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Research Article

Lipid-based Solid Self-emulsifying Delivery System of Pitavastatin Calcium: Development and Characterization

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ABSTRACT

Solid self-emulsifying delivery system containing pitavastatin calcium was developed using oil and hydrophilic surfactants. Pitavastatin calcium has low solubility and low bioavailability; hence, it was meaningful to improve solubility and dissolution properties by using suitable formulation component and process. Based on preliminary study, oleic acid, Tween 20 and PEG 400 were utilized for development of self-emulsifying system. Microemulsion region was identified by pseudo-ternary phase diagrams. The liquid system: adsorbent (Aerosil 200) at a ratio of 2:1 was employed for spray drying. The system was evaluated for emulsification time, percent drug content, in-vitro dissolution. The other analytical techniques used for characterization were fourier transform infrared spectroscopy (FTIR), DSC, standard error of the mean (SEM), particle size, zeta potential and XRD. The optimized formulation had particle size of 172.2 nm and the drug content found was 96.38%. It also had shown 95.98% drug release at the end of 1 hr which was more when compared to pure drug. It was observed that increase in surfactant concentration decreases dispersion time and particle size with concomitant increase in amount of drug released. The XRD diffractogram confirmed the conversion of drug from crystalline to amorphous form. The spray dried particles had smoother surface. The DSC thermogram showed no melting endotherm in the system indicating well dispersed drug with amorphous nature.

Introduction

As it is reported in many literatures that nearly 40% of new drug candidates exhibit low solubility in water, which leads to poor oral bioavailability, high intra- and intersubject variability indicating dissolution process is a rate limiting step. Numbers of approaches are utilized by many researchers including salt formation, particle size reduction, solid dispersion and inclusion complex and use of surfactant. However, these methods have their own limitations including aggregation of particles, stability and commercial viability.[1] Thus, the use of lipid/oil and surfactant-based formulation is among several approaches found to be capable of improving the bioavailability of poorly water soluble drugs. In recent years, self- emulsifying drug delivery systems (SEDDS) formulations showed a practical achievement in improving the oral bioavailability of poorly soluble drug compounds by presenting and maintaining the drug in a dissolved state, in small droplets of oil, throughout its transit through the GI tract.[2]

In this research work an attempt was made to enhance the solubility and dissolution of pitavastatin; a synthetic lipid-lowering agent (hyperlipidemic) drug. It inhibit 3- hydroxyl-3-methyl glutaryl coenzyme A (HMG –CoA) reductase pivotal enzyme in cholesterol biosynthesis. It lowers both total cholesterol and low-density lipoprotein cholesterol. Under Biopharmaceutic Classification System (BCS) it is class II drug having low aqueous solubility (0.0394 mg/mL), high permeability and low bioavailability (51%). Hence, to overcome these constrains; it was decided to develop SEDDS to improve dissolution and impart stability by presenting it in a solid form.[3]

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Materials and Methods

Materials

Pitavastatin calcium was received from Enaltec labs (Mumbai, India). Tween 20 and Tween 80 were purchased from SD Fine (Mumbai, India). Oleic acid, PEG 400 was purchased from Thomas Baker (Mumbai, India). Methanol was purchased from Merck (Mumbai, India). Aerosil 200 was purchased from Research Lab Fine Chem Industries (Mumbai, India).

Methods

Screening of Oils, Surfactants, and Cosurfactants

It was determined by dissolving an excess amount of drug in 2 ml of each selected individual oils, surfactants and co surfactants contained in stoppered vials (5 mL capacity) separately. The liquids were mixed using a vortex mixer and the vials were then shaken using orbital shaker at 37°C ± 1°C for 72 hours (100 rpm) to reach equilibrium. The supernatants filtered through a membrane and the concentration of pitavastatin calcium were determined by UV spectrophotometer (1800, Shimadzu, Japan) at 245 nm.[4]

Pseudo-ternary Phase Diagram

Water titration method was used to determine the microemulsion region and detect the possibility of making microemulsions with different possible compositions of oil and surfactant, cosurfactant. The ratios of surfactant to cosurfactants were chosen as 1:1, 2:1, and 3:1. These mixtures (S_{mix}) were mixed with the oil phase to give the weight ratios of 90:10 to 10:90. Water was added drop by drop and end point of the titration was noted where the solution becomes cloudy or turbid. Phase diagrams were constructed using CHEMIX school software (trial version, V. 3.5).[5, 6]

Formulation of Liquid Self-microemulsifying Drug Delivery System (L-SMEDDS)

From the solubility study and comparison of the constructed ternary phase diagram, oil and Smix ratio were selected for the formulation of L-SMEDDS are given in Table 1. The formulations were prepared by using oleic acid (oil), Tween 20 (surfactant), PEG 400 (co-surfactant). Pitavastatin calcium was added to the oil phase and vortexed for 10 mins; to it surfactant and co-surfactant were added. The resultant mixtures were vortexed for 15 min and heated over a water bath maintained at 40^0 ± 2°C for 10 mins to facilitate solubilization of pitavastatin calcium. The mixture was stored at room temperature until further use.[7,8] The L-SMEDDS were evaluated visually, self-emulsifying ability and *in-vitro* release.[9-12]

Table 1: Formulation batches of liquid SEDDS

Batches	*Drug (gm)*	*Oleic acid (gm)*	*Tween 20 (gm)*	*PEG 400 (gm)*	*Total quantity (gm)*
L1	0.04	1	6	3	10.04
L2	0.04	2	5.334	2.667	10.04
L3	0.04	3	4.668	2.334	10.04
L4	0.04	4	4	2	10.04
L5	0.04	5	3.334	1.667	10.04

Drying of L-SMEDDS

A lab scale spray dryer (Labultima LU 222, Mumbai) was used for the preparation of solid SMEDDS. Aerosil 200 was used as an inert carrier. Aerosil 200 was added in 250 ml of ethanol, followed by stirring using magnetic stirring to form suspension. To this solution, liquid SMEDDS was added (SMEDDS to carrier ratio of 2:1) and stirred continuously at a 40°C until a suspension was formed. The resulting suspension was spray dried using below mentioned operating conditions:

Feed flow rate (2 mL/min), inlet temperature (60°C), outlet temperature (50°C), cool temperature (45°C), aspirator (35 Nm^3/hr), and vacuum (90 mm of Wc), ethanol as solvent. The powder was collected and stored in a desiccator until further use.[13, 14]

Evaluation of Solid-SMEDDS (S-SMEDDS)

Percentage Practical Yield

The percentage practical yield of spray-dried powder was calculated using the following formula.[15]

$$\% \text{ Practical yield} = \frac{\text{Wt. of spray dried powder obtained}}{\text{Wt. of (liquid SEDDS + Aerosil 200)}} \times 100$$

Emulsification Time

About 0.5 g of the SMEDDS formulations were introduced into 250 mL of 0.1 N HCl in 500 mL conical flask under action of magnetic stirrer rotating at constant speed and emulsification time was noted.[2]

In-vitro Drug Release

Drug release of pitavastatin calcium was determined by using USP type II dissolution test apparatus. Powder system (Equivalent to 2 mg) was enclosed in gelatin capsule. The dissolution medium used was 900 mL 0.1 N HCl maintained at 37 ± 0.5°C and rotated at 50 rpm. Sample solutions were withdrawn at predetermined time intervals; filtered; diluted and analyzed by UV spectrophotometer at 245 nm. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. The dissolution study of pure drug and marketed formulation was also conducted at same operating conditions in order to compare the profiles.[7]

FTIR Study

The FTIR spectrums of pitavastatin calcium and S-SEDDS were recorded using a FTIR spectrophotometer (Shimadzu IR Affinity-1) using KBr disk. Analyses were performed at room temperature over a wave number range of 4000 to 400 cm^{-1}.

DSC Study

The DSC study was carried out using Differential Scanning Calorimeter (Mettler Toledo, USA). The samples of 2 mg were weighed accurately and sealed into aluminum pans. The samples were held at initial temperature for 5 minutes and then heated from 25 to 300°C with a heating rate of 10°C/min under a pure nitrogen gas purge (20 mL/min).[15]

Globule Size and Zeta Potential

The S-SMEDDS formulation was diluted with distilled water (1:250) and mixed using magnetic stirrer. Samples were filtered through 0.45 µm micropore filters and analyzed by Zetasizer (Malvern Zetasizer Nano ZS 90).[16-18]

SEM Study

The morphology of Aerosil 200 and S-SMEDDS was examined using a scanning electron microscope (Jeol, USA) with an image analysis system (Image Inside version 2.32). The samples were mounted on a brass stub using double-sided adhesive tape and vacuum coated with platinum at 15 kV.[19]

XRD Study

Powder X-ray diffractometer (PANalytical XPert PRO, Netherlands) was employed for the powder X-ray diffraction analysis of lipid, drug and drug loaded NLC. Cu K-alpha (wavelength 1.54060Å) radiation was used as an X-ray source. For the analysis, samples were placed in the glass sample holders made up of polystyrene. The sample holder was placed in the X-ray diffractometer equipped with scintillation counter detector. XRD pattern was measured with a voltage of 45 kV and a current of 40 mA over a range of 0º to 89º with a scan angular speed of 2º/min.[20]

Results and Discussion

Evaluation Liquid SMEDDS

The oil represents one of the most important excipients in the SMEDDS formulation because it can solubilize the lipophilic drug and to facilitate self-emulsification surfactants and co-surfactants are essential. Thus, drug should be sufficiently solubilized in the oil to be emulsified. It is observed that, drug was highly soluble in oleic acid as compared to other oils, soluble in Tween 20 and in PEG 400. Hence; it was decided to use oleic acid, Tween 20 and PEG 400 for formulation of L-SMEDDS. The results are summarized in Table 2.

Pseudo Ternary Phase Diagram

Microemulsion formulation area was increased with an increase in ratio of Smix, because emulsification of oil increases. Fig. 1 showed the boundary indicates microemulsion region area where clear and transparent formulations were obtained. The phase study showed that the microemulsion region was found maximum with a surfactant to cosurfactant ratio 2:1 as compare to other ratio. Further increase in the Smix 3:1 ratio resulted in loss of flow ability due to increase in viscosity of formulation.

All the Liquid SMEDDS were transparent and appeared like a homogenous single phase liquid when observed for visual clarity against light. No traces of undissolved drug or other solid ingredient were found; indicating optically transparent formulation. The formulations were stable and not showed phase separation upon heating, cooling and centrifugation. Further there was no effect of dilution of the formulation by water and 0.1N HCl (pH 1.2) confirming the robustness to dilution. The self-emulsifying capacity of the formulation varies with S_{mix} concentration. As the

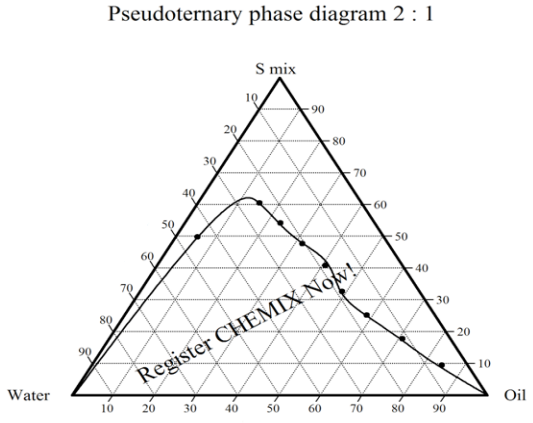

Fig.1: Ternary phase diagram with different oils, surfactants and co-surfactants

Table 2: Solubility of drug in different oils, surfactants, and co-surfactants

Oils	*Solubility (mg/mL) (mean ± SD)*	*Surfactant, co-surfactant (mean ± SD)*	*Solubility (mg/mL) (mean ± SD)*
Castor oil	4.90 ± 0.782	Tween 20	104.5 ± ± 0.5
Isopropyl myristate	20.7 ± 0.628	Tween 80	30.54 ± ± 0.75
Oleic acid	32.5 ± 0.842	Labrasol	18.92 ± ± 0.91
Olive oil	1.20 ± 0.51	PEG 400	71.8 ± ± 0.721
Cottonseed oil	8.21 ± 1.16	Propylene glycol	14.67 ± ± 0.56
Peceol	2.19 ± 0.965	Glycerol	7.26 ± ± 0.804

(n = 3)

concentration increases decrease in emulsification time was found which was in between 36 to 69 seconds. The percent drug content of all formulations was in the range 95.83–98.58% (L2 formulation).

FTIR Study

The comparison of spectrums of pitavastatin calcium, Tween 20, PEG 400 and their solid formulation is presented in Fig. 2. The FTIR spectra of pitavastatin calcium exhibited principle peaks at wave numbers 3441.0, 3336.85 for carboxylic group, 3066.82 for –OH stretching, 1732.08 stretching band for carbonyl group and 1674.21 for C-N stretching. The spectra of formulation did not show significant variation in the wave number. All the principal peaks of drug were present in the spectrum so it can be concluded that the drug and excipients were compatible with each other.

Evaluation of Solid SMEDDS

All the previously developed liquid formulations were dried by adsorption on carrier followed by spray drying. It was reported that the % practical yield is low in case of spray drying. The percent practical yield was in the range of 69.33 to 72.86 %. Highest yield was found in S2 batch. The drug content was fall between 87.5 to 96.38% and all the formulation had shown rapid emulsification.

Drug content was in the range of 87.5 to 96.38% which was within acceptable limit. The emulsification time for all solid formulation was determined. Rapid emulsification was observed in case of formulation S1 (49 sec.) while S5 took more time (95 sec.) as compared to other formulations. This was because of S1 contained high concentration of surfactant while S5 had lesser concentration.

In-vitro Drug Release

Maximum drug release was found in L2 batch (liquid formulation) and the reason behind improved release may be amount of oil which was optimum for self-emulsification. The proportion of oil decreases with increase in surfactant concentration to form droplets of smaller size so that maximum surface area is available to contact dissolution medium and hence maximum release. The % cumulative drug release was ranged from 88.57 to 97.46%. In case of liquid formulations drug release was little bit more as were available in isotropic liquid forms which get emulsified rapidly with dissolution medium.

In case of solid spray dried formulation % release was ranged from 86.65 to 95.98%. Among all batches; formulation S2 showed about 95.98% release within 60 min. In case of pure drug, it was observed only 45.69% while marketed tablet formulation showed 57.18%. The possible mechanism for improved dissolution may be larger surface area provided by adsorption of L-SMEDDS; conversion of crystalline material to amorphous one by drying process; particle size reduction, spontaneous formation of microemulsion with fine droplets etc. The results of drug release of solid formulations and the comparison of optimized formulation with pure drug and marketed formulation is shown in Figs. 3 and 4.

Droplet Size and Zeta Potential

The globule size of optimized solid formulation was 172.2 nm while the polydispersity index (PDI) is 0.324. As the globule size is less than 250 nm indicating the formation of S-SMEDDS. The value of PDI was acceptable and suggested that the formulation had narrow particle size distribution.

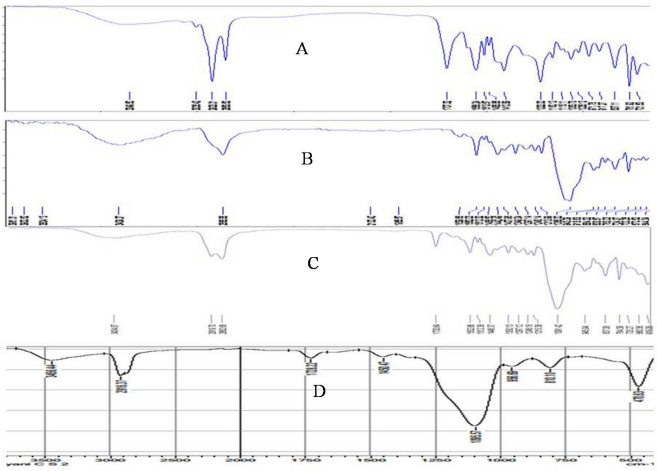

Fig. 2: FT-IR spectrum of drug: excipient interaction (A,B and C) and FT-IR spectrum of S-SEDDS (D)

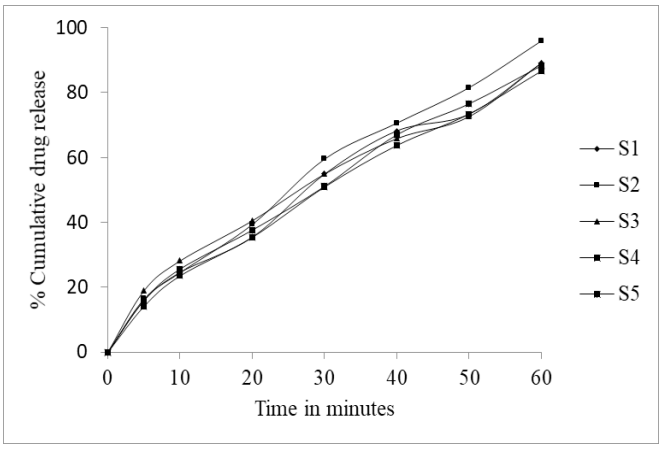

Fig. 3: Dissolution profiles of S-SEDDS by spray drying

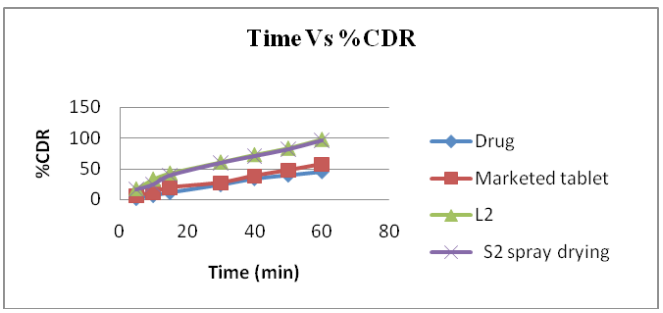

Fig. 4: Dissolution kinetic of pure drug with optimized formulation and marketed tablet

Further the value of zeta potential was -14.7 mV indicating good stability. The results of globule size and zeta potential of the liquid self emulsifying system are given in Figs. 5 and 6.

DSC Study

The DSC thermograms of pitavastatin and its solid self-microemulsifying drug delivery system (SMEDDS) are shown in Fig. 7. The formulation did not show the endothermic peak corresponding to melting of drug. This could be due to either the drug is encapsulated, or in dissolved state or exist in amorphous form.

SEM Study

The SEM images showed that pitavastatin calcium was appeared as crystalline shape material; Aerosil 200 powder had rough surface, highly porous structure of agglomerated particle. The surface of S-SMEDDS was appeared as smooth-surface indicating that liquid SMEDDS was adsorbed onto or coated inside the pores of Aerosil 200 however, they are aggregated. The photomicrographs are shown in Fig. 8.

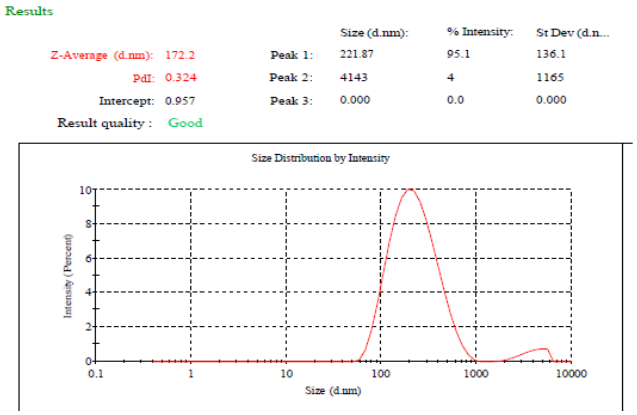

Fig. 5: Globule size of Solid SEDDS

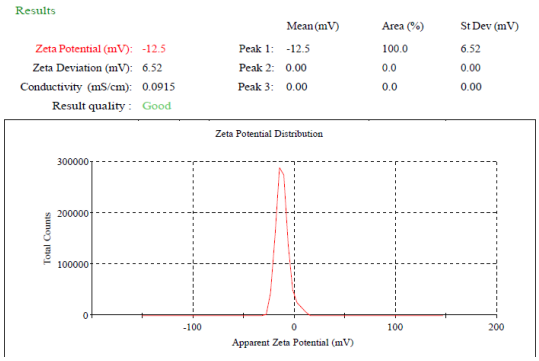

Fig. 6: Zeta potential of liquid SEDDS

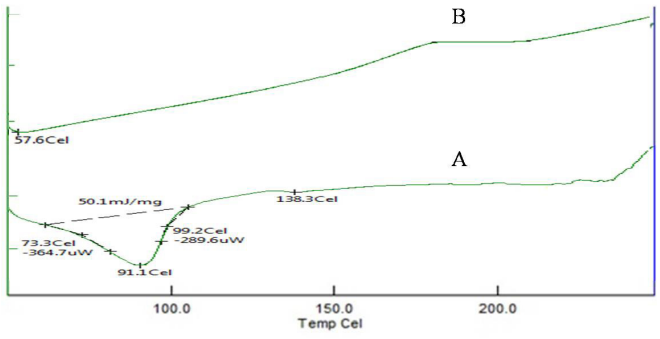

Fig. 7: DSC thermograms of pitavastatin calcium (A) and S-SEDDS (B)

In this research study liquid and solid SMEDDS were developed using mixture of oil, surfactant and co-surfactant. Both the system showed rapid emulsification with smaller droplet size and good zeta potential. The in-vitro drug release from the formulations was rapid as compare to pure drug and marketed formulation. Both the systems were stable. The analytical characterization showed that the drug and excipients were compatible; the drug was converted to amorphous form and present in dissolved state. The dried particles had smooth surface due to adsorption of the drug either onto the surface or inside the porous structure of the carrier. Because of employment of self emulsifying approach, and transformation from crystalline to amorphous form, dissolution pitavastatin calcium was increased which was evident from comparative dissolution profile. This approach could be used for overcoming the dissolution problem.

XRD Study

The XRD of pitavastatin calcium and optimized solid formulation was recorded (Fig. 9) to determine physical state. PXRD of pitavastatin calcium consists of sharp peaks confirming its crystalline nature (A). The solid SEDDS did not show significant crystalline peaks because it is converted to amorphous form (B). This could be one of the mechanisms for improved dissolution.

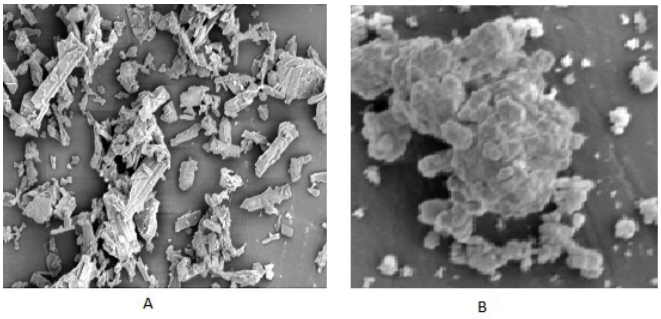

Fig. 8: SEM of pitavastatin calcium (A) and S-SEDDS (B)

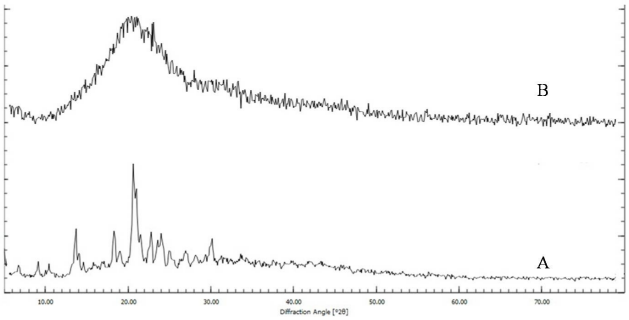

Fig. 9: XRD of pitavastatin calcium (A) and S-SEDDS (B)

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