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Original Article

FORMULATION AND *IN VITRO* CHARACTERIZATION SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM OF RAMIPRIL PREPARED BY ADSORPTION TECHNIQUE

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ABSTRACT

Objective: The primary goal of the present work was to formulate solid self-emulsifying drug delivery systems (S-SEDDS) in order to improve the solubility of the highly lipophilic antihypertensive drug, ramipril.

Methods: SEDDS are generally liquid form preparations obtained by homogeneously mixing oils, surfactants and co-surfactants along with drug component. Based on solubility studies Capmul PG8 NF, Gelucire 44/14 and Transcutol P were selected as oil, surfactant, co-surfactant respectively in order to prepare liquid SEDDS (L-SEDDS). Nine different liquid SEDDS were prepared and subjected to various evaluation tests in order to obtain optimized L-SEDDS. Finally, the optimized formulation was converted to S-SEDDS by physical adsorption technique using an inert carrier. Further, S-SEDDS were also subjected to solid state characterization.

Results: Out of 9 different L-SEDDS**,** S9 formulation was optimized as it formed thermodynamically stable emulsion without any drug precipitation and phase separation on storage and also showed least globule size (22.56 nm). The optimized formulation was loaded onto inert carrier (Sylysia FCP 350) to obtain S-SEDDS. S-SEDDS showed acceptable flow properties. They were further processed for solid state characterization such as XRD, DSC and SEM and the results confirmed the transformation of native crystalline nature of drug to an amorphous state. FTIR analysis also confirmed no drug-excipient interaction. S-SEDDS showed improved *in vitro* dissolution behaviour of ramipril over that of pure drug.

Conclusion: Ramipril S-SEDDS retained emulsification characteristics of L-SEDDS. Further, S-SEDDS was encapsulated in hard gelatin capsules and this formulation proved to have improved solubility for ramipril.

Keywords: Liquid self-emulsifying drug delivery system (L-SEDDS), Solid self-emulsifying drug delivery system(S-SEDDS), Ramipril, Emulsification, Sylysia FCP 350.

INTRODUCTION

Over decades, oral route is easiest and most preferred route of drug administration for the chronic treatment of many diseases. Most of the new chemical entities and existing drug candidates have low water solubility, which leads to poor bioavailability, high intrasubject/intersubject variability, therapeutic failure and lack of dose proportionality [1]. The availability of the drug for absorption can be enhanced by the presentation of the drug as a solubilizate within a colloidal dispersion [2].

According to BCS classification, the class II drugs have poor aqueous solubility and high permeability and their absorption is dissolution rate limited. To overcome these problems, various formulation strategies have been exploited, such as micronization, solid dispersions[3], inclusion complexes (cyclodextrins) [4].

In the recent past, lipid and surfactant based systems e. g. lipid solutions, surfactant dispersions, emulsions, liposomes, microemulsions, dry emulsion and self-(micro) emulsifying formulations have been developed and found to have a great potential in improving the bioavailability of poorly soluble drugs. SEDDS (self-emulsifying drug delivery systems) belong to lipid-based formulations and has proved to be the promising carriers for improving the drug solubility and dissolution rate thus facilitating improved oral absorption and bioavailability of poorly water-soluble drugs. SEDDS are isotropic mixtures comprising of oil, surfactant, co-surfactant, drug substance and sometimes contain co-solvents which emulsify spontaneously upon mild agitation and dilution with aqueous media to produce a fine oil-in-water emulsion. They readily spread in the GIT and its motility provides the agitation necessary for self-emulsification. SEDDS produce emulsions of droplet size ranging from 100-300 nm, whereas SNEDDS (self-nano emulsifying drug delivery systems) from transparent/clear emulsions with bluish tinge having droplet size less than 50 nm. The emulsification time of SEDDS, size of globules formed and the stability of the resultant emulsion, when introduced into water with mild agitation not only depends on the type of oil, surfactant and co-surfactant combination but also the weight percentage of oil and surfactant/co-surfactant mixture, is also equally important [5]**.**

Furthermore, the commercialization of few SEDDS like Fortovase® (saquinavir), Norvir® (ritonavir) and Neoral®(cyclosporine) established interest in the commercial viability of using SEDDS as a delivery strategy [6]. Despite the potential of SEDDS in improving the bioavailability of poorly soluble drugs few limitations remain to be unresolved for the delivery system which includes stability, the interaction of the fill with the capsule shell and storage temperature [7]. Hence, the current research is focused in the conversion of SEDDS into solid form by adsorbing onto an inert carrier. Apart from adsorption other techniques were also utilized for conversion of liquid to solid SEDDS such as spray drying, freeze drying, melt granulation, extrusion/spheronization and rotary evaporation.

Ramipril {(2S,3aS,6aS)-1-[(2S)-2-[[(1S)-1-(ethoxy-carbonyl)-3-phenpropyl] amino]-1-oxopropyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid}, a potent antihypertensive drug,belonging to category of ACE inhibitor is widely used to treat high blood pressure, congestive heart failure and also to improve survival after a heart attack. Ramipril is highly lipophilic [logP (octanol/water), 3.32)], poorly water soluble (3.5 mg/l) drug belonging to BCS Class II. Poor water solubility resulted in erratic absorption in the gastrointestinal tract which further lead to poor bioavailability of 28%. The main intention behind choosing SEDDS formulation for ramipril drug was that lipid-based formulations enhance the solubility of lipophilic drugs that may further enhance dissolution rate and absorption in GIT. Keeping this point in view, an attempt was made to improve the dissolution of ramipril by formulating into S-SEDDS.

MATERIALS AND METHODS

Materials

Ramipril was a generous gift sample from Ranbaxy Laboratories, Dewas, India. Gelucire 44/14, Transcutol-P, Labrafil M1944CS, Labrafil M2125CS, Capryol 90, Labrasol®, Maisine were obtained as gift samples from Gatteffose, France. Captex-100, Captex-200, Captex-355, Capmul® PG 8 NF, Capmul® MCM C8, Acconon E, Caprol Micro Express blend were kind gift samples from ABITEC Corporations, Cleveland, USA. Purified soybean oil was obtained from Lipoid, Germany. Sylysia FCP 350 (silicon dioxide) was generously donated by Fuji chemicals, Japan. Tween 80 was supplied by Merck, Mumbai, India. TPGS-E was supplied by BASF corporation, U. S. A. Cremophor EL was provided by BASF, Mumbai. All other chemicals used were of analytical grade.

Methods

Solubility Studies

The screening of different vehicles is a prerequisite for the formulation of SEDDS. The solubility of ramipril in various vehicles like oils, surfactants and co-surfactants were determined by addition of excess amount of ramipril to a glass vial containing 2 ml of the selected vehicle. The components were mixed by gentle stirring and then vortexed using a cyclomixer until drug completely dissolved in the vehicle at 37 °C. Further, it was kept in a rotary shaker and constantly agitated at room temperature for 48h (Remi equipment, Mumbai, India). After reaching equilibrium, samples were centrifuged at 10,000 rpm for 15 min. The supernatant was suitably diluted with methanol and amount of ramipril was quantified using UV-VIS spectrophotometer at 210 nm.

Formulation of L-SEDDS

SEDDS formulations of ramipril were prepared using that vehicle selected as oil, surfactant and co-surfactant based on solubility study results. The contents were vortexed using cyclomixer and then heated at 40 °C (if necessary) until a homogenous mixture was obtained. The obtained SEDDS formulations were stored at room temperature until used.

Characterization of L-SEDDS

Evaluation of self-emulsification time and stability

The self-emulsifying properties of SEDDS formulations were performed by visual assessment [8]. For this about 100 µl of SEDDS formulation was added dropwise to a beaker containing about 300 ml SGF at 37 °C. The beaker was placed on a magnetic stirrer and the contents were kept under continuous stirring (~100 rpm) using a magnetic bead. The time taken for the emulsion formation for each formulation was recorded as the self-emulsification time. In order to determine the stability of SEDDS, the formed emulsion was stored at 37 °C and observed for phase separation and drug precipitation, if any for 48 h [9]. The stable SEDDS formulations were selected and subjected to further characterization.

Globule size and zeta potential analysis

The mean globule size(z-average), zeta potential as well as the polydispersity index (PI) of emulsions formed from stable SEDDS formulations were determined by photon correlation spectroscopy using zeta sizer Nano ZS 90 (Malvern instruments, UK). Before analysis, each formulation was diluted to a suitable concentration with SGF. Size analysis was performed at 25 °C with an angle of detection of 90°. All studies were repeated thrice and the average values obtained were used.

Preparation of S-SEDDS

The optimized L-SEDDS formulation was finally selected for conversion into S-SEDDS by the process of physical adsorption using Sylysia FCP 350 as an inert carrier. A fixed weight i.e. 250 mg of SEDDS formulation (equivalent to single dose) was initially taken in a china dish and 100 mg of Sylysia was added slowly and mixed thoroughly to get a uniform granular mass. The process was continued till free flowing powder was obtained and then passed through sieve no. 120 to get uniform size mass. Final product was stored over anhydrous calcium chloride in a desiccator until further evaluation was performed [10].

Reconstitution properties of S-SEDDS

Emulsification time determination

The emulsification time of S-SEDDS was performed using USP dissolution apparatus II. In brief S-SEDDS (equivalent to single dose) was introduced into 500 ml of SGF at 37 °C under gentle agitation by a standard stainless steel dissolution paddle rotating at 50 rpm. The emulsification time was assessed by visual observation [8] and all the experiments were carried out in triplicate.

Emulsion droplet size and charge determination

Zeta potential and droplet size of the emulsion formed from reconstituted S-SEDDS after suitable dilution was determined by photon correlation spectroscopy using zetasizer Nano ZS 90 (Malvern instruments, UK). Size analysis was performed at 25 °C with an angle of detection of 90 °. All studies were repeated thrice and the average values obtained were used.

Characterization of S-SEDDS

Flow properties of S-SEDDS

The content uniformity of the powder formulations is determined by the flow properties of powder. The flow properties or rheological characteristics of S-SEDDS were assessed by measuring the angle of repose(θ), Carr's compressibility index and Hausner's ratio. The angle of repose was performed by using conventional fixed funnel method. The Carr's compressibility index and Hausner's ratio were calculated from the bulk and tapped density of the S-SEDDS which were obtained by using USP Type I Tap Density Tester apparatus using 10 ml measuring cylinder.

In vitro dissolution studies

In vitro dissolution study of S-SEDDS and pure drug was performed using USP type II (paddle) apparatus (Electrolab, TD L8, Mumbai, India) in SGF (pH 1.2) without enzyme. The volume of dissolution medium used was 500 ml, paddle speed was set at 50 rpm and the temperature was maintained at 37±0.5 °C throughout the experiment. At predetermined time intervals 5 ml of sample was withdrawn and replenished with fresh dissolution medium (SGF) to maintain constant volume and also to provide sink condition. The samples were analyzed spectrophotometrically at 210 nm to detect amount of drug released at each sampling point.

Determination of dissolution parameters

Cumulative percent drug release was plotted as a function of time and percentage drug released in 15 and 60 min (Q_{15} and Q_{60} respectively) was interpolated from the graph. Dissolution efficiency (DE_{15}) was calculated from the area under the dissolution curve at 15 min (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [11]. The relative dissolution rate (RDR) was determined by dividing the dissolution efficiency of S-SEDDS formulation with control formulation [12].

Surface morphological analysis of S-SEDDS

The surface morphology of ramipril, sylysia and S-SEDDS formulation was investigated by scanning electron microscope (S-4100, Hitachi, Japan). Samples were fixed on a brass stub using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 15 kev accelerating voltage.

Differential scanning calorimetry

The molecular state of ramipril in S-SEDDS was characterized by DSC studies. The DSC thermograms of ramipril, sylysia and S-SEDDS were recorded using differential scanning calorimeter (Perkin Elmer, USA). Each sample of weight of 5±2 mg was heated in hermitically sealed aluminum pan over a temperature range of 20 °C to 300 °C under a constant nitrogen gas flow of 30 mL/min at a heating rate of 10

°C/min. The instrument was calibrated with indium (calibration standard, purity>99.9%) for melting point and heat of fusion.

Powder X-ray diffraction studies

The PXRD patterns of pure drug, sylysia and S-SEDDS formulation were obtained using X-ray diffractometer (X' Pert PRO PANalytical, USA). The measuring conditions were as follows: CuKα radiation, nickel filtered; graphite monochromator; 45 kV voltage; 40 mA current with X'celerator detector and all samples were run at 1 ° (2θ) min^{-1} from 3 ° to 45 ° (2θ).

Fourier transforms infrared spectroscopy

Infrared spectra of ramipril, sylysia and S-SEDDS formulation were obtained using FT-IR spectrophotometer (Paragon 1000, Perkin Elmer, USA) by the conventional KBr pellet method. The scanning range was 4000–400 cm^{-1} and the resolution was 4 cm^{-1} using Happ-Genzel apodization.

RESULTS AND DISCUSSION

Solubility Studies

The selection of oil, surfactant and the co-surfactant mixture is based on the solvent properties and should allow the drug in solution. The solubility of ramipril was carried out in various oils, surfactants and co-surfactants and the data is represented in the table 1. Among the excipients screened Capmul PG8NF, Gelucire 44/14 and Transcutol-P have shown the highest solubility and hence they were selected as oil, surfactant and co-surfactant respectively.

Formulation of L-SEDDS

SEDDS formulations were prepared using Capmul PG8 NF, Gelucire 44/14 and Transcutol P as oil, surfactant and co-surfactant respectively based on solubility study results. Initially, a single dose of ramipril (2.5 mg) was accurately weighed and dissolved in calculated amount of oil, surfactant and co-surfactant in a glass vial. Here nine L-SEDDS formulations were prepared and coded as S1, S2, S3, S4, S5, S6, S7, S8 and S9 as shown in table 2.

Table 1: Solubility of ramipril in different vehicles (oils, surfactants, and co-surfactants) (mean±SD, n=3)

S. No.	Vehicle	Drug soluble(mg/ml)
Oils		
1	Capmul MCM C8	37±1.5
2	Capmul PG8NF	73±2.0
3	Labrafil M 1944 CS	38±1.0
4	Labrafil M 2125 CS	44±2.0
5	Captex 355	2±0.9
6	Captex 200	1.5±0.8
7	Captex 100	0.6±0.6
8	Capryol 90	9±1.6
9	Cremophore EL	24±1.0
10	Maisine	5±1.3
11	Soybean oil	13±1.6
Surfactants		
12	Gelucire 44/14	66±1.0
13	Tween 80	53±0.5
14	Acconon-E	6±0.6
15	Caprol micro express blend	17±0.3
16	Labrasol	23±0.5
Co-surfactants		
17	Transcutol-P	85±1.0
18	TPGS-E	11±0.5

Table 2: Formulation of ramipril L-SEDDS with different ratios of oil: surfactant: co-surfactant

L-SEDDS formulation code	Oil: smix	Surfactant: co-surfactant (smix)	Oil (mg)	Surfactant (mg)	Cosurfactant (mg)	Drug (mg)
S 1	1:1	1:1	123.75	61.875	61.875	2.5
S 2	1:3	1:1	61.875	92.8125	92.8125	2.5
S 3	1:5	1:1	41.25	103.125	103.125	2.5
S 4	1:1	3:1	123.75	92.8125	30.9375	2.5
S 5	1:3	3:1	61.875	139.21875	46.40625	2.5
S 6	1:5	3:1	41.25	154.6875	51.5625	2.5
S 7	1:1	5:1	123.75	103.125	20.625	2.5
S 8	1:3	5:1	61.875	154.6875	30.9375	2.5
S 9	1:5	5:1	41.25	171.875	34.375	2.5

Characterization of L-SEDDS

Evaluation of self-emulsification time and stability

The efficiency of self-emulsifying systems will be assessed from the rate of emulsification upon hydration with mild agitation [8]. Surfactant systems in SEDDS formulation reduce the interfacial tension between oil and aqueous phases resulting in easy dispersion and formation of o/w emulsion. Self-emulsification time of all formulation formulations was shown in table 3.

Table 3: Evaluation of self-emulsification time of ramipril SEDDS (mean±SD, n=3)

L-SEDDS	Oil: Smix	Self-emulsification time (sec)
S 1	1:1	45±3.0
S 2	1:3	37±2.0
S 3	1:5	30±2.0
S 4	1:1	26±2.0
S 5	1:3	21±1.0
S 6	1:5	18±3.0
S 7	1:1	15±2.0
S 8	1:3	12±2.0
S 9	1:5	9±2.0

With the increase in oil proportion, there was a decrease in the rate of emulsification and increase in emulsification time. The higher interfacial tension between larger volume of oil and aqueous phase and a decrease in concentration of surfactant system may be responsible for the increased emulsification time.

The formulations S3, S6, S8 and S9 formed stable emulsions without any phase separation and precipitation of drug upon standing at room temperature for 48 h (table 4). Thus, these formulations were processed for further characterization.

Table 4: Phase separation and precipitation of the drug from L-SEDDS formulation

L-SEDDS	Phase separation	Drug precipitation
S1	yes	no
S2	yes	no
S3	no	no
S4	yes	no
S5	yes	no
S6	no	no
S7	yes	no
S8	no	no
S9	no	no

Globule size and zeta potential analysis

Since globule size is one of the prime factors which significantly contribute for the drug absorption, the globule size and size distribution after self-emulsification is an important parameter to be evaluated. From formulations S3 to S9, globule size was significantly decreased (table 5). This resulted because surfactant concentration increased and oil concentration decreased from S3 to S9. High surfactant enabled rapid dispersion of globules in SGF. The higher the zeta potential, greater will be the energy barrier to coalescence between oil globules and so higher will be the stability. Negative zeta potential values also enable long circulation half-life *in vivo* as described by Jung [13].

Formulation S9 showed a least globule size with negative zeta potential when dispersed in SGF. Polydispersibility index of S3, S6, S8, S9 formulations was below 0.3 indicating homogeneous dispersion, so they were processed for further characterization.

Table 5: Globule size and zeta potential of stable L-SEDDS formulations in SGF (pH 1.2)

L-SEDDS	Z average (nm)	Zetapotential (mV)	P. I
S3	200.8	-4.16	0.237
S6	126.75	-4.34	0.254
S8	65.2	-4.49	0.276
S9	22.56	-4.68	0.297

Preparation of S-SEDDS

Physical adsorption technique was employed for the preparation of S-SEDDS formulations. The optimized S9 SEDDS formulation was finally selected for conversion into S-SEDDS. It was adsorbed onto sylysia FCP 350 which was chosen as carrier for S-SEDDS formation. 100 mg of sylysia was added slowly to 250 mg of S9 SEDDS formulation, initially taken in a china dish, mixed thoroughly and then passed through sieve no. 120 to get uniform size mass.

Reconstitution properties of S-SEDDS

Emulsification time determination

The S-SEDDS dispersed quickly and completely when introduced into aqueous medium upon mild agitation. The self-emulsification efficiency in case of S-SEDDS (350 mg) can be determined by measuring the rate of emulsification and droplet size distribution. The rate of emulsification of S-SEDDS formulation is measured by visual observation as reported previously [14-16]. It was observed that emulsification time of optimized S9 SEDDS formulation was 9±2.0 s and for S-SEDDS it was 17±1.0 s as shown in table 6. In S-SEDDS formulation Gelucire 44/14 with HLB value 11 is used as primary surfactant for proper self-emulsification and it might be the reason for good emulsification properties.

Emulsion droplet size and charge determination

It has been reported that the nature of the oil affects the emulsion droplet size. Variation in penetration of oil molecules into the surfactant alkyl chain region affects interfacial film composition and flexibility. Any change in interfacial film influences the surface curvature of the drop let leading to differences in the droplet size [17, 18]. The emulsion droplet size and polydispersity index (PDI) of S9 SEDDS and S-SEDDS were shown in table 6. The droplet size and P. I was 22.56±1.7 nm and 0.297±0.014 for S9 SEDDS, 36.11±2.1 nm and 0.317±0.035 for S-SEDDS, respectively. Both formulations showed reasonable homogeneity. These results suggested the capability of the lipid components of S-SEDDS to retain its emulsification properties irrespective of physical form change. The zeta potential of S9 SEDDS and S-SEDDS were-4.68±0.21 and-3.42±0.28, respectively. No significant difference between the charges of two formulations was noted. It is reported that in addition to particle size, zeta potential also plays an important role in the interactions with the mucus of the gastrointestinal tract [17, 18]. The results were described in table 6.

Table 6: Comparision of parameters between S9 SEDDS and S-SEDDS

Parameter	S9 SEDDS	S-SEDDS
Emulsification time (s)	9±2	17±5
Zeta potential (mV)	-4.68±0.21	-3.42±0.28
Droplet size (nm)	22.56±1.7	36.11±2.1
Polydispersity index(P. I)	0.297±0.014	0.317±0.035

Mean values of three samples±SD

Table 7: Micromeritics of ramipril loaded S-SEDDS (mean±SD, n=3)

Formulation	Angle of repose (θ)	Carr's index	Hausner's ratio
S-SEDDS	34.6±1.6	27.1±0.53	1.37±0.15

Characterization of S-SEDDS

Flow properties of S-SEDDS

The flow properties of S-SEDDS are vital in handling and processing operations because the dose uniformity and ease of filling is dictated by the powder flow properties. In general, three types of flow measurements can be used to evaluate the nature of powder flow i.e. angle of repose; Carr's index and Hausner's ratio and the results were depicted in table 7. The smaller the value of the angle of repose, lesser the internal friction or cohesion between the particles and greater the flow characteristics and vice-versa. As per general rule, powders having θ>50 ° have unsatisfactory difficult flow properties and those are having θ value between 25–40 ° have reasonable flow potential, whereas minimum angles close to 25 ° represent very good flow properties.

The results exhibit a small angle of repose (around 30 °) which assure passable flow properties for S-SEDDS formulation. In addition to the angle of repose, Carr's index and Hausner's ratio were also less than 27.1±0.53 and 1.37±0.15 respectively ensuring acceptable flow for S-SEDDS formulation (table 7).

***In vitro* dissolution studies**

To understand the release behavior of ramipril from S-SEDDS and pure drug, *in vitro* dissolution test was performed and the cumulative percentage of drug release profiles were depicted in fig. 1. The amount of ramipril released from S-SEDDS was 97.29±2.9 % in 60 min and was significantly higher compared to the pure drug (51.43±2.2%) ($p<0.05$) (table 8).

Table 8: *In vitro* dissolution profile of ramipril S-SEDDS and pure drug (mean±SD, n=3)

Time(min)	Pure drug (% release)	S-SEDDS (% release)
0	0	0
15	15.24±3.0	31.67±2.8
30	26.19±2.9	51.13±2.6
45	38.57±2.4	75.11±3.0
60	51.43±2.2	97.29±2.9

Table 9: Dissolution parameters of ramipril from S-SEDDS and pure drug in SGF (pH 1.2)

Formulation	Q_{15}	Q_{60}	DE_{60}	RDR
Pure drug	15.25±3.0	51.43±2.2	26.43±1.1	--
S-SEDDS	31.67±2.8*	97.29±2.9*	51.64±2.1*	1.95±0.22*

Each data expressed as mean±SD; n=3, -Q15 and Q60 indicate percent drug release in 15 and 60 min respectively., -DE, RDR indicate dissolution efficiency and relative dissolution rate respectively., -*, ** and *** indicate significant difference at p<0.05, p<0.01 and p<0.001respectively vs. pure drug.

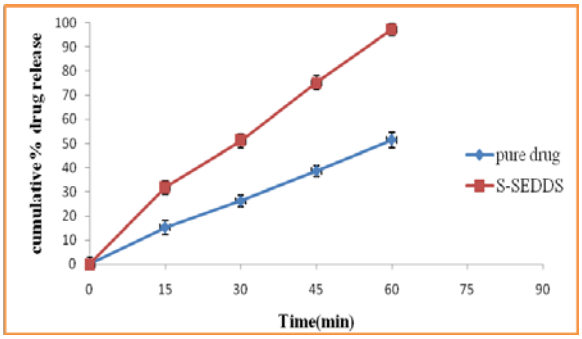

Fig. 1: *In vitro* dissolution profiles of ramipril from S-SEDDS formulation and pure drug (mean±SD; n=3)

Determination of dissolution parameters

The dissolution efficiency of insoluble drug ramipril has been significantly improved when formulated into S-SEDDS (table 9) (P<0.05).

This might be due to the enhanced solubility of ramipril because of the enormous increase in effective surface area due to the presence of surfactants used in the formulation and transformation of the crystalline state of the drug to an amorphous state. Further these results were consistent with the PXRD studies. Overall a twofold improvement in the dissolution was observed with S-SEDDS formulation with respect to pure drug.

Surface morphological analysis of S-SEDDS

The surface morphology of the pure drug (ramipril), sylysia and S-SEDDS were examined by SEM and the images are represented in fig 2. The typical crystalline structures of ramipril as shown in fig. 2A were absent in S-SEDDS which indicates the transformation of the drug to amorphous or molecular state. Further, the granular and porous structure of sylysia as evident in fig. 2B was unclear in S-SEDDS because of the deposition of liquid formulation (L-EDDS-S9) on the surface of sylysia as seen in fig. 2C.

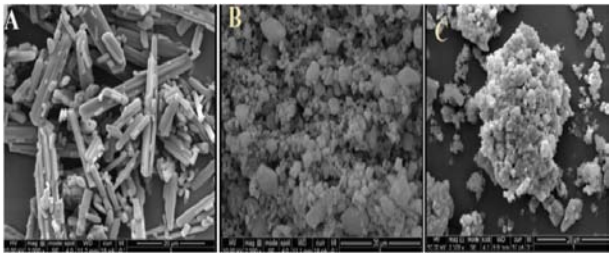

Fig. 2: SEM images of A) ramipril B) sylysia and C) S-SEDDS

Differential scanning calorimetry

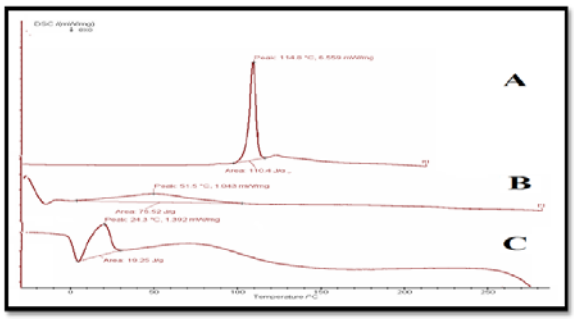

Fig. 3: DSC thermograms of A) ramipril B) sylysia and C) S-SEDDS

The thermotropic behavior and the physical state of the drug in S-SEDDS were evaluated by performing DSC analysis. Fig. 3 illustrates the DSC thermograms of ramipril, sylysia and S-SEDDS. The phase transition peak for the pure drug at 114.8 °C with an enthalpy of 110.4 J/g reveals the crystalline nature of ramipril (fig. 3A). Sylysia which was used as a carrier exhibited a broad endothermic peak which indicates the amorphous nature (fig. 3B). The absence of conspicuous peak in S-SEDDS formulation over the melting range of ramipril unravels the transformation of the physical state of the drug (crystalline to amorphous) which was further confirmed by PXRD analysis (fig. 3C).

Powder X-ray diffraction studies

The PXRD patterns of ramipril, sylysia FCP and S-SEDDS were represented in fig. 4. The pure drug showed numerous characteristic high-intensity diffraction peaks at 2θ of 19.3, 26.1, 36.2, 38.8, 39.7, 40.7, 55.2 and 83.2 demonstrating the crystalline nature of the drug (fig. 4A). The sylysia FCP exhibited diffuse peaks (fig. 4B) as indicative of amorphous state, and the disappearance of characteristic peaks of ramipril in S-SEDDS formulation indicates the absence of crystallinity (fig. 4C).

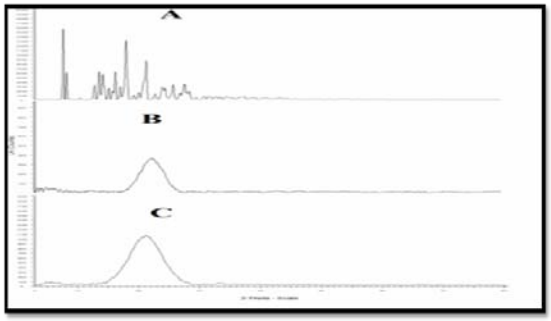

Fig. 4: Powder X-ray diffraction patterns of A) ramipril B) sylysia and C) S-SEDDS

Fourier transform infrared spectroscopy

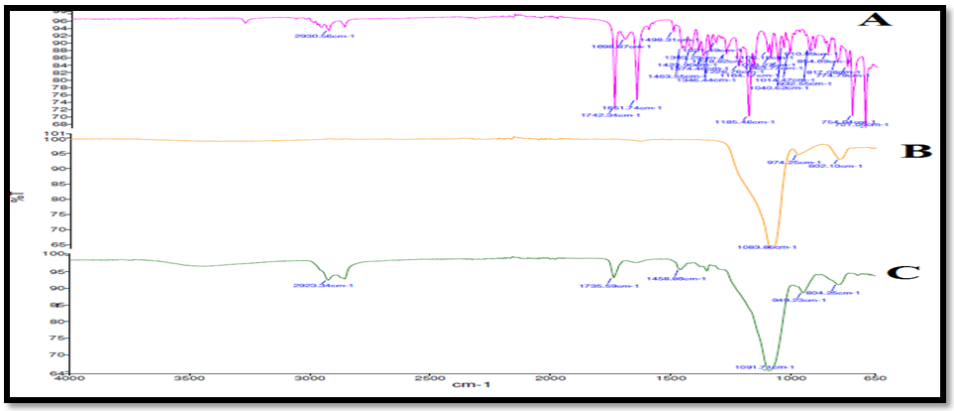

Fig. 5: FT-IR spectra of A) ramipril B) sylysia and C) S-SEDDS

Fig. 5 illustrates the FT-IR spectra of ramipril, sylysia and S-SEDDS formulation. The pure drug ramipril exhibit characteristic peaks at 2930 cm^{-1} (COOH-stretching), 1742 cm^{-1}(NH-stretching), 1698 cm^{-1}(C=O-stretching) (fig. 5A). The peaks at 1083 cm^{-1} were characteristic to that of sylysia (fig. 5B). Decrease in intensity of peaks at 2923, 1735 and 1691 cm^{-1} was observed in S-SEDDS. This slight shift was obtained due to processing parameters of the formulation. Hence, the presence of peaks at respective wave numbers and absence of extra peaks suggest that there was no possible chemical interaction between the drug and ingredients used in the formulation (fig. 5C).

CONCLUSION

The main intention of the present research work was to develop stable solid SEDDS of ramipril in order to enhance solubility as well as dissolution rate of this highly lipophilic drug. The optimised S9 L-SEDDS have shown good clarity, the spontaneity of emulsification and good stability. Finally, ramipril loaded S-SEDDS was successfully prepared by adsorption of optimized formulation on to sylysia which showed good flow properties. SEM, DSC, PXRD studies suggested that ramipril in S-SEDDS exist in amorphous state. FTIR studies proved no significant drug-excipient interaction. Prepared S-SEDDS showed significantly higher dissolution efficiency compared to that of pure drug. Ramipril loaded S-SEDDS preserved the self-emulsification performance of the liquid SEDDS. S-SEDDS formulation was encapsulated in hard gelatin capsules and this may provide a useful solid dosage form for ramipril.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest

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