ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Preparation of self micro emulsifying drug delivery system(smedds) of poorly soluble drug eprosartan mesylate and its *in vitro* evaluation

Sabitri Bindhani*[1], Snehamayee Mohapatra[1], Rajat Ku. Kar[2], Utkalika Mahapatra[1]

[1]Department of Formulation and Development, School of Pharmaceutical Sciences, Siksha 'o'Anusandhan, Deemed to be University, Bhubaneswar, Odisha- 751030, India
[2]Department of Pharmaceutics, Dadhichi College of Pharmacy, Cuttack, Odisha- 754002, India

Article History:

Received on: 26.05.2019
Revised on: 14.08.2019
Accepted on: 20.08.2019

Keywords:

Eprosartan Mesylate, Poorly soluble drug, Pseudo ternary phase diagram, Self micro emulsifying drug delivery system, Solubility and dissolution rate

ABSTRACT

Eprosartan Mesylate (EM), an angiotensin II receptor blocker used in the treatment of high blood pressure. But poor solubility and bioavailability (13%) of eprosartan mesylate is a major challenging factor for improving its drug release rate. The main objective of the present work to develop and characterize self micro emulsifying drug delivery system of eprosartan mesylate by using compatible oil, surfactant and co-surfactant. For the selection of oil, surfactant and cosurfactant, solubility screening studies has been carried out. The nine formulations are prepared using peppermint oil, tween 80 and PEG 400. A pseudo ternary phase diagram was prepared to determine the self emulsion region. Four optimized formulations were prepared at 1:1 ratio(a mixture of surfactant and cosurfactant). These four formulations were evaluated for self-emulsification time, droplet size measurement, drug content analysis robustness to dilution test, viscosity analysis, f.t.i.r. The study and in-vitro diffusion studies. The ratio of scosmix (a mixture of surfactant and cosurfactant) of optimized formulation (pf5) was varied to pfa1 (2:1), pf2 (3:1), pfa3 (1:2) and compared with pure drug. The formulation having pfa1 (2:1) shown drug release of 93.13 % in 330 minutes where as pure drug showed a drug release of 54.51% in 330 minutes. So the prepared SMEDDS formulations were efficient and better than the pure drug, and it followed Korsmeyer pappes due to highest r^2 value followed by Hixon crowel. It was concluded that incorporation of eprosartan mesylate in selfmicroemulsifying system is a great potential for improving the solubility and dissolution rate of eprosartan mesylate.

*Corresponding Author

Name: Sabitri Bindhani
Phone: +91-7381906266
Email: sabitribindhani@soa.ac.in

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v10i4.1636

Production and Hosted by

IJRPS | https://ijrps.com

INTRODUCTION

Oral drug delivery is the most convenient and preferable route for administration of drugs because of low cost and easy administration (Bindhani *et al.*, 2019). The oral route is the preferred route for chronic drug therapy. The drug is having poor solubility, and least dissolution has been reduced bio availability, which is improved by enhancing its drug absorption in gastro-intestinal fluids (Krishnaiah, 2010). In the pharmaceutical industry, most new developed small chemical compounds belong to the BCS class II, which have the limitation of low absorption capability in g.i. Fluids. The rate-

controlling step for lipophilic compounds is the absorption process (Porter *et al.*, 2007). Various efforts are made, those are not only helping to enhance the oral bioavailability but also increase their effectivity towards the clinical region. The incorporation of the active lipophilic entity into solid dispersion, self emulsifying drug delivery system, inert lipid vehicles, such as oils, surfactant dispersions, and liposomes, which give a special advantage towards bioavailability. Out of the several formulation approaches, self-emulsifying drug delivery systems (SEDDS) have been proved an advanced and reliable approach in improving the oral bioavailability of poorly water-soluble and lipophilic drugs (Katteboina *et al.*, 2009; Balakrishnan *et al.*, 2009). The clinical usefulness of the SEDDS is evident from the commercially available formulations containing cyclosporin A, ritonavir and Saquinavir. SEDDS are oil, surfactants and/or cosolvents mixture which develops a fine oil/water and/or water/oil emulsions upon dilution with aqueous fluid. Upon invivo administration, self emulsifications perseverate within g.i. Fluid by the help of agitation produced by digestive motility of the stomach and intestine (Porter *et al.*, 2008). SEDDS have the capacity to form small oil droplets (<5 μm) which stimulate the release of the drug faster and rapid into the aqueous phase (Porter *et al.*, 2008). Formation of the large interfacial area by the smaller size of oil droplets which provide a large interfacial area for pancreatic lipase hydrolyze triglycerides and formation of mixed micelles which influence the drug release rapidly (Shah *et al.*, 1994). The use of surfactant for improving bioavailability by various mechanisms: (a) improved drug dissolution, (b) increased intestinal epithelial permeability, (c) increased tight junction permeability and (d) decreased GM efflux.

Eprosartan mesylate (EM) is an angiotensin II receptor antagonist used in the treatment of high blood pressure (Plosker, 2009). It is worked on vascular AT1 receptors (postsynaptically) and presynaptic AT1 receptors and is not afflicted by cytochrome P 450. It inhibits noradrenaline release and has a low potential for metabolic drug interaction (Ruilope and Jager, 2003). It is a class II drug which has low aqueous solubility and high intestinal permeability (Borker and Pawar, 2013). It has 13% absolute bioavailability and exhibited 98% protein binding, and the volume of distribution is 13L (Robins and Scott, 2005). The critical aspect is low oral bioavailability which due to its low solubility and dissolution rate. So our aimed to develop lipid-based drug delivery system by which dissolution and ultimately bioavailability is absolutely be improved.

MATERIALS AND METHODS

Eprosartan mesylate (EM) was a present sample from Mylan Laboratories Ltd. (Nashik, India). Almond oil, rice bran oil, Soybean oil, Peppermint oil was supplied by Merck Pvt. Ltd. Castor oil was supplied by Merck Pvt. Ltd. Tween 80, tween 20, span 20 and span 80 were supplied from Sisco research laboratories Pvt. Ltd. PEG 400, PEG200, propylene glycol, glycerol, PEG 600 were supplied from Sisco research laboratories Pvt. Ltd.

Solubility studies

Various oils, surfactants and cosurfactants was taken for identifying the maximum solubility of the drug. An excess amount of drug was dissolved in 2ml of each oil, surfactants and cosurfactants. Then each mixture were sonicated for 15 min at 40-50^{0}C to facilitate solubilization. Then the mixtures were vortexed for at least 5min for complete solubilization of the drug. Then the mixture was centrifuged at 3500 rpm for 30min. Then it is filtered, and the supernatant was suitably diluted with ethanol and analyzed using UV spectrophotometer at 241 nm placing ethanol as a blank (Sapra *et al.*, 2012)

Construction of phase diagram

Pseudo-ternary phase diagram determines the self-emulsifying region between oil, surfactant and cosurfactant. Based on the analysis from solubility studies, the maximum solubility containing oil, surfactant and cosurfactant were selected. At different ratio, nine self-emulsifying preparation was made without a drug in which surfactants and cosurfactants were blended together in 1:1 and 1:2 ratio individually. Pseudo ternary phase diagram was prepared by water titration method. In the above process, water is added dropwise into each and every ratio of a mixture with constant stirring. The amount of water at turbidity produced was noted and was considered as the endpoint of the titration. Here water, oil, a mixture of surfactant and cosurfactant are variables to construct ternary phase diagram. A phase diagram was built up for identifying the self-emulsifying region using CHEMIX school 4.0, ternary software (Chopade and Chaudhari, 2013).

Preparation of SEDDS of Eprosartan

SEDDS formulations were prepared by using oil (peppermint oil), surfactant (tween 80) and co-surfactant (PEG 400) at 1:9 to 9:1 ratio (oil: SCOS-mix). The amount of eprosartan mesylate was kept constant in all the formulations (i.e-300mg/10ml). Initially, surfactant and co-surfactant were properly mixed with the help of magnetic stirrer. After that, oil is added and mixed by gentle stirring. Accurately

Table 1: The observation of fine micro emulsion and phase separation of formulations after 24hr

Form.code	Oil (ml)	scosmix (1:1)	Physical Appearance	Stability checking after 24hr.
Pf1	9	1	Fine microemulsion; immediate no phase separation	No phase separation; stable
Pf2	8	2	Fine microemulsion; immediate no phase separation	No phase separation; stable
Pf3	7	3	Fine microemulsion; immediate no phase separation	No phase separation; stable
Pf4	6	4	Fine microemulsion; immediate no phase separation	No phase separation; stable
Pf5	5	5	Milky appearance: but no immediate phase separation	No phase separation; stable
Pf6	4	6	Milky appearance: but no immediate phase separation	No phase separation; stable
Pf7	3	7	Milky appearance: but no immediate phase separation	No phase separation; stable
Pf8	2	8	Milky appearance: but no immediate phase separation	Phase separation; Unstable
Pf9	1	9	Milky appearance: but no immediate phase separation	Phase separation; Unstable

Table 2: The performance of formulations during thermodynamic stability studies; ✓ (stable) and × (unstable)

Formulations code	Heating cooling cycle	Centrifugation test	Freeze thaw stress cycle
pf1	✓	✓	×
pf2	✓	✓	✓
pf3	✓	✓	✓
pf4	✓	✓	✓
pf5	✓	✓	✓
pf6	✓	×	×
pf7	✓	×	×

Table 3: The data of self emulsification time of formulations under visual grading system

Formulation cod	Visual observation based on grades		Self-emulsification time (min:sec)	
	pH 6.8	pH 7.4	pH 6.8	pH 7.4
pf2	C	C	01.15	01.33
pf3	C	C	01.26	01.39
pf4		C	00.21	01.46
pf5		C	00.29	01.53

Table 4: The data of droplet size, drug content analysis and viscosity of self micro emulsifying formulation

Formulation code	Droplet size(nm)	Drug content (%)		Viscosity(cp)
		pH6.8	pH7.4	
pf2	248.3	88.71±0.41	84±0.52	41.19
pf3	242	90.44±1.24	88±0.41	44.24
pf4	237.1	92.61±1.46	91±0.69	46.47
pf5	218.5	95.49±1.52	93±0.35	49.11

Table 5: The performance of formulations to determine robustness on dilution after 24 hour

Formulation code	Phosphate buffer (pH 6.8)		Phosphate buffer (pH 7.4)	
	Phase separation (p.s.)	Drug precipitation (d.p.)	P.S.	D.P.
Pf2	No p.s	No d.p	p.s	d.p
pf3	No p.s	No d.p	p.s	d.p
Pf4	No p.s	No d.p	No p.s	d.p
Pf5	No p.s	No d.p	No p.s	d.p

Table 6: Represents calculated value of mean and standard deviation from the drug release data of formulations and pure drug. (*n=3; mean± standard deviation (sd))

Formulation code	Mean ($\bar{x}$) ± standard deviation of mean(SE $\bar{x}$)
*pfa1	93.1333± 0.0639
pfa2	83.6233± 0.0769
pfa3	75.2767± 0.0809
*Pure drug	54.2467±0.1426

Table 7: Represents the statistical value of one-way anova using post-hoc test

Source	Sum of squares SS	Degrees of freedom $\nu\nu$	Mean square MS	F statistic	p-value
Treatment	2,472.2923	3	824.0974	29,795.6292	1.1102e-16
Error	0.2213	8	0.0277		
Total	2,472.5136	11			

Table 8: The data obtained from one way anova using bonferroni multicomparison test

Treatment pair	Bonferroni p value	Bonferroni inferfence
*pfa1 vs pure drug	0.0000e+00	p< 0.05
Pfa1 vs pfa2	1.1543e-11	p< 0.05
Pfa1 vs pfa3	7.4607e-14	p<0.05

weighed drug (300mg) was added, and the mixture was mixed properly with the help of magnetic stirrer to obtain a homogenous solution. Then it was kept at room temperature for further studies.

Thermodynamic stability studies

Thermodynamic stability study was done to observe whether the formulations were showing any signs of phase separation, drug precipitation, creaming or cracking with the variation of temperature. The thermodynamic stability study was done under three stress condition, i.e. centrifugation test, heating cooling cycle and freeze-thaw stress testing. Formulations were subjected to centrifugation test and centrifuge at 3500 rpm for 30min. The formulations which does not show any sign of phase separation were subjected to the heating-cooling cycle. After centrifugation testing, formulations were subjected to heating-cooling cycle (4 and 45°C) for 48 hours to observe any sign of phase separation, drug precipitation, creaming and cracking. Those formulations which were stable, were subjected to freeze-thaw stress cycle (-21 and 25°C) for 48hr. The formulations which are showing better stability were continued for the next evaluation studies. The stability studies were performed in triplicate (Patel *et al.*, 2010).

Visual assessment and self emulsification time

After thermodynamic stability studies, the stable SEDDS formulations were examined for self emulsification efficiency by visual assessment. The self emulsification time is assessed by using a standard USP XXII dissolution apparatus in which 1ml of each formulation was added into 500ml of phosphate buffer (pH 6.8 and pH 7.4) at 37°C ± 5°C at 100 rpm by providing gentle agitation. The time taken for self emulsification efficiency was noted and analyzed by using the grading system (Patil *et al.*, 2007).

Microscopic evaluation

The morphology and structure of self-emulsion was studied using a light microscope. To perform the microscopic observation, emulsion formulation was diluted with water. The sample was mounted on a glass slide and covered with a coverslip and viewed under a microscope.

Drug content analysis

Drug content analysis was done by taking formulation equivalent to 100mg of Eprosartan mesylate. Then it is dissolved in a small quantity of solvent and made up the volume up to 100ml of phosphate buffer PH 6.8 and pH 7.4. 20μg of the sample was taken, and dilution was made up to the 10ml of solvent and analyzed spectrophotometrically at 231nm (Patel *et al.*, 2008).

Droplet size analysis

The droplet size of smedds formulation was determined using a zeta sizer Nano ZS (Malvern instrument, UK) at a wavelength of 635nm and at a scattering angle of 90°C at 25°C. The formulation (0.1ml) was diluting with 100 times with double distilled water and sonicated for at least 30min. For reduction of particle size of emulsion (Date and Nagarsenker, 2007).

Rheological determination

The viscosity of the formulations was measured by the help of cup and bub viscometer (Brookfield viscometer) DV+II Pro and spindle no. SC 4-31. 9ml of the sample was taken in the cup, and the bub was inserted into the cup. Then the viscosity was measured by the help of the software provided by the Company (Mahajan *et al.*, 2011).

Robustness to dilution

All the formulations were taken for checking the robustness of emulsion in diluting with enzyme-free phosphate buffer pH 6.8 and pH 7.4. 1ml of each formulation was subjected to 50, 100, 500, 1000 fold dilution and kept them for 24hr. After that, all the formulations in different pH condition were checked for any change in physical appearance, i.e. coalescence of oil droplets, drug precipitation or phase separation (Kallakunta *et al.*, 2012).

Fourier Transform Infrared (FTIR) spectroscopy

Ftir analyzes the compatibilities between drug and excipients present in the formulation. Each samples were scanned in ftir spectrophotometer (Spectrum 2 FTIR spectrophotometer, Perkin Elmer) at a range of 4000-400cm-1. A small amount of sample is placed in the plate in such a way that the crystal is covered by the sample. Then the arm is locked over the crystal surface slowly until the metal tip is close to the plate. Then the process of scanning is persuing.

In-vitro drug diffusion studies

The in-vitro diffusion study was done in USP XXIII rotating paddle method using dialysis membrane. After that, the previously prepared smedds formulations (10ml/300mg) were filled in a dialysis membrane bag and closed properly with the thread for preventing any leakage. Then it was put into the vessel containing 900ml of fresh dissolution media carefully by which the dialysis membrane can easily rotate. The diffusion study was performed at 37±0.5°C and rotated at 100 rpm for 6hr. At predetermined time intervals, 0.5ml of samples were withdrawn and diluted it with the same media. Then the dilution was filtered through 0.45μm membrane

filter and assessed spectrophotometrically at λmax 231nm. The same volume of the withdrawn amount should be replenished to maintain the sink condition of dissolution. The dissolution of each formulation was performed in triplicate. The in vitro diffusion profile of stable formulations were prepared, and the highest percentage of drug release containing formulation was taken for further studies The mixture of surfactant and the cosurfactant ratio was varied to 2:1, 3:1and1:2. The dissolution was performed in the same way as it was previously done. The dissolution profile was made and compared with a release profile of a pure drug.

Release kinetic study

To study the release kinetics , the release data was fitted into carious kinetic model: zero-order(cumulative % of drug release/ time), first-order(log cumulative % drug remaining / time, Higuchi model(cumulative % of drug release / root time), Hixson-Crowell (cube root (Wo)-cube root (Wt) / time), and Korsmeyer Peppas model(log% of drug release / log time). From all the above model, the r^2 is obtained and compared. The presence of the highest r^2 value will be selected as the best- fit model for release kinetic.

Statistical analysis

Statistical analysis was done by one-way analysis of variance (one way ANOVA) with post-hoc test. All the experimental results were presented as mean$\pm$SD; n=3. Probability level (p) < 0.05 was studied as statistically significant (P < 0.05). All the data obtained from the analysis were established by Bonferroni's multiple comparisons as a post-hoc test.

RESULTS AND DISCUSSION

Solubility studies

The main aim of solubility studies is to find the most compatible excipients such as oil, surfactant and cosurfactant, which shown maximum solubility with a drug. From the various oil, peppermint oil (46.14$\pm$0.75) was selected as an oily phase due to its highest solubility with a drug. Tween 80 (36.20$\pm$0.31) was identified as a surfactant, and PEG 400(31.65$\pm$0.50) was found as cosurfactant due to its maximum solubility with a drug. The data obtained from the solubility analysis is represented in Figure 1.

Ternary phase diagram

Pseudo ternary phase diagrams were constructed by using a water titration method at ambient temperature to determine the emulsification region. The phase diagram was constructed by using peppermint oil (oil), tween 80 (surfactants) and PEG400 (cosurfactants) in $scos_{mix}$(a mixture of surfactant and cosurfactant) 1:1 ratio and 1:2 ratio. Figure 2 (A) represents a ternary diagram of peppermint oil, tween 80 and PEG 400 at 1:1 ratio and Figure 2 (B) represents ternary diagram at 1:2 ratio. 1:1 ratio was selected as superlative ratio due to its larger self emulsification region.

Preparation of self-emulsifying formulation

Nine sedds formulations(pf1 to pf9) were prepared at 9:1,8:2,7:3,6:4,5:5,4:6,3:7,2:8,1:9 ratio(oil:$scos_{mix}$) in which $scos_{mix}$ was 1:1 ratio. pf8(2:8) and pf9(1:9) was shown phase separation due to improper proportion of oil, surfactant and cosurfactant. Pf1 to pf7 formulations showed stable after storing at 25°C for 24hr. The formulations containing oil (30%-90%), surfactants (5-35%), cosurfactants (5-35%) were shown fine microemulsion. So out of nine formulations, seven formulations were stable after 24hr. After that accurate quantity of the drug was mixed with the help of magnetic stirrer. The observation of the production of fine microemulsion and phase separation of all formulation is represented in Table 1.

Thermodynamic stability studies

Self micro emulsifying formulations were thermodynamically stable formulation which means that the formulation does not undergo any production of precipitation, the appearance of creaming or cracking under any change in temperature and pressure. Seven formulations, i.e. pf1to pf7 formulations, were exposed to three different stress condition, i.e. centrifugation test, heating cooling cycle and freeze-thaw stress cycle. This study was done to ensure the kinetic stability of formulations and also to examine the chemical reaction occurring between the components of a formulation. Out of seven formulations, four formulations, i.e. pf2, pf3, pf4, pf5 did not show any sign of phase separation because of the proper concentration of excipients which produce the formulation with greater stability. The performance of the above formulation during thermodynamic stability studies is given in Table 2.

Selfemulsification time

After thermodynamic stability studies, Self emulsification efficiency of pf2, pf3, pf4, pf5 was assessed in buffer pH 6.8 and pH 7.4. The formulations should be dispersed completely and quickly when contacted with aqueous g.i. Fluid. Here self emulsification was done in two buffer media, i.e. PH6.8, PH 7.4. Under visual observation, pf4 and pf5 formulations show clear and bluish appearance, but pf2 and

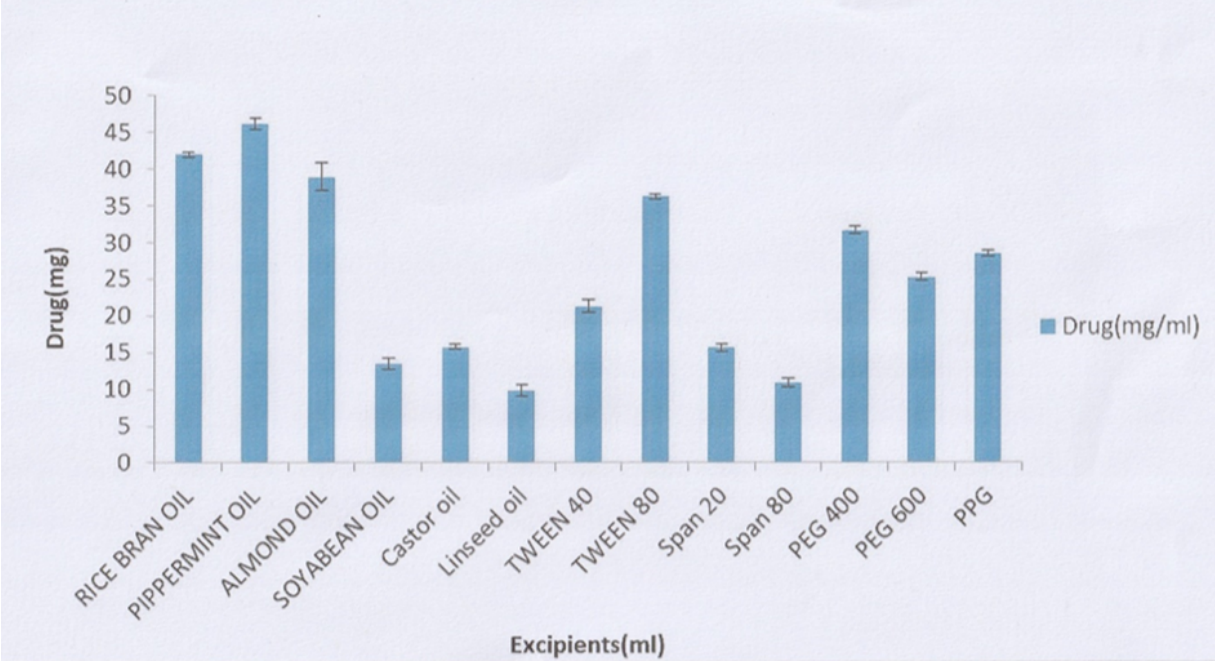

Figure 1: Saturation solubility studies using various oil, surfactant and cosurfactant

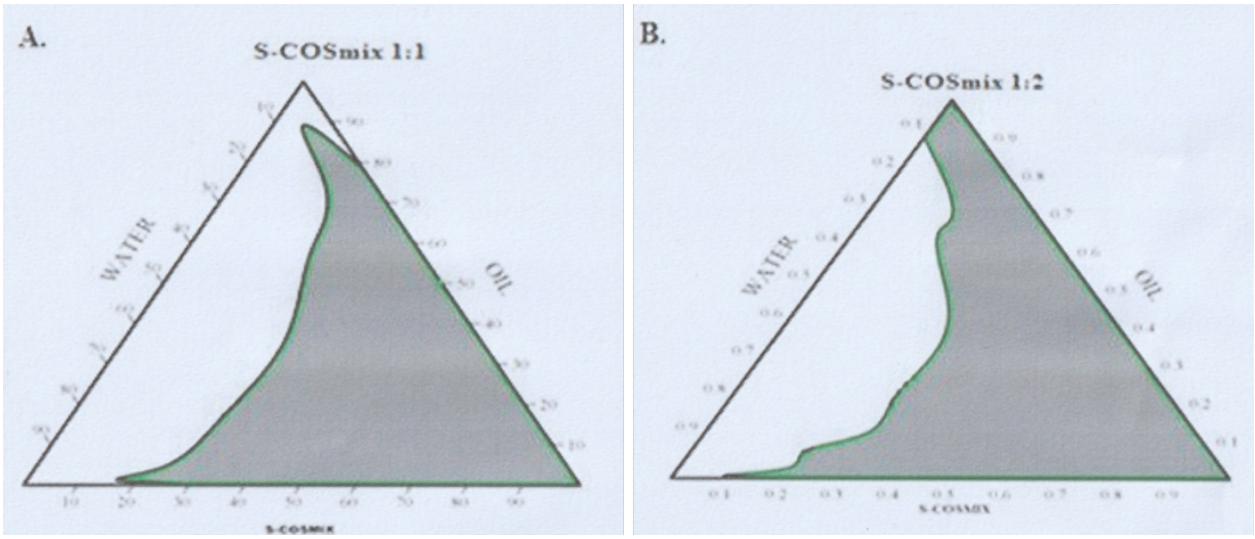

Figure 2: Pseudoternary diagram of peppermint oil, tween 80 and peg 400 at scosmix 1: 1(a) and 1:2(b)

pf3formulations showed the slightly less clear solution in pH6.8 buffer solution. But in pH7.4, all the four formulations showed slightly less clear solution (more than 1min.).The data was analyzed according to the grading system of the visually observed self-emulsifying formulation. All the data obtained from self emulsification process has been given in Table 3.

Determination of drug content, droplet size and viscosity

Drug content analysis was performed in both pH 6.8 and pH 7.4. Out of four formulations, the percentage of drug content in pf5 formulation was high, maybe due to the high concentration of oil present in the formulation. An increase in the ratio of the oil phase resulted in a proportional increased in particle size, because of the simultaneous decrease in the S-COSmix proportion. A smaller particle size provides a large interfacial area by which drugs can diffuse into g.i. Fluid and improves drug release. The viscosity of prepared formulations were in the following order pf5 (5:5) > pf4 (6:4) > pf3 (7:3) > pf2 (8:2). During viscosity determination, it was observed that as the concentration of surfactant and co-surfactant was increased, a significant increase in viscosity of formulation was observed. Increase in viscosity produces more viscous to the formulation. The data obtained from drug content analysis,

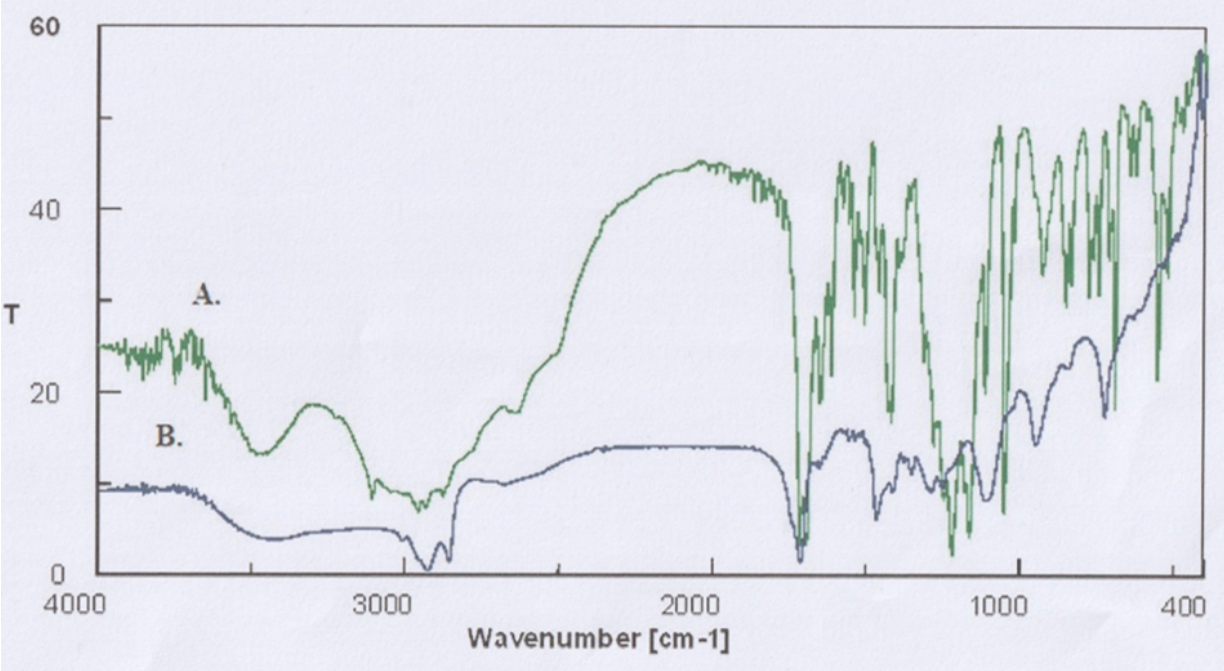

Figure 3: Fourier transform infrared spectrum of pure drug (a)and smedds (b)

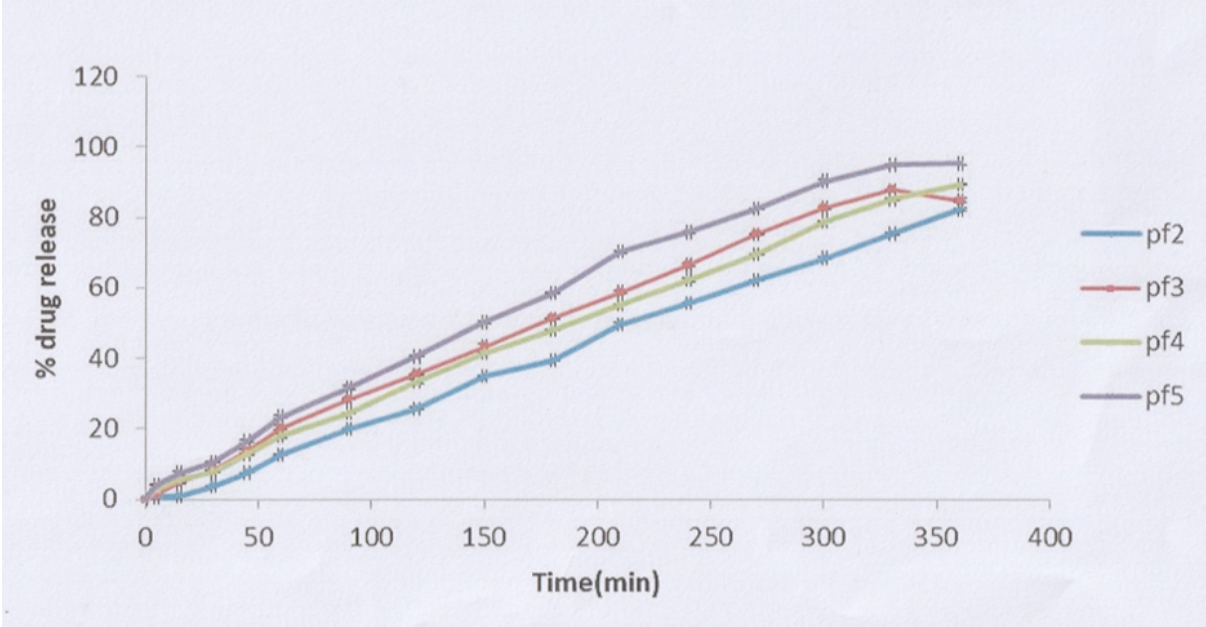

Figure 4: Invitro drug release profile of pf2, pf3, pf4, pf5 formulations

droplet size and viscosity is represented in Table 4.

Robustness to dilution

Robustness to dilution is measured because it determines the properties of the robustness of smedds at different concentration and at different pH condition. The four formulations were diluted with 50, 100, 500, 1000 times of P.B.S. PH 6.8 and PH 7.4. And allow to keep them for 24 hrs. The formulations were checked at every interval of 4 hrs. for any phase separation and drug precipitation. After 8hrs of dilution at pH 7.4, pf2 and pf3 found both phase separation and drug precipitation, while pf4 and pf5 did not found any phase separation, but some amount of drug was precipitated. But at pH 6.8, all the formulations didn't show any sign of phase separation and drug precipitation. The data of robustness to dilution is given in Table 5.

Fourier Transform Infrared (FTIR) spectroscopy

The FTIR spectrum of the pure drug (A) and pf5 (B) are shown in Figure 3. The compatibility study between drug and the excipients was studied by Fourier transform infrared spectroscopy. Figure 3

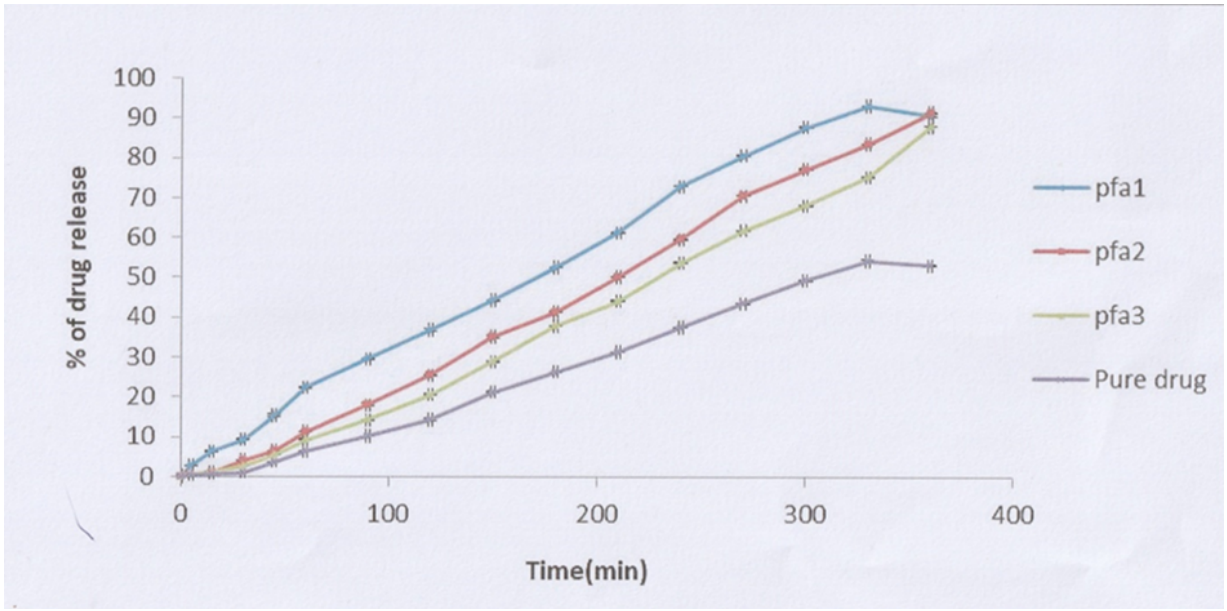

Figure 5: Invitro drug release profile of pfa1, pfa2, pfa3 with pure drug

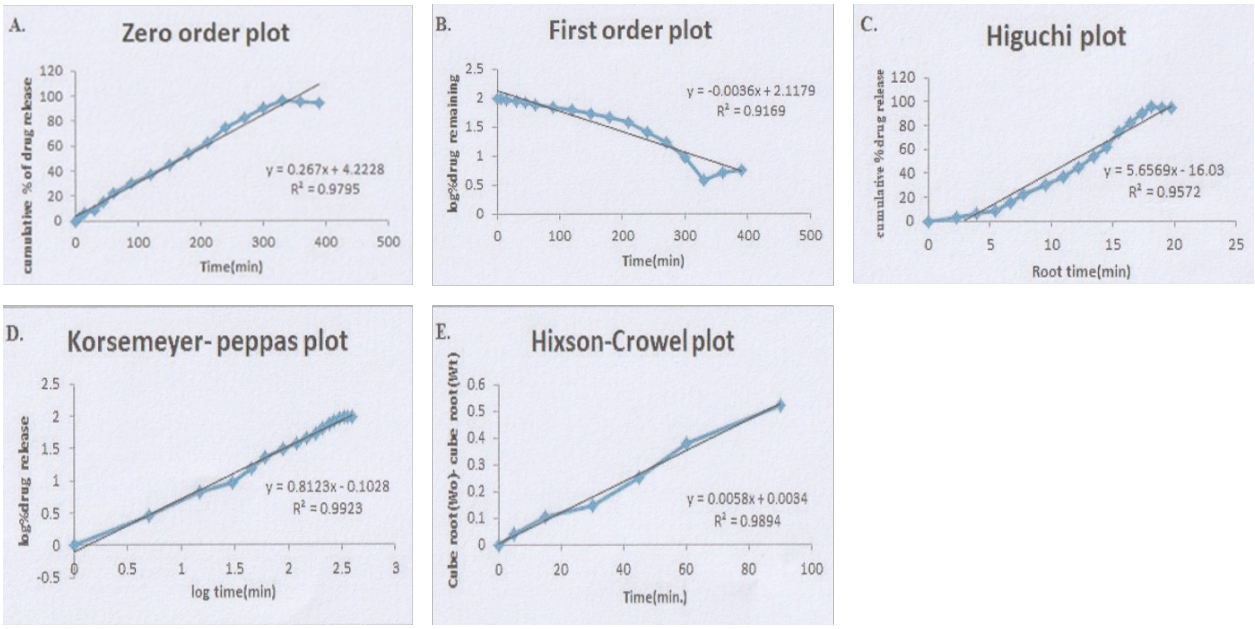

Figure 6: Determination of release kinetic study of eprosartan mesylate using different kinetic model. A. Zero order plot(r^2- 0.9795), b. First order plot (r^2- 0.9169), c. Higuchi plot(r^2- 0.9572), d. Korsemeyer-peppas plot (r^2-0.9923), e. Hixson crowel plot(r^2- 0.9894)

(A) showed that showed the characteristic peaks of pure drug are 1714.41cm-1 (C=O stretching of carboxylic acid), 1648.84 cm-1 (C=O stretching of carboxylate ion), 1614.13 cm-1 (C=C stretching of aromatic ring), 1540.85cm-1 (CH stretching of aromatic ring), 2956.34 cm-1 (CH2 stretching of mesylate group), 3479.92 cm-1 (OH stretching of carboxylic acid), 1049.09 cm-1 (C-N stretching of imidazole), 1163.83cm-1 (SO2 stretching of sulphonic acid (symmetrical), 1418.39 cm-1 of sulphonic acid(asymmetrical). The observed prominent peaks of smedds (pf5) are 1714.41 cm-1, 1648.84 cm-1, 1540.85 cm-1, 2956.34 cm-1, 1418.39 cm-1, 3479.92 cm-1 which are absolutely observed in the ftir spectrum of pure drug. So it was confirmed that there was no drug-polymer interaction observed within the formulation.

In-vitro drug diffusion study

SMEDDS have the capability to rapidly migrate in the aqueous fluid. On the basis of self emulsification time, drug content analysis and robustness test, P.B.S. pH6.8 was selected as dissolution media. Four optimized formulations, i.e. pf2, pf3, pf4,

pf5, was performed for in-vitro diffusion study for 6hr. In every specific time interval, the sample was withdrawn and analyzed using a spectrophotometer. The in-vitro dissolution profile of four formulations is represented in Figure 4. The cumulative % of drug release from all the formulation was ranged between 82.29±0.57, 87.75±0.23, 89.32±0.21 and 96.59±0.29. pf5 formulation having the same concentration of oil:scos$_{mix}$ was shown the highest release of 96.59% as a comparison with the other three formulations. So pf5 can be taken to further studies by varying the ratio of s-cos$_{mix}$ into pfa1 (2:1), pfa2 (3:1), pfa3 (1:2). This was exhibited to determine the highest release of drug and compared with the dissolution profile of a pure drug. The diffusion process was performed for 6 hrs. The in-vitro diffusion profile of pfa1, pfa2, pfa3 and the pure drug was represented in Figure 5. At 330min. pfa1, pfa2 and pfa3 released drug between 87% to 93%, where pure drug release only 54.24%±0.24. At 330 min. pfa1 released 93.13%, which was significantly higher than the pure drug ($p<0.05$). The mean value and standard deviation of pfa1, pfa2, pfa3 and the pure drug is given in Table 6. Table 7 represents the statistical value obtained from one-way ANOVA using a post hoc test. Table 8 gives *p*-value, which was obtained using Bonferroni's multiple comparison test. Drug release from pfa1 was faster because, at scos$_{mix}$ (2:1), the concentration of surfactant is double from the concentration of cosurfactant. The more amount of surfactant increases more solubilization of drug, which influences increased drug release pfa1formulation.

Release kinetic study

From the release kinetic study, It has been shown that all the kinetic models showed good release kinetic. But in comparison, pfa1 in which 2:1 ratio of surfactant and cosurfactant follows korsemeyer pappes model (r^2- 0.9923) in which n value is 0.8123. This value is characteristic of Anomalous kinetic i.e. non fickian transport (0.45 < n < 0.89). Figure 6 represents the release kinetic study of eprosartan mesylate from pfa1 (optimized formulation) using different kinetic model. Hence the release mechanism was investigated as a diffusion mechanism through

CONCLUSION

Self micro emulsifying drug delivery system of eprosartan mesylate was successfully prepared by using suitable oil, surfactant and cosurfactant. Among all formulations, pf2, pf3, pf4 and pf5 evaluated its emulsification efficiency, drug content analysis, particle size analysis, robustness to dilution test, viscosity determination and in-vitro diffusion study. Pf5 formulation became an optimized formulation due to its good emulsification, the highest percentage of drug content, less particle size and the highest percentage of drug release. To compare with the dissolution of pure drug, the concentration of surfactant and co-surfactant of pf5 was varied to 2:1, 3:1, 1:2 and evaluated for its solubility and dissolution rate. From the dissolution study, pfa1[(2:1)] showed a maximum drug release of 93.13% as compared to a pure drug, which releases only 54.24% at 330 min. From the release kinetic study, the mechanism of drug release from formulation (pfa1) followed a diffusion mechanism followed by Hixon crowel. From the FTIR study, maximum characteristic peaks of a drug are also present in the formulation. So there was no incompatibilities between drug and polymer. So SMEDDS provides an interesting prospect for the development of a formulation for use as a vehicle to deliver hydrophobic drugs to the body. In conclusion, self micro emulsifying drug delivery system has been proved as a potential delivery system for eprosartan mesylate and as an excellent approach for oral delivery of a poorly soluble drug.

ACKNOWLEDGEMENT

We are highly thankful to OUAT, Bhubaneswar for analyzing FTIR of various samples. We also thank Prof. Pradipta Kumar Nanda. Dean (Research & Development) and Prof. (Dr.) Sudam Chandra Si, Dean, School of Pharmaceutical Sciences (SPS), Siksha O Anusandhan University, Bhubaneswar for providing required facilities to carry out this research work.

REFERENCES

Balakrishnan, P., Lee, B. J., Oh, D. H., Kim, J. O., Lee, Y. I., Kim, D. D., Choi, H. G. 2009. Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. *International Journal of Pharmaceutics*, 374(1-2):66–72.

Bindhani, S., Mohapatra, S., Kar, R. K. 2019. Self Emulsifying Drug Delivery System: A Recent Approach. *Asian Journal of Chemistry*, 31(4):751–759.

Borker, S., Pawar, A. 2013. Eprosartan Mesylate Nanosuspension with HPMC E3 for Improving Solubility and Bioavailability. *Advanced Science, Engineering and Medicine*, 5(12):1297–1304.

Chopade, V. V., Chaudhari, P. D. 2013. Development and evaluation of self-emulsifying drug delivery system for lornoxicam. IJRDPL. pages 531–538.

Date, A., Nagarsenker, M. 2007. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. *International Journal of Pharmaceutics*, 329(1-2):166–172.

Kallakunta, V. R., Bandari, S., Jukanti, R., Veerareddy, P. R. 2012. Oral self emulsifying powder of lercanidipine hydrochloride: Formulation and evaluation. *Powder Technology*, 221:375–382.

Katteboina, S., Chandrasekhar, P., Balaji, V. S. R. 2009. Approaches for the development of solid self-emulsifying drug delivery systems and dosage forms. *Asian Journal of Pharmaceutical Sciences*, 4(4):240–253.

Krishnaiah, Y. S. 2010. Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs. *Journal of Bioequivalence & Bioavailability*, (02):2–2.

Mahajan, H. D., Shaikh, T., Baviskar, D., Wagh, R. D. 2011. Design and development of solid self-microemulsifying drug delivery system (SMEDDS) of fenofibrate. *Int J Pharm Pharm Sci*, 3(4):163–166.

Patel, M. J., Patel, N. M., Patel, R. B., Patel, R. P. 2010. Formulation and evaluation of self-microemulsifying drug delivery system of lovastatin. *Asian Journal of Pharmaceutical Sciences*, 5(6):266–75.

Patel, P. A., Chaulang, G. M., Akolkotkar, A., Mutha, S. S., Hardikar, S. R., Bhosale, A. V. 2008. Self emulsifying drug delivery system: A review. *Research Journal of Pharmacy and Technology*, 1(4):313–323.

Patil, P., Patil, V., Paradkar, A. 2007. Formulation of a self-emulsifying system for oral delivery of simvastatin: In vitro and in vivo evaluation. *Acta Pharmaceutica*, 57(1):111–122.

Plosker, G. L. 2009. Eprosartan: a review of its use in hypertension. *Drugs*, 69(17):2477–2499.

Porter, C. J. H., Pouton, C. W., Cuine, J. F., Charman, W. N. 2008. Enhancing intestinal drug solubilisation using lipid-based delivery systems. *Advanced Drug Delivery Reviews*, 60(6):673–691.

Porter, C. J. H., Trevaskis, N. L., Charman, W. N. 2007. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. *Nature Reviews Drug Discovery*, 6(3):231–248.

Robins, G. W., Scott, L. J. 2005. Eprosartan: a review of its use in the management of hypertension. *Drugs*, 65(16):2355–2377.

Ruilope, L., Jager, B. 2003. Eprosartan for the treatment of hypertension. *Expert opinion on pharmacotherapy*, 4(1):107–114.

Sapra, K., Sapra, A., Singh, S. K., Kakkar, S. 2012. Self emulsifying drug delivery system: A tool in solubility enhancement of poorly soluble drugs. *Indo global journal of pharmaceutical sciences*, 2(3):313–332.

Shah, N. H., Carvajal, M. T., Patel, C. I., Infeld, M. H., Malick, A. W. 1994. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. *International journal of pharmaceutics*, 106(1):15–23.

