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Original Article

SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM OF RAMIPRIL: FORMULATION AND *IN VITRO* EVALUATION

KASTURI MADHAVI[1*], AGRAWAL SHIKHA[1], JANGA KARTHIK YADAV[2]

[1]Department of Pharmaceutics, Swami Vivekanand College of Pharmacy, Indore 452020, Madhya Pradesh, India, [2]Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal 506009, Telangana, India
Email: madhavi2386@gmail.com

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ABSTRACT

Objective: The primary goal of the present work was to formulate and evaluate self-nano emulsifying drug delivery systems (SNEDDS) of ramipril in order to improve the solubility of this highly lipophilic antihypertensive drug.

Methods: SNEDDS are generally liquid form preparations obtained by homogeneously mixing drug substance with oils, surfactants and co-surfactants using cyclomixer. Based on solubility studies Capmul PG8 NF, Gelucire 44/14 and Transcutol P were selected as oil, surfactant and co-surfactant respectively in order to prepare SNEDDS. Nine different SNEDDS formulations were prepared and subjected to various evaluation tests in order to obtain optimized SNEDDS formulation.

Results: The SNEDDS formulations with 16.5-24.75 % of oil, 24.75-68.75 % of surfactant and 12.375-41.25 % of co-surfactant formed thermodynamically stable emulsion with droplet size ranging from 22.6-188.8 nm. Finally, out of 9 different SNEDDS formulations, SN9 formulation was optimized containing 16.5 % of oil, 68.75 % of surfactant and 13.75 % of co-surfactant as it formed a thermodynamically stable emulsion with least globule size (22.6 nm) and without any drug precipitation or phase separation.

Conclusion: Finally, stable, optimized SNEDDS formulation of ramipril was successfully prepared that showed significant improvement in the rate of dissolution of ramipril.

Keywords: Self nano emulsifying drug delivery system (SNEDDS), Ramipril, Emulsification time, Ternary phase diagram, Simulated Gastric Fluid (SGF).

INTRODUCTION

Over decades, the oral route is considered as the easiest and most preferred route of drug administration for the chronic treatment of many diseases. Despite the unique advantages of oral drug delivery, the majority of prospective and existing drug molecules pose a challenge to the pharmaceutical scientist limiting their potential uses and increasing the difficulty of formulating low bioavailable products [1]. There are several constraints responsible for this, but a particularly widespread problem is poor absorption due to slow and/or incomplete drug dissolution in the lumen of the gastrointestinal tract and systemic metabolism by the gut wall and hepatic enzymes [2, 3]. In this case, improved bioavailability can be achieved by the use of delivery systems which can enhance the rate and/or the extent of drug solubilizing into aqueous intestinal fluids.

Drugs belonging to BCS class II and IV have motivated the formulators for the development of drug delivery technologies to overcome the difficulty in their solubilization by either chemical or mechanical modification of the environment surrounding the drug substance, or physically altering the macromolecular characteristics of aggregated drug particles. Various traditional approaches for solubility enhancement include micronization, solid dispersions and inclusion complexes [4-7]. In the recent past, colloidal carriers like solid-lipid nanoparticles [8, 9], also lipid and surfactant based systems such as lipid nanocapsules [10, 11], nanoemulsions [12, 13], microemulsions [14, 15] and nano vesicular systems such as liposome [16, 17] or noisome [18] are being explored for oral delivery of drugs. Apart from them recently, self-nano emulsifying drug delivery systems (SNEDDS) have shown great assurance for enhancing bioavailability of poorly soluble compounds such as vinpocetine, carvedilol, zaleplon, repaglitinide etc.

SEDDS (self-emulsifying drug delivery systems) belong to lipid-based formulations and has proved to be 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 (API) and sometimes contain co-solvents which emulsify spontaneously upon mild agitation and upon dilution with aqueous media to produce a fine oil-in-water emulsion. Whereas, SNEDDS are defined as self-nano emulsifying drug delivery system in which the globule size of formed emulsion ranges in a few nanometers(<50 nm). They readily spread in the GIT motility (stomach and intestine) that provide the agitation necessary for self-emulsification. 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 [19]**.** 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 [20].

Ramipril {(2S, 3aS, 6aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl] amino]-1-oxopropyl] octahydrocyclopenta [b] pyrrole-2-carboxylic acid}, a potent antihypertensive drug, belonging to the category of ACE inhibitor is widely used in the treatment of high blood pressure and congestive heart failure. Ramipril is highly lipophilic [log P (octanol/water), 3.32)], poorly water soluble (3.5 mg/l) drug belonging to BCS Class II. Ramipril, being poorly water soluble resulted in erratic absorption in GIT which further lead to poor bioavailability (about 28 %). It also showed high first pass metabolism. Hence, increasing the aqueous solubility and dissolution of ramipril in GIT is of therapeutic importance. The main intention behind choosing SNEDDS formulation for ramipril drug was that lipid-based formulations enhance the solubility of lipophilic drugs that may further enhance the dissolution rate and absorption in the GIT. Hence, the main objective of current research work was to develop SNEDDS of ramipril in order to enhance the solubility of the drug.

MATERIALS AND METHODS

Materials

Ramipril was a generous gift sample from Ranbaxy Laboratories, Dewas, India. Transcutol-P, Labrafil M1944CS, Labrafil M2125CS, Gelucire 44/14, Capryol 90, Labrasol and Maisine were obtained as gift samples from Gatteffose, France. 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. Tween 80 was supplied by Merck, Mumbai, India. TPGS-E was supplied by BASF Corporation, U. S. A and 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 were determined by addition of an excess amount of ramipril to a glass vial containing 2 ml of the selected vehicle. The contents were vortexed using a cyclomixer until drug completely dissolved in the vehicle at 37 °C, then kept in a rotary shaker (Remi equipment, Mumbai, India) and constantly agitated at room temperature for 48h. After reaching equilibrium, samples were centrifuged at 10,000 rpm for 15 min and then the supernatant solution (100 µl) was suitably diluted with methanol. The amount of ramipril was quantified using UV-VIS spectro-photometer at 210 nm.

Preparation of SNEDDS

SNEDDS formulations were prepared by dispersing ramipril into the mixture of oil, surfactants and co-surfactants those selected based on solubility studies. The contents were initially mixed by gentle stirring and then subjected to vortex mixing at 37 °C using cyclomixer until the homogenous isotropic mixture was obtained. The obtained SNEDDS were kept at room temperature until used.

Evaluation of SNEDDS

Evaluation of self-emulsification time and stability

Self-emulsifying properties of SNEDDS formulations were performed by visual assessment [21]. For this, about 100 µl of SNEDDS formulation was added dropwise to a beaker containing about 300 ml SGF at 37 °C which was kept under continuous stirring (~100 rpm) using magnetic stirrer. The time taken for the emulsion formation for each formulation was recorded. In order to determine the stability of SNEDDS, the formed emulsion was stored at 37 °C and observed for phase separation and precipitation of the drug, if any for 48 h [22]. The stable SNEDDS formulations were selected and subjected to further characterization.

Thermodynamic stability studies

The formulations were subjected to heating-cooling, centrifugation, and freeze-thaw cycle, where the physical appearances of the formulations were observed at the end of each testing. In heating cooling, all nine formulations were heated at 45 °C and then cooled to 4 °C, with the duration of 24 h at each temperature, for 2 cycles. Then, formulations which passed the heating-cooling cycles were subjected to centrifugation at 3500 rpm (temp 18 °C) for 15 min using REMI Cooling Centrifuge, and the extent of phase separation was monitored. [23]. Finally, only formulations which passed the previous two steps were stored at alternating temperature of-21 °C and 25 °C, with storage at each temperature for not less than 48 h was done for the formulations using REMI Quick Freezer, for 2 cycles [23].

Cloud point measurement

The cloud point measurement was carried out for the formulations as reported earlier [24]. About 50 µl of stable SNEDDS was added to 300 ml of SGF and emulsion was obtained *in vitro* by using magnetic stirrer. From which, 10 ml of the emulsion sample was taken and heated with a gradual rise in temperature. The cloud point was determined by visual inspection of cloudy appearance in emulsions at a particular temperature.

Robustness to dilution

SNEDDS formulations were subjected to various folds of dilution i.e. 1:50, 1:100, 1:500 and 1:1000 with SGF (pH 1.2). The diluted emulsions were stored for 24 h and monitored for any physical changes such as precipitation or phase separation [25].

Ternary phase diagram

About 100µl of SNEDDS formulation was introduced into a beaker containing 300 ml SGF at 37 °C. The contents were mixed using magnetic stirrer, set at 100 rpm. The existence of SNEDDS that could self-emulsify under dilution and gentle agitation was identified from ternary phase diagrams of systems containing oil, surfactant, and cosurfactant.

Precipitation of drug and phase separation was evaluated by visual inspection of the resultant emulsion after 24 h. The formulations were then categorized as clear (transparent or translucent or transparent with bluish tinge), unclear (turbid), stable (no precipitation at the end of 24 h), or unstable (showing precipitation within 24 h) [21]. Ternary phase diagram was constructed identifying the good self-emulsifying region. Ternary phase diagram was constructed identifying the good self-emulsifying region using Tri-plot v1-4 software [26]. The experiment was conducted in triplicate and similar observations being made between the repeats.

Globule size and zeta potential analysis

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

In vitro dissolution studies

Dissolution studies were carried out using USP Type II Dissolution Apparatus (paddle type) (Electrolab, TD L8, Mumbai, India) in 900 ml of SGF (pH 1.2) without enzyme, the temperature at 37±0.5°C and paddle rotation of 50 rpm. 250 mg of formulation containing 2.5 mg of ramipril (equivalent to a single dose) was encapsulated and then installed to the dissolution medium. At predetermined time intervals 5 ml of sample was withdrawn and replenished with fresh dissolution medium (SGF) to maintain a constant volume. The samples were analyzed spectrophotometrically at 210 nm to detect the amount of drug released at each sampling point. The *in vitro* drug release data was analyzed by one-way analysis of variance (ANNOVA).

RESULTS AND DISCUSSION

Solubility Studies

The solubility of ramipril was carried out in various oils, surfactants, co-surfactants and among the excipients screened Capmul PG8 NF, Gelucire 44/14 and Transcutol-P have shown the highest solubility and hence they were selected as oil, surfactant and co-surfactant respectively. All the studies were conducted in triplicate, and the mean of three measurements was recorded. The results were depicted in fig. 1.

Preparation of SNEDDS

The selection of oil, surfactant and the co-surfactant mixture is based on the solvent properties of the vehicle that should allow the drug in solution.

SNEDDS 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. A series of self-emulsifying systems were prepared in each set with varying percent ratios of oil (16.5-49.5 %), surfactant (24.75–68.75 %) and co-surfactant (8.25–41.25 %). Here nine different SNEDDS formulations were prepared and coded as SN1, SN2, SN3, SN4, SN5, SN6, SN7, SN8 and SN9 as showed in table 1.

Capmul PG-8 NF is chemically Propylene Glycol Monocaprylate. It is lipophilic in nature, having HLB value 5-6 and is generally practiced to create stable emulsions. Gelucire 44/14 belongs to a group of poly oxy glycerides. Polyoxyglycerides (also named macrogol glycerides by EP) are a well-established class of pharmaceutical excipients for enhancing solubility and bioavailability [27, 28].

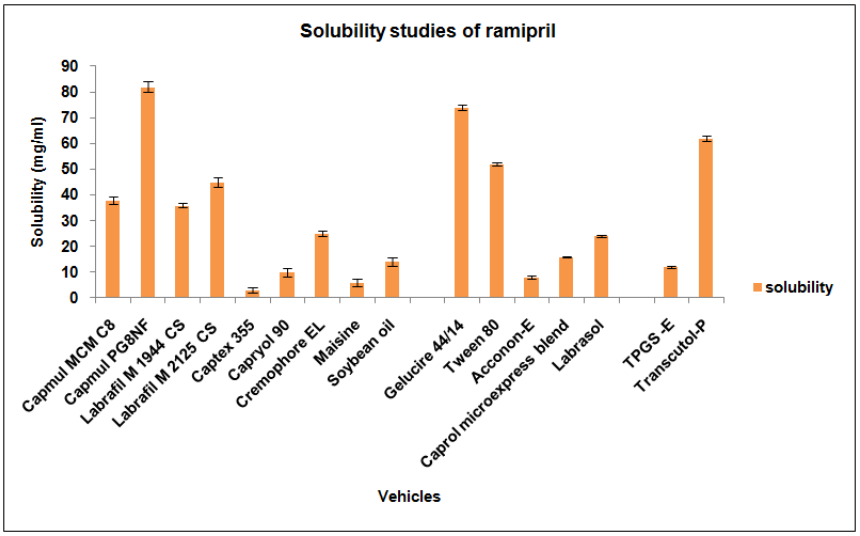

Fig. 1: Solubility studies of ramipril in different vehicles. Mean of three measurements±SD (n=3)

Table 1: Composition of ramipril SNEDDS with different ratios of oil: surfactant: co-surfactant

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

SNEDDS: Self nano emulsifying drug delivery system, S mix: ratio of surfactant to co-surfactant

Evaluation of SNEDDS

Evaluation of self-emulsification time and stability

The efficiency of self-emulsifying systems will be measured from the rate of emulsification upon hydration with mild agitation [21]. Surfactant systems in SNEDDS 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 SNEDDS formulation formulations was shown in table 2.

Table 2: Assessment of self-emulsification time of ramipril SNEDDS

SNEDDS formulation	Oil: s mix	Self-emulsification time (sec)
SN 1	1:1	44±3.0
SN 2	1:3	36±2.0
SN 3	1:5	30±2.0
SN 4	1:1	26±2.0
SN 5	1:3	21±1.0
SN 6	1:5	18±2.0
SN 7	1:1	15±1.0
SN 8	1:3	12±2.0
SN 9	1:5	8±2.0

Mean of three measurements±SD (n=3).

As the oil proportion increased from SN 9 to SN 1 formulation, there was a decrease in the rate of emulsification and increase in emulsification time. The higher interfacial tension between oil and aqueous phase and a decrease in concentration of surfactant may be in charge of the increased self-emulsification time.

The formulations SN 3, SN 6, SN 8 and SN 9 formed stable emulsions without any phase separation and precipitation of drug upon standing at room temperature for 48 h as showed in table 3. Hence, these formulations were treated for further characterization.

Table 3: Results for phase separation and precipitation of drug from ramipril SNEDDS

SNEDDS formulation	Phase separation	Drug precipitation
SN 1	yes	No
SN 2	yes	No
SN 3	no	No
SN 4	yes	No
SN 5	yes	No
SN 6	no	No
SN 7	yes	No
SN 8	no	No
SN 9	no	No

Thermodynamic stability studies

The resultant emulsions of the formulations were tested for stability at different temperature conditions and rpm. The emulsions were stable during heating and cooling cycle, centrifugation at 3500 rpm and alternative temperature cycles of-21 °C and+25 °C. SN 3, SN 6, SN 8 and SN 9 formulations did not show any phase separation and precipitation which indicated that they were stable at different temperatures and speed of centrifugation (table 4).

Table 4: Results for thermodynamic stability studies of ramipril SNEDDS under different stability conditions

SNEDDS formulation	Heating cooling cycle	Centrifugation	Freeze-thaw cycle
SN 3	P	P	P
SN 6	P	P	P
SN 8	P	P	P
SN 9	P	P	P

P=Passed

Cloud point measurement

The temperature at which cloudiness appeared was considered as the cloud point temperature. Higher cloud point values indicate higher thermal stability of emulsions formed from SNEDDS formulation. The cloud point is the temperature above which clarity of emulsion turns into turbid or unclear. In this study cloud point of stable formulations were found in the range of 64-72 °C (table 5).

Table 5: Results for cloud point measurement of ramipril SNEDDS

SNEDDS formulation	Cloud point temperature (°C)
SN 3	64±1.0
SN 6	68±1.00
SN 8	70±2.0
SN 9	72±1.0

Mean of three measurements±SD (n=3).

Since both drug solubility, as well as formulation stability, will decrease with phase separation, the cloud point temperature of the formulation should be over 37 °C. Cloud points of all formulations were very high which indicate the stability of these SNEDDS formulations towards separation in the GIT temperature which is about 37°C. The cloud point value is affected by factors such as drug hydrophobicity, kind, combination, mixing ratio and amount of each of the oils, surfactants and co-surfactants used [24, 29].

Robustness to dilution

SNEDDS formulations which were passed in previous tests were exposed to different folds of dilution in SGF in an attempt to mimic the *in vivo* conditions where the formulations would encounter gradual dilution. The resultant SNEDDS formulation was stable after dilution up to 50X, 100X, 500X, 1000X with SGF(pH1.2) and there were no signs of drug precipitation and phase separation (table 6). The clarity of dispersion might be due to a higher percentage of surfactant to oil ratio.

Ternary phase diagram

In order to determine the composition of oil and S mix (surfactant to co-surfactant) used for SNEDDS formulation, a ternary phase diagram was constructed, and the efficient emulsification region was identified. Fig. 2 illustrates the formation of a stable emulsion without any phase separation and precipitation of drug with SN3, SN6, SN8 and SN9 formulations. The emulsification time of SNEDDS formulations, the size of globules formed and the stability of the resultant emulsion when introduced into the water with mild agitation not only depend on the type of oil, surfactant, and co-surfactant combination but also on the weight percentage of oil and surfactant/co-surfactant mixture [19]. Depending on the weight percentages of lipid vehicles in stable SNEDDS formulations, phase diagram was plotted using Triplot software. Here in these four stable SNEDDS formulations i.e. SN3, SN6, SN8 and SN9 weight percentage of oil, surfactant and co-surfactant ranges from 16.5-24.75 %, 41.25-68.75 %, and 12.375-41.25 % respectively. Ternary phase diagram including oil (Capmul PG8 NF), surfactant (Gelucire 44/14) and co-surfactant (Transcutol P) was plotted each of them representing an apex of the triangle.

Table 6: Results for robustness to dilution of ramipril SNEDDS

SNEDDS formulation	Dilution factor 50	Dilutionfactor100	Dilution factor500	Dilutionfactor1000
SN 3	P	P	P	P
SN 6	P	P	P	P
SN 8	P	P	P	P
SN 9	P	P	P	P

P=Passed

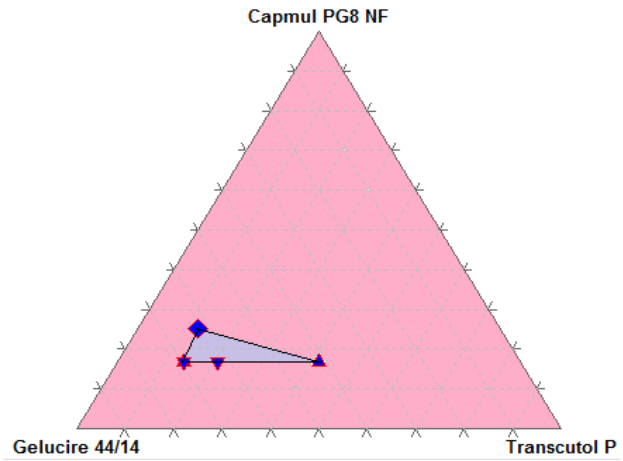

Fig. 2: Ternary phase diagram of ramipril SNEDDS with different ratios of oil: surfactant: co-surfactant

Globule size and zeta potential analysis

Since globule size is one of the prime factors which significantly contribute to the absorption of the drug, the globule size and size distribution after self-emulsification is an important parameter that has to be evaluated. Of formulations from SN3 to SN9, globule size was significantly decreased (table 7). This resulted because of the concentration of surfactant increased, and that of oil decreased from SN3 to SN9. High surfactant levels enabled rapid dispersion of globules in SGF. A surfactant having hydrophilic nature (high HLB) assists information of O/W emulsion rapidly spreading in an aqueous medium. Surfactants are amphiphilic in nature & they can dissolve or soluble relatively high amount of hydrophobic drug compound. This can prevent precipitations of the drug within the GI lumen & for prolong the existence of drug molecules. Since droplet surface area is inversely proportional to diameter, smaller lipid droplets with their associated, greater surface area are thought to facilitate digestion, resulting in more lipid and uniform drug release and absorption [30].

The higher the zeta potential, greater will be the energy barrier to coalescence between oil globules and so higher will be the stability

of the obtained emulsion. Negative zeta potential values also enable long circulation half-life *in vivo* as described by Jung [31].

Formulation SN9 showed the least globule size with negative zeta potential when dispersed in SGF. Polydispersibility index (P. I) of SN3, SN6, SN8, SN9 formulations was below 0.3 indicating homogeneous dispersion.

***In vitro* dissolution studies**

To understand the release behavior of ramipril from stable SNEDDS and pure drug, *in vitro* dissolution test was performed and the cumulative percentage of drug release profiles was depicted in fig. 3. The amount of ramipril released from stable SNEDDS formulation, SN9 was 97.65±3.1 % in 60 min and was significantly higher compared to the pure drug (50.98±2.7) ($P<0.05$) and the final results were demonstrated in table 8. This might be because of small globule size and the eventually higher surface area in case of nanoemulsions compared to that of pure drug, which permitted faster rate of drug release. The reason behind this might be the use of excellent surfactant Gelucire 44/14 (lauroyl macro glyceride) which is good solubilizer as well as a wetting agent having HLB value of 14. This property enhanced solubility and wettability of API *in vitro*. Gelucire also possesses the property of bioavailability enhancement associated with improved *in vivo* drug solubilization which facilitates absorption [32].

Table 7: Globule size and zeta potential of ramipril SNEDDS

SNEDDS formulation	Z-average (nm)	Zeta potential (mV)	P. I
SN 3	188.8	-4.26	0.238
SN 6	126.7	-4.35	0.255
SN 8	65.5	-4.48	0.278
SN 9	22.6	-4.69	0.299

P. I: Polydispersity Index

Table 8: Cumulative % drug release of ramipril SNEDDS and pure drug

Time (min)	Pure drug	SN 3	SN 6	SN 8	SN 9
0	0	0	0	0	0
15	15.45±2.3	19.76±2.4	22.54±2.7	26.32±2.7	31.78±3.3
30	26.32±2.6	30.32±2.5	35.66±2.9	42.12±2.6	51.33±3.5
45	33.52±2.9	42.32±2.1	53.44±2.4	62.22±2.5	75.45±2.8
60	50.98±2.7	62.12±3.1	71.32±2.3	84.45±2.9	97.65±3.1*

Mean of three measurements±SD (n=3)., *p<0.05 indicate significant difference compared to that of pure drug.

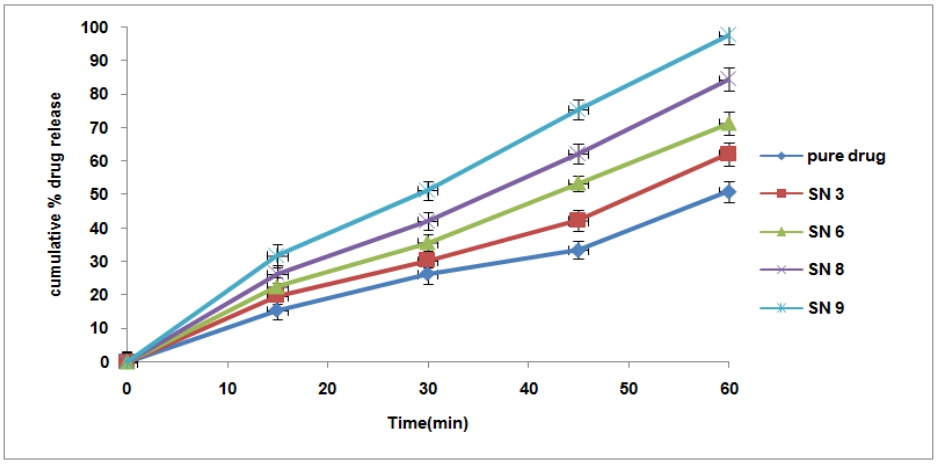

Fig. 3: Cumulative % drug release of ramipril SNEDDS and pure drug (mean±SD; n=3)

CONCLUSION

As per the plan of research work, stable self-nano emulsifying drug delivery system (SNEDDS) of ramipril was prepared successfully which showed improved solubility of the drug. The stable SNEDDS has shown good clarity, thermodynamic stability, the spontaneity of emulsification, robustness to dilution, high cloud point temperatures and good stability towards precipitation and phase separation throughout the examination. Out of which SNEDDS formulation (SN 9) proved to have a high percentage release of ramipril compared to that of pure drug and other SNEDDS formulation. Thus finally, stable SNEDDS formulation, SN 9 was selected as optimized SNEDDS formulation which showed improved solubility of the drug.

CONFLICT OF INTERESTS

Declare none

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