pure drug. In order to determine the release mechanism of SV from PLGA nanoparticles, the *in vitro* release data of the optimized formulation was compared with different kinetic models to select the best fitting model. Good correlation coefficients ($R^2 \geq 0.993$) could be obtained [Figure 4], indicating that after a burst effect, the SV release from PLGA nanoparticles was consistent with the Higuchi diffusion mechanism [Figure 5] which describes the release of the drug from an insoluble matrix as a square root of a time-dependent process.

In vivo studies

Hypolipidemic drugs like SV (HMG-CoA reductase inhibitors) are known to reduce elevated total CH and TG levels in blood. At the same time, they cause elevation of high density lipoprotein levels, which promote the removal of total CH from peripheral cells and facilitate its delivery back to the liver. This pharmacodynamic effect is reported to be dose dependent.[31] Hence, it was used as a basis for the comparison of *in vivo* performance of SV and SV-loaded PLGA nanoparticles. Administration of excess coconut oil, which is a rich source of saturated fatty acids, promotes biosynthesis of CH in liver and leads to hypercholesterolemia.[32] The serum lipid profiles of all the experimental groups at initial, 7 and 14-day time intervals are shown in Table 3 and the corresponding % changes in lipid profiles are plotted in Figures 6 and 7. After 7 days of treatment with excess coconut oil, the control group showed a significant 29% increase in total CH and 75% increase in TG levels in serum. However, the reference group showed approximately 9% decrease in CH and 26% increase in TG. It is interestingly

Table 3: Plasma total CH and TG levels of experimental groups at 7 and 14-day time intervals, respectively

Experimental groups	Time intervals	Total cholesterol (mg/dl)[a]	Triglyceride (mg/dl)[a]
Control group	Initial	57.6±1.08	69.5±1.72
	7 days	74.3±1.36	121.4±2.83
	14 days	95.8±1.52	194.2±4.66
Reference group	Initial	59.6±1.10	72.6±1.85
	7 days	54.4±0.68[b]	91.3±2.39[b]
	14 days	51.7±0.75[b]	119.2±2.73[b]
Test group	Initial	58.7±1.17	71.1±1.97
	7 days	45.4±0.73[c]	78.5±1.44[c]
	14 days	42.2±0.59[c]	83.4±2.81[c]

[a]Mean ± SD (n=3); [b]Indicates P<0.001 between control and reference; [c]Indicates P < 0.001 between reference and test

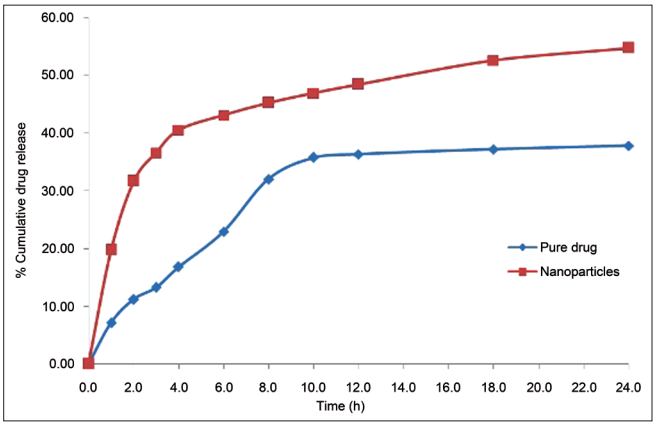

Figure 4: Cumulative percent drug release as a function of time of SV and optimized SV-loaded PLGA nanoparticles in pH 6.8 phosphate buffer

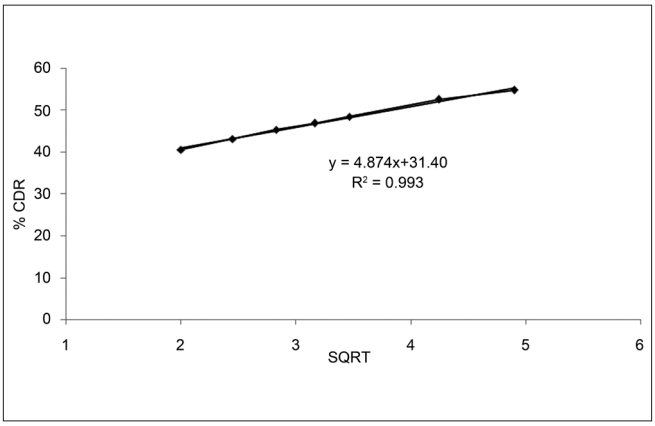

Figure 5: Higuchi kinetics (plot of cumulative percent drug release vs square root of time)

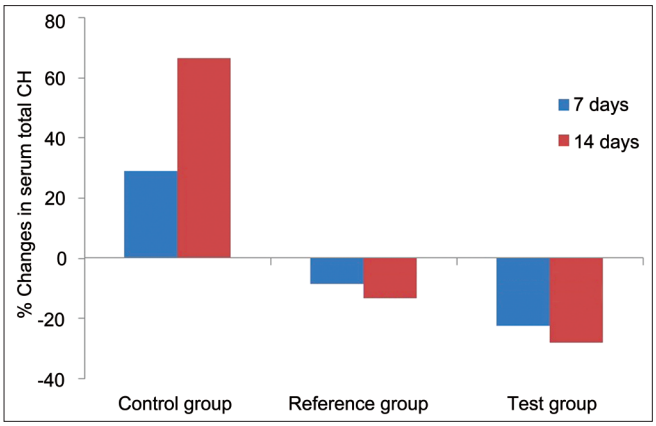

Figure 6: Plasma total CH levels of experimental groups at 7 and 14-day time intervals, respectively (*n*=3, mean ± SD)

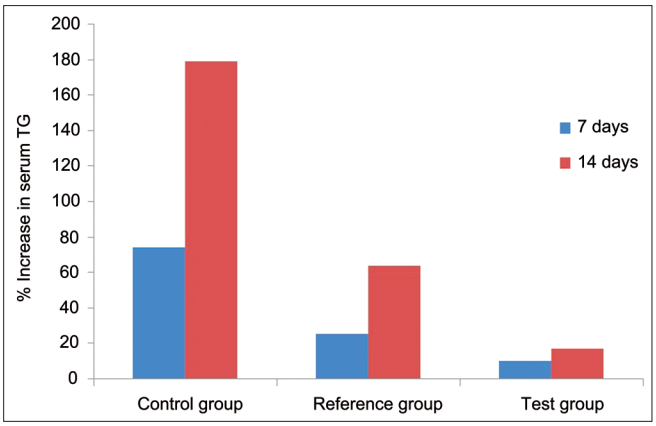

Figure 7: Plasma TG levels of experimental groups at 7 and 14-day time intervals, respectively (*n*=3, mean ± SD)

observed that serum CH and TG levels were significantly lower (2.6-fold and 2.5-fold, respectively) in the case of the test group compared to the reference group. After 14-days of similar treatment, the control group showed a further significant increase of 66% total CH and 179% TG indicating the inducement of hypercholesterolemia due to administration of excess coconut oil. The reference group showed an approximately 5-fold decrease in total CH and 2.8-fold decrease in TG compared to the control group. On the other hand, the test group presented a further 2.1-fold decrease in total cholesterol and a 3.7-fold decrease in TG in comparison with the reference group. Thus, SV-loaded PLGA nanoparticles showed a significantly better *in vivo* performance than SV in reducing total CH and TG levels which is primarily attributed to the improved solubility and dissolution of nanoparticles.

CONCLUSION

The present study has been a satisfactory attempt to prepare SV-loaded PLGA nanoparticles by an emulsification-solvent evaporation technique. Various formulation parameters like drug-polymer ratios, different organic solvents (methanol/dichloromethane), and different surfactants (PVA/tween-80) had significant influence on the characteristics of nanoparticles. Aqueous solubility studies indicated that the dissolution rates were remarkably increased in SV-loaded PLGA nanoparticles, compared with the drug alone. The *in vitro* drug release profile of the nanoparticles shared a common characteristic of an initial burst release which can be helpful to improve the penetration of drug followed by a slow release consistent with a Higuchi diffusion mechanism. *In vivo* data showed that SV-loaded PLGA nanoparticles performed better than SV in reducing total CH and TG levels which is primarily attributed to the improved solubility and dissolution of nanoparticles. Thus, SV-loaded PLGA nanoparticles can be effective in improving the oral bioavailability and sustaining the drug release, thereby minimizing the dose-dependent adverse effects and maximizing the patient's compliance.

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