ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2015; 6(6): 10 - 17

RESEARCH ARTICLE

Development and Characterization of Ramipril Loaded Solid self Nanoemulsifying Drug Delivery System (SNEDDS) for Improved Oral Delivery of Lipophilic Drugs

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Received 18 Aug 2015; Revised 09 Nov 2015; Accepted 21 Nov 2015

ABSTRACT

SNEDDS are lipid based liquid formulations which are defined as self nanoemulsifying drug delivery systems (SNEDDS) that offer potential vehicle for improved oral delivery of poorly water soluble and low bioavailable drugs. The primary goal of the present work was to formulate solid SNEDDS (S-SNEDDS) in order to improve the solubility of highly lipophilic drug Ramipril. The main intention behind choosing SNEDDS formulation for Ramipril was that lipid based formulations enhance solubility of lipophilic drugs and as a result dissolution rate and absorption may be further enhanced. SNEDDS are generally liquid form preparations obtained by homogenously mixing drug along with oils, surfactants and co-surfactants using cyclomixer. After screening various vehicles for solubility studies, Capmul MCM C8, Gelucire 50/13 and Transcutol P were selected as oil, surfactant and co-surfactant respectively in order to prepare ramipril loaded SNEDDS. Nine different liquid SNEDDS (L-SNEDDS) formulations were prepared and subjected to various evaluation tests. Out of these nine different L-SNEDDS**,** L-SN9 formulation was optimized as it formed thermodynamically stable emulsion without any drug precipitation and phase separation on storage and also showed least globule size (22.5nm).This optimized formulation, was loaded on to inert carrier (Sylysia FCP 350) to obtain solid SNEDDS (S-SNEDDS). They were further processed for solid state characterization such as PXRD, SEM and the results confirmed the transformation of native crystalline nature of drug to amorphous state. FTIR analysis was also performed and showed no drug-excipient interaction. Finally, Ramipril loaded S-SNEDDS formulation was successfully prepared, encapsulated in hard gelatin capsules and this formulation proved to have improved solubility for Ramipril.

Key words: Liquid self nanoemulsifying drug delivery system (L-SNEDDS), solid self nanoemulsifying drug delivery system (S-SNEDDS), emulsification time, zeta potential, *in vitro* dissolution.

INTRODUCTION

Therapeutic effectiveness of a drug mainly depends on the bioavailability of drug which ultimately upon the solubility of drug molecules. Over decades oral route was considered to be the 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 presentation of the drug as a solubilizate within a colloidal dispersion [2]. Solubility is important key parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. BCS 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 order to improve solubility of drug.

Recently lipid and surfactant based systems such as lipid solutions, surfactant dispersions, emulsions, liposomes, microemulsions, dry emulsion and self- (micro) emulsifying

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formulations have been developed to improve bioavailability of poorly soluble drugs. Apart from them, self nanoemulsifying drug delivery systems (SNEDDS) is one which is applicable for enhancing bioavailability of poorly water soluble compounds. 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. SNEDDS are isotropic mixtures comprising of drug along with oil, surfactant, co-surfactant and sometimes contain co-solvents which emulsify spontaneously upon mild agitation and dilution with aqueous media to produce 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 100-300nm, whereas SNEDDS form transparent/clear emulsions with bluish tinge having droplet size less than 50nm. 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]**.** Despite the potential of SNEDDS in improving bioavailability of poorly soluble drugs few limitations remain to be unresolved for the delivery system which includes stability, interaction of the fill with the capsule shell and storage temperature [6]. Many techniques were employed for conversion of liquid to solid SNEDDS such as adsorption to solid carriers, spray drying, freeze drying, melt granulation, extrusion/spheronization, rotary evaporation, high pressure homogenization, etc. Hence the current research is focused in the conversion of liquid SNEDDS (L-SNEDDS) to solid SNEDDS (S-SNEDDS) by adsorbing onto an inert carrier.

Ramipril {(2S,3aS,6aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl] amino]-1-oxopropyl] octahydrocyclopenta [b]pyrrole-2-carboxylic acid}, is a potent antihypertensive drug, belonging to category of ACE inhibitor which is used to treat high blood pressure, congestive heart failure. Ramipril belongs to BCS Class II having very low water solubility of 3.5mg/L. Ramipril is highly lipophilic drug having log P (octanol/water) value of 3.32. The half life of Ramipril is 2 hours which is very low which results into poor bioavailability after oral administration. Poor water solubility resulted in erratic absorption in GIT which further lead to low bioavailability of about 28%. The main intention behind choosing SNEDDS formulation for Ramipril drug was that lipid based formulations enhance 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 as S-SNEDDS.

MATERIALS AND METHODS

MATERIALS

Ramipril was a generous gift sample from Ranbaxy Laboratories, Dewas, India. Gelucire 50/13, Transcutol-P, Labrafil M1944CS , Labrafil M2125CS, Capryol 90 , Labrasol® were obtained as gift samples from Gatteffose, France. Captex-200 , Captex-355, Capmul® PG 8 NF, Capmul® MCM C8, Acconon E were kind gift samples from ABITEC Corporations, Cleveland, USA. Purified soybeanoil 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 solubility of Ramipril in various vehicles like oils, surfactants and co-surfactants was determined by addition of excess amount of Ramipril to vial containing 2 ml of the selected vehicle. The components in glass vial were mixed gently by stirring and then vortexed using a cyclomixer until drug completely dissolved in the vehicle at 37ºC. Later it was kept in rotary shaker and constantly agitated at room temperature for 48h (Remi equipments, Mumbai, India). After reaching equilibrium, samples were centrifuged at 10,000 rpm for 15 min. The supernatant was suitably diluted with methanol and Ramipril content was quantified using UV-VIS spectrophotometer at 210 nm.

Formulation of L-SNEDDS:

Liquid SNEDDS formulations of Ramipril were prepared using vehicle which was selected as oil, surfactant and co-surfactant based on solubility study results. All the components were vortexed

using cyclomixer until homogenous mixture was obtained. The obtained L-SNEDDS formulations were stored at room temperature until used.

Characterization of L-SNEDDS:

Evaluation of self-emulsification time and stability:

The self-emulsifying properties of SNEDDS formulations were performed by visual assessment [7]. For this about 100 µl of SNEDDS formulation was added drop wise to beaker containing about 300 ml SGF at 37°C.The beaker was placed on magnetic stirrer and the contents were kept under continuous stirring (~100 rpm) using magnetic bead. The time taken for the emulsion formation for each formulation was noted as the self-emulsification time. In order to determine stability of SNEDDS, the formed emulsion was stored at 37°C and observed for phase separation and drug precipitation, if any for 48 h [8]. The stable SNEDDS 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 polydispersity index(PI) of emulsions formed from stable SNEDDS formulations were determined by photon correlation spectroscopy using zetasizer 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-SNEDDS:

The optimized L-SNEDDS formulation was finally selected for conversion into S-SNEDDS by the process of physical adsorption using Sylysia FCP 350 as inert carrier. A fixed weight i.e. 250mg of L-SNEDDS formulation (equivalent to single dose) was initially taken in china dish and 100 mg of Sylysia FCP 350 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 [9].

Characterization of S-SNEDDS:

Flow properties of S-SNEDDS:

The flow properties or rheological characteristics of S-SNEDDS 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 fixed funnel method. The Carr's compressibility index and Hausner's ratio were calculated from the bulk and tapped density of the S-SNEDDS which were obtained by using USP Type I Tap Density Tester apparatus using 10ml measuring cylinder.

The angle of repose (θ) was calculated using the following formula:

$$\theta = \tan^{-1} H/R$$

where; θ= angle of repose, H = height of pile and R = radius of pile

The bulk density and tapped density were calculated in g/ml, using the formula:

Bulk Density (BD) = Weight of powder / Bulk volume

Tapped Density (TD) = Weight of powder / Tapped Volume

The compressibility Index and the Hausner's Ratio were calculated using following formula:

Carr's Compressibility Index (CI) = (TD-BD) / TD X 100

Hausner's Ratio= TD / BD

***In vitro* dissolution studies:**

In vitro dissolution study of S-SNEDDS and pure drug was performed using USP type II (paddle) apparatus (Electrolab, TD L8, Mumbai, India) in simulated gastric fluid (pH 1.2) without enzyme. The volume of dissolution medium used was 500 ml, paddle speed was set at 50 rpm and 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 medium (SGF) to maintain constant volume and also to provide sink condition. The samples were analyzed spectrophotometrically at 210nm to detect amount of drug released at each sampling point.

Surface morphological analysis of S-SNEDDS:

The surface morphology of Ramipril, Sylysia and S-SNEDDS 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.

Powder X-ray diffraction studies:

The PXRD patterns of pure drug, Sylysia and S-SNEDDS 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 transform infrared spectroscopy:
Infrared spectra of Ramipril, Sylysia and S-SNEDDS formulation were obtained using FT-IR spectrophotometer (Paragon 1000, PerkinElmer, 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 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 MCM C8, Gelucire 50/13 and Transcutol-P have shown the highest solubility and hence they were selected as oil, surfactant and co-surfactant respectively.

Formulation of L-SNEDDS:
L-SNEDDS formulations were prepared using Capmul MCM C8, Gelucire 50/13 and Transcutol P as oil, surfactant and co-surfactant respectively based on solubility study results. Initially, single dose of Ramipril comprising 2.5 mg drug was accurately weighed and dissolved in calculated amount of oil, surfactant and co-surfactant in glass vial. Here nine L-SNEDDS formulations were prepared and coded as L-SN1, L-SN2, L-SN3, L-SN4, L-SN5, L-SN6, L-SN7, L-SN8 and L-SN9 as shown in (**Table 2**).

Characterization of L-SNEDDS:

Evaluation of self-emulsification time and stability:
The efficiency of self emulsifying systems will be assessed from the rate of emulsification up on hydration with mild agitation [7]. Surfactant systems in SNEDDS formulation will reduce interfacial tension between oil and aqueous phases resulting in easy dispersion and formation of o/w emulsion. Self emulsification time of all L-SNEDDS was shown in the (**Table 3**).

The point to be noticed here that with the increase in oil proportion there was decrease in rate of emulsification and increase in emulsification time. With the increase in interfacial tension between oil and aqueous phase and decrease in concentration of surfactant system, higher will be the emulsification time and lower will be rate of emulsification.

The formulations L-SN3, L-SN6, L-SN8 and L-SN9 formed stable emulsions without any phase separation and precipitation of drug up on standing at room temperature for 48 h (**Table 4**). Thus these formulations were processed for further characterization.

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 L-SN3 to L-SN9, globule size was significantly decreased (**Table 5**). This resulted because of increased surfactant concentration and decreased oil concentration from L-SN3 to L-SN9. High surfactant ratio 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 of emulsion. Negative zeta potential values also enable long circulation half life *in vivo* as described by Jung [10].

Formulation L-SN9 showed a least globule size with negative zeta potential when dispersed in SGF. Polydispersibility index of L-SN3, L-SN6, L-SN8, L-SN9 formulations was below 0.3 indicating homogeneous dispersion so these formulations were processed for further characterization.

Preparation of S-SNEDDS:
Physical adsorption technique using inert solid carrier was employed for the preparation of S-SNEDDS formulations. The optimized L-SN9 formulation was finally selected for conversion into S-SNEDDS. It was adsorbed onto Sylysia FCP 350 which was chosen as inert carrier for S-SNEDDS formation. 100 mg of Sylysia was added slowly to 250 mg of L-SN9 formulation, initially taken in china dish, mixed thoroughly and then passed through sieve no. 120 to get uniform size mass.

Characterization of S-SNEDDS:
Flow properties of S-SNEDDS:
The rheological properties of S-SNEDDS 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 6**). The smaller the value of angle of repose, lesser is the internal friction or cohesion between the particles and greater the flow characteristics. As per general rule, powders having $\theta>50°$ have unsatisfactory difficult flow properties and those having θ value between 25–40° have reasonable flow potential, whereas those having angles $\theta<25°$ represent very good flow properties.

The results exhibit small angle of repose (around 30°) which assure passable flow properties for S-SNEDDS formulation. In addition to angle of repose, Carr's index and Hausner's ratio were also 28.1±0.52 and 1.34±0.12 respectively ensuring acceptable flow for S-SNEDDS formulation (Table 6).

***In vitro* dissolution studies:**

To understand the release behavior of Ramipril from S-SNEDDS and pure drug, *in vitro* dissolution test was performed and the cumulative percentage drug release profiles were depicted in (**Fig 1**). The amount of Ramipril released from S-SNEDDS was 98.11±2.9% in 60 min which was significantly higher compared to that of pure drug (52.43±2.2%) ($p<0.05$) (**Table 7**).

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

Surface morphological analysis of S-SNEDDS:

The surface morphology of the pure drug (Ramipril), Sylysia and S-SNEDDS 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-SNEDDS which indicates the transformation of drug from crystalline to amorphous or molecular state. Further, the porous and granular nature of Sylysia which was evident in (**Fig 2B**) was unclear in S-SNEDDS because of the deposition of liquid formulation (L-SNEDDS-S9) on the surface of Sylysia as seen in (**Fig 2C**).

Powder X-ray diffraction studies:

The PXRD patterns of Ramipril, sylysia FCP and S-SNEDDS were depicted in (**Fig 3**). The pure drug showed numerous characteristic high intensity diffraction peaks at 2theta values 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 3A**). The sylysia FCP exhibited diffuse peaks (**Fig 3B**) which is indicative of amorphous state and the disappearance of characteristic peaks of Ramipril in S-SNEDDS formulation indicates the absence of crystallinity of drug (**Fig 3C**).

Fourier transform infrared spectroscopy:

(**Fig 4**) illustrates the FT-IR spectra of Ramipril, Sylysia and S-SNEDDS 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 4A**). The peaks at 1083 cm^{-1} were characteristic to that of Sylysia (**Fig 4B**).Decrease in intensity of peaks at 2923, 1735 and 1691 cm^{-1} was observed in S-SNEDDS. This slight shift was obtained as a result of processing parameters of 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 excipients used in formulation (**Fig 4C**).

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	73 ± 1.5
2	Capmul PG8NF	55 ± 2.0
3	Labrafil M 1944 CS	33 ± 1.0
4	Labrafil M 2125 CS	45 ± 2.0
5	Captex 355	3 ± 0.9
6	Captex 200	6 ± 0.8
7	Capryol 90	12 ± 1.6
8	Cremophore EL	22 ± 1.0
9	Soybean oil	14 ± 1.6
Surfactants		
10	Gelucire 50/13	66 ± 1.0
11	Tween 80	51 ± 0.5
12	Acconon-E	9 ± 0.6
13	Labrasol	21 ± 0.5
Co-surfactants		
14	Transcutol-P	60 ± 1.0
15	TPGS -E	16 ± 0.5

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

L-SNEDDS Formulation Code	Oil: Smix ratio	Surfactant : co-surfactant (Smix)	Oil (mg)	Surfactant (mg)	Cosurfactant (mg)	Drug (mg)
L-SN 1	1:1	1:1	123.75	61.875	61.875	2.5
L-SN 2	1:3	1:1	61.875	92.8125	92.8125	2.5
L-SN 3	1:5	1:1	41.25	103.125	103.125	2.5
L-SN 4	1:1	3:1	123.75	92.8125	30.9375	2.5
L-SN 5	1:3	3:1	61.875	139.21875	46.40625	2.5
L-SN 6	1:5	3:1	41.25	154.6875	51.5625	2.5
L-SN 7	1:1	5:1	123.75	103.125	20.625	2.5
L-SN 8	1:3	5:1	61.875	154.6875	30.9375	2.5
L-SN 9	1:5	5:1	41.25	171.875	34.375	2.5

Table 3: Self-emulsification time assessment of Ramipril SNEDDS (mean ± SD, n=3).

L-SNEDDS Formulation Code	Self-emulsification time (sec)
L-SN 1	45 ± 3.0
L-SN 2	37 ± 2.0
L-SN 3	30 ± 2.0
L-SN 4	26 ± 2.0
L-SN 5	21 ± 1.0
L-SN 6	18 ± 3.0
L-SN 7	15 ± 2.0
L-SN 8	12 ± 2.0
L-SN 9	9 ± 2.0

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

L-SNEDDS Formulation Code	Phase separation	Drug Precipitation
L-SN 1	yes	no
L-SN 2	yes	no
L-SN 3	no	no
L-SN 4	yes	no
L-SN 5	yes	no
L-SN 6	no	no
L-SN 7	yes	no
L-SN 8	no	no
L-SN 9	no	no

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

L-SNEDDS Formulation Code	Z average (nm)	Zetapotential (mV)	P.I
L-SN3	200.8	-4.16	0.237
L-SN6	126.75	-4.34	0.254
L-SN8	65.2	-4.49	0.276
L-SN9	22.5	-4.68	0.297

Table 6: Micromeritics of Ramipril loaded S-SNEDDS (mean ± SD, n=3)

Formulation Code	Angle of repose (θ)	Carr's index	Hausner's ratio
S-SNEDDS	33.6±1.5	28.1±0.52	1.34±0.12

Table 7: *In vitro* dissolution profile of ramipril S-SNEDDS and pure drug (mean ± SD, n=3)

Time(min)	Pure drug(%release)	S-SNEDDS(%release)
0	0	0
15	16.24±3.0	30.67±2.8
30	27.19±2.9	49.13±2.6
45	39.57±2.4	74.11±3.0
60	52.43±2.2	98.11±2.9

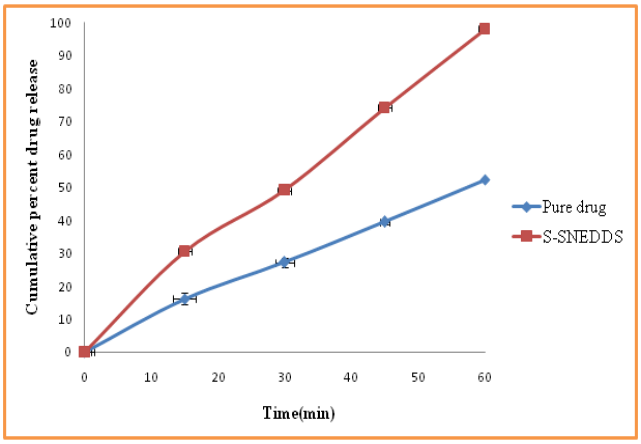

Fig 1: *In vitro* dissolution profiles of Ramipril from S-SNEDDS formulation and pure drug (mean ± SD; n=3)

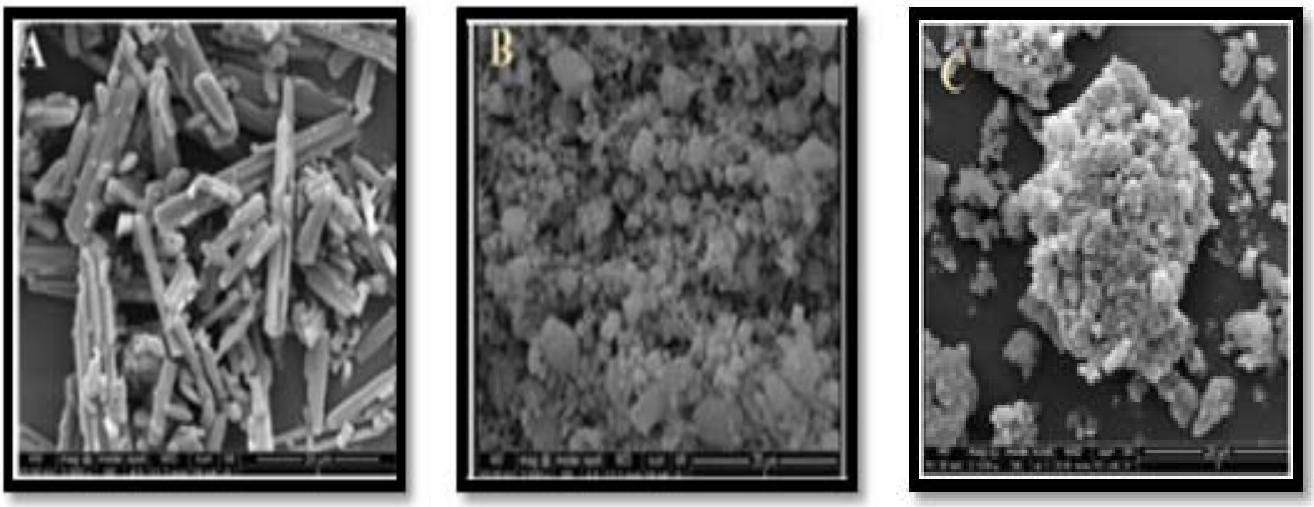

Fig 2: SEM images of A) Ramipril B) Sylysia FCP 350 and C) S-SNEDDS

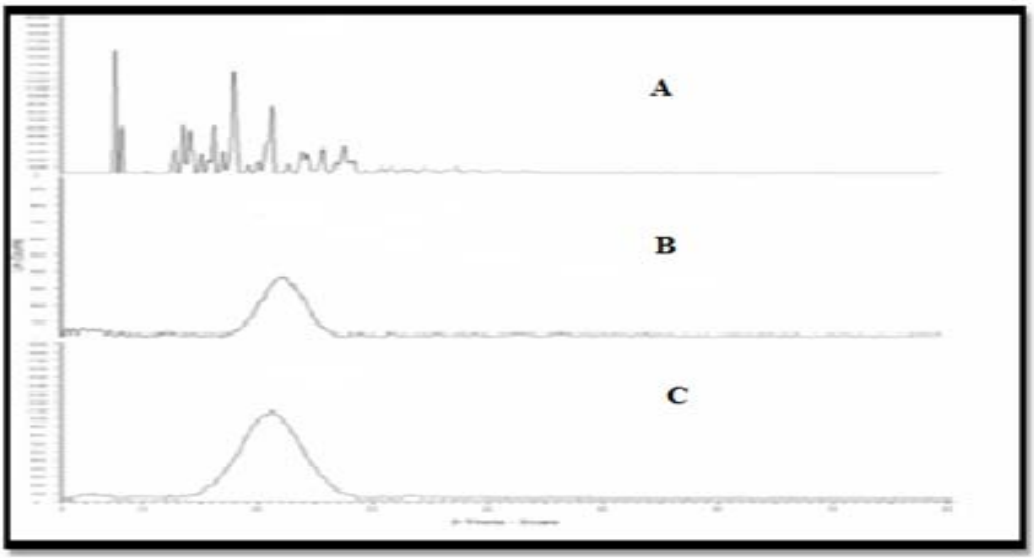

Fig. 3: Powder X-ray diffraction patterns of A) Ramipril B) Sylysia FCP 350 and C) S-SNEDDS

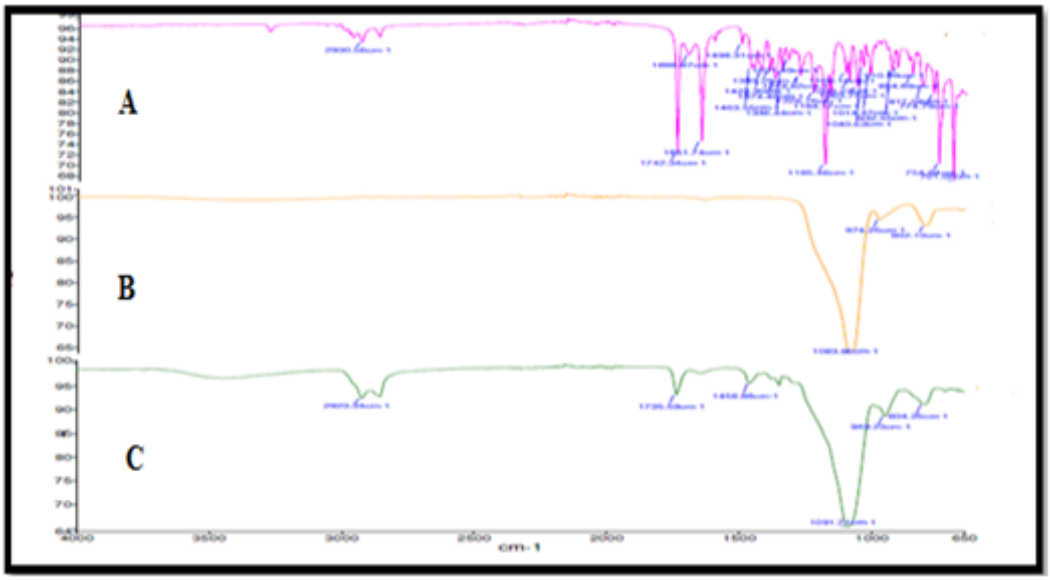

Fig 4: FT-IR spectra of A) Ramipril B) Sylysia FCP 350 and C) S-SNEDDS

CONCLUSION

The main intention of the present research work was to develop stable solid SNEDDS of Ramipril in order to enhance solubility as well as dissolution rate of this highly lipophilic drug. The optimised L-SNEDDS (L-SN9) formulation has shown good clarity, spontaneity of emulsification and good stability. Finally Ramipril loaded S-SNEDDS formulation 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-SNEDDS exist in amorphous state. FTIR studies proved no significant drug-excipient interaction. Prepared S-SNEDDS showed significantly higher dissolution efficiency compared to that of pure drug. Ramipril loaded S-SNEDDS preserved the self-emulsification performance of the liquid SNEDDS. S-SNEDDS formulation was successfully prepared and encapsulated in hard gelatin capsules, finally this may provide a useful solid dosage form for Ramipril drug.

ACKOWLEDGEMENT

The author is grateful to Department of Pharmaceutics, St. Peter's Institute of Pharmaceutical Sciences for providing the facilities to perform research work**.**

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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