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Vegetable Oil-Based Self-Microemulsifying Drug Delivery System of Eprosartan Mesylate: *in vitro* and *ex vivo* Evaluation

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This study was planned to increase the intestinal permeability and thereby bioavailability of eprosartan mesylate (EPM) by designing a self-microemulsifying drug delivery system (SMEDDS) by the use of vegetable oils. Various SMEDDS-based formulations were prepared with oleic acid and peppermint oil. Tween 80 was used as surfactant and PEG 400 as co-surfactant. Pseudo ternary phase diagrams were constructed for identifying emulsification region between 1:1, 1:2, 2:1, 3:1 ratio of SCOS mix. Eight batches of SMEDDS were found to be thermodynamically stable and from which SMEDDSOF9 and PF5 were best formulations due to their highest drug content, minimum particle size. They have shown highest release of drug *in vitro* and higher *in vitro* drug diffusion and *ex vivo* permeation analysis than pure drug. FTIR study ascertained no incompatibility between drug and excipients present in formulation. From the accelerated stability study, slight effect on particle size and zeta potential, assay content along with cumulative % of drug release was found. The results demonstrated the SMEDDS of EPM are potent drug delivery system to increase dissolution rate and bioavailability of drug *via* increased intestinal permeability and consequently improving the therapeutic efficacy of eprosartan mesylate.

Keywords: Self-microemulsification, Vegetable oils, Eprosartan mesylate, Bioavailability, *ex vivo*, Intestinal permeability.

INTRODUCTION

Oral administration of drugs has always been the preferable route for both patients as well as manufacturers in most of the diseases. It is a big challenge for scientists working on drug delivery system to develop an efficient system for drug delivery of lower bioavailability drugs such as BCS class II and class IV. A large percentage of newly discovered chemical entities have poor solubility in water, which hinders their continuous oral absorption in a magnitude to ascertain their therapeutic potential [1]. Dissolution rate limits the absorption of these drugs because of less solubility. Dissolution rate and solubility of the compound are directly proportional [2,3]. Performances of formulated products are determined by the rate and extend of absorption of these compounds. Formulations designed for oral administration of these compounds have a prime objective of consistent oral bioavailability [4,5]. Self-microemulsifying drug delivery system (SMEDDS) are proven to be most efficient technique for delivery of BCS class II and class IV drugs in context of improved rate and extends of absorption [6]. SMEDDS is an isotropic combination of oils (natural or synthetic), surfactants (hydrophilic/lipophilic) and cosurfactants and is emulsified simultaneously with gastrointestinal media to form oil in water microemulsion under simple agitation [7,8]. On the basis of surfactants used along with the presence or absence of oils, emulsions have been classified into four different types. Type III is considered as SMEDDS having a globule size less than 250 nm [9]. Improved solubility of drug and maintaining solution state of drug throughout gastrointestinal tract along with inhibiting drug efflux mediated by *p*-glycoprotein and preabsorptive metabolism of drug by gut membrane bound cytochrome enzymes are promoted by SMEDDS [10,11]. It also improves drug absorption by avoiding first-pass metabolism and increasing gastrointestinal membrane permeability [12].

Eprosartan mesylate is a non-peptide angiotensin II antagonist that antagonizes angiotensin II type 1 receptor and prevents angiotensin II-induced vasoconstriction. It also prevents

aldosterone secretion by the adrenal cortex and increases the excretion of potassium [13,14]. It has ≈ 13% absolute bioavailability and its peak plasma concentration reached 1-2 h. The volume of distribution is ~13 L and 98% of protein binding [15]. Due to low solubility and dissolution, the bioavailability of EPM is low, which is a challenging aspect of the formulation.

Eprosartan mesylate (EPM) also exhibits low oral bioavailability due to its pH dependent solubility. Koteshwara *et al.* [16] reported that the solubility and dissolution rate was decreased due to its ionization at alkaline pH. So, an attempt has been taken by for improving the solubility and dissolution rate of EPM by preparing enteric coated capsule containing drug and maleic acid as pH modifier. Maleic acid reduces the pH of intestinal environment and fascilitate absorption of drug [16]. Dangre *et al*. [17] attempted to improve the dissolution and bioavailability of eprosartan mesylate by solid dispersion technique. Improved dissolution and bioavailability were shown by solid dispersion of eprosartan mesylate prepared with the use of PVP K-30 by kneading method. The bioavailability of eprosartan mesylate orally in wistar rats was significantly improved to 2.4-fold than the pure drug [17].

This study was designed with an aim to develop a stable SMEDDS formulation of an antihypertensive class II drug eprosartan mesylate (EPM), which is less soluble and has high biomembrane permeability. Vegetable oil and non-ionic surfactant with high HLB value have been selected as oil and surfactant, respectively. The SMEDDS was evaluated by thermodynamic stability, self-emulsification assessment, robustness to dilution study, globule size and zeta potential, cloud point determination, analysis of drug content, *in vitro* study for drug release, *in vitro* diffusion study, *ex vivo* permeability study and FTIR study.

EXPERIMENTAL

Eprosartan was obtained from Mylan Laboratories Ltd. (Nashik, India). Almond oil, rice bran oil, oleic acid, soybean oil, Peppermint oil was supplied by Merck Pvt. Ltd. Tween 80, Tween 20, Span 20, PEG 400, PEG 200, propylene glycol, glycerol, PEG 600, Span 80 were supplied from Sisco Research Laboratories Pvt. Ltd.

Solubility: Extra quantity of eprosartan (EPM) was added to 2 mL of oil, surfactant and co-surfactant to assess highest solubility. Each sample was vortexed for 48 h at 25 ºC, followed by centrifugation (5000 rpm, 30 min). The separated supernatant was mixed with methanol and analyzed spectrophotometrically by UV-visible spectrophotometer at 238 nm.

Preparation of SMEDDS containing eprosartan (EPM): Different concentration combinations of oil, surfactant and cosurfactant were used for preparing SMEDDS formulations [17]. The ratios of surfactant and cosurfactant were 1:1, 1:2, 2:1 and 3:1. Eprosartan (300 mg) was loaded in a single dose in all the SMEDDS formulations. Homogenous isotropic mixture was obtained by vortexing and heating at 40 ºC. Formulations were kept at ambient temperature for 24 h to investigate turbidity or phase separation [18].

Pseudo ternary phase diagram: Water titration method was used to construct pseudo ternary phase diagrams containing oil, SCOS mix and water [19,20]. Distilled water was used dropwise to dilute a pre-decided quantity of oil-surfactant mixture. Oil-surfactant mixture was taken in different ratios of surfactant and cosurfactant. Each mixture was titrated with water to obtain equilibrium. Turbidity and viscosity of the resulting emulsions were decided by naked eye [21]. Phase diagrams were compared to determine final oil and surfactant mixture. CHEMIX ternary plot software was used to identify the self-emulsifying region.

Characterization of SMEDDS containing eprosartan (EPM)

Thermodynamic stability: Centrifugation of formulations at 3500 rpm for 30 min was followed by stress conditions of freeze-thaw cycle (-21 and + 25 ºC) and heating-cooling cycle (4 and 45 ºC) each for 48 h. Thermodynamic stability was visually assessed in terms of extent of phase separation or any instability.

Self-emulsification study: USP dissolution apparatus II was used for determining the self-emulsification of SMEDDS [22]. Self-emulsification properties of SMEDDS formulations were visually assessed and graded according to the visibility grading system [23].

Cloud point measurement: Each formulation after 250 folds dilution with distilled water was kept in water bath. Temperature was gradually increased at 5 ºC/min and observed for any sign of turbidity [24,25].

Percent transmittance study: SMEDDS formulations (1 mL) was diluted with distilled water at 1:100 and observed visually for any turbidity. The sample was analyzed against distilled water as blank at a suitable wavelength using a UV-vis spectrophotometer [26].

Rheological determination: The viscosity of the formulations was measured using cup and bub viscometer (Brookfield viscometer) DV+II Pro and spindle no. SC 4-31.

Drug content analysis: SMEDDS formulation (equivalent to 30 mg) was diluted in methanol followed by centrifugation (5000 rpm, 15 min) and filtered using 0.45 µm Millipore. The separated supernatant was quantified using a UV-visible spectrophotometer at λ_{max} 238 nm [27].

Droplet size and zeta potential evaluation: Dilution of all the prepared formulations was performed with distilled water in a ratio of 1:100 (v/v) and analyzed with particle size analyzer (Malvern zeta sizernanozs 90) [28].

***in vitro* Dissolution study:** *in vitro* Dissolution of optimized SMEDDS (equivalent to 300 mg EPM) and pure drug (300 mg) was studied using USP dissolution Apparatus II (Electrolab (TDT062) at 37 ± 0.5 ºC and 50 rpm rotating speed using 900 mL of phosphate buffer pH 7.4, pH 1.2, respectively. A 1 mL aliquot withdrawn at each time point was replaced by 1 mL fresh dissolution media. Samples were analyzed at λ_{max} of 231 nm [29].

***in vitro* Drug diffusion study:** Dialysis bag method was used for *in vitro* drug release experiments as described earlier [30]. Drug release profile of formulation and pure drug were compared. Analysis of EPM concentration in the sample was done with a UV spectrophotometer at 231 nm [17,31].

***ex vivo* Intestinal permeation study:** *ex vivo* Intestinal permeation study of selected SMEDDS and pure drug was checked through the goat intestine as per previously reported protocol [20,32]. Thorough washing of tissue with buffer for removing mucus and lumen contents was followed by filling it with formulation (equivalent to 30 mg). Intestine with both ends tied was kept under continuous aeration at 37 ± 2 ºC in organ bath and then 40 mL of phosphate buffer was filled in receptor compartment. Withdrawal of sample at a periodic interval of 30 min upto 6 h was carried out from the receiver compartment and equal volume of fresh buffer was added for maintaining sink condition. The withdrawn sample was analyzed at λ_{max} 231 nm and a graph was plotted using the percent diffusion *versus* time data. Repeated permeation studies were conducted with plain EPM suspension and results were compared.

FTIR study: After mixing pure drug with IR grade KBr (ratio 100:1), hydraulic pressure was applied for pellet formation. The selected formulation was filmed on the surface of KBr pellets. Measurements were carried out in 4000-400 cm^{-1} in Fourier transform infrared spectrophotometer using spectra manager software version 2.0.

Statistical analysis: Data was expressed as mean ± standard error with experiments repeated thrice. Analysis of variance, following post hoc analysis, was used for possible pair-wise comparisons of means between different treatments. *p*-value < 0.01 indicates statistical significance.

RESULTS AND DISCUSSION

This study was conducted with an objective for developing a stable SMEDDS formulation of an antihypertensive class II drug eprosartan mesylate having low solubility and high permeability across biomembranes. For getting a clear and monophasic self-emulsifying microemulsion, selection of appropriate excipients, *i.e.* oil, surfactant and cosurfactant is an essential process.

Solubility studies: From the solubility studies, two oils were selected for oil phase *i.e.* oleic acid and peppermint oil and based on highest solubility, Tween 80 as surfactant and peg 400 as co-surfactant were selected (Fig. 1).

The excipients showing maximum solubility and produce stable formulation were selected. In the self-micro emulsifying system, the drug solubilizes in the oil phase and interfacial barrier are reduced by surfactants and co-surfactants along with providing mechanical barrier to coalescence. Oil with higher solubility are much needed so as to avoid drug precipitation on dilution and therefore, oleic acid and peppermint oil were selected for the same. Once selected, these oils were used in different concentrations with surfactant and co-surfactant for preparing SMEDDS [29,33].

Preparation of SMEDDS: Thirty-six batches of each oil containing SMEDDS formulations were prepared at various ratio of oil:SCOS mix (surfactant:co-surfactant) to determine existence of turbidity and phase separation (Tables 1 and 2).

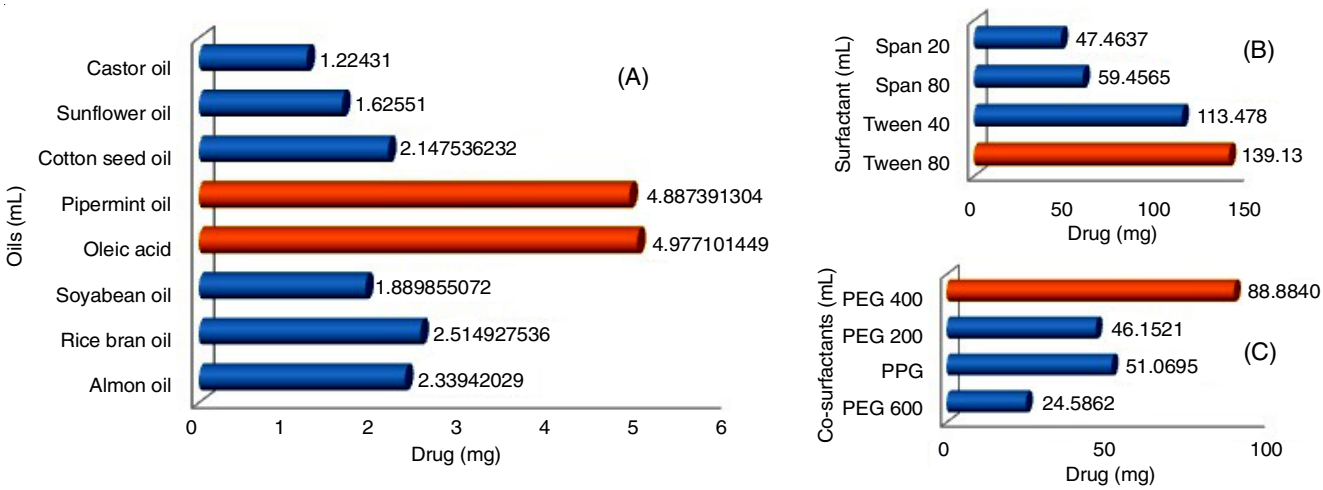

Fig. 1. Solubility screening studies of EPM in various oils (A), surfactants (B) and co-surfactants (C). (n = 3; mean ± SD)

TABLE-1
PREPARATION OF SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) USING OLEIC ACID, TWEEN 80 AND PEG 400.EPM: EPROSARTAN MESYLATE; SCOSmix: MIXTURE OF SURFACTANT AND CO-SURFACTANT)

Formulation batch (oil: SCOSmix)	Surfactant: co-surfactant (mL)				EPM (mg)	Observation after 24 h at ambient temperature
OF1 (9:1)	1:1	1:2	2:1	3:1	300	No phase separation
OF2 (8:2)	1:1	1:2	2:1	3:1	300	No phase separation
OF3 (7:3)	1:1	1:2	2:1	3:1	300	No phase separation
OF4 (6:4)	1:1	1:2	2:1	3:1	300	No phase separation
OF5 (5:5)	1:1	1:2	2:1	3:1	300	No phase separation
OF6 (4:6)	1:1	1:2	2:1	3:1	300	No phase separation
OF7 (3:7)	1:1	1:2	2:1	3:1	300	No phase separation
OF8 (2:8)	1:1	1:2	2:1	3:1	300	No phase separation
OF9 (1:9)	1:1	1:2	2:1	3:1	300	No phase separation

TABLE-2
PREPARATION OF SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) USING PIPPERMINT OIL, TWEEN 80 AND PEG 400.EPM: EPROSARTAN MESYLATE; SCOS MIX: MIXTURE OF SURFACTANT AND CO-SURFACTANT)

Formulation batch (oil: SCOSmix)	Surfactant: co-surfactant (mL)				EPM (mg)	Observation after 24 h at ambient temperature
PF1 (9:1)	1:1	1:2	2:1	3:1	300	No phase separation
PF2 (8:2)	1:1	1:2	2:1	3:1	300	No phase separation
PF3 (7:3)	1:1	1:2	2:1	3:1	300	No phase separation
PF4 (6:4)	1:1	1:2	2:1	3:1	300	No phase separation
PF5 (5:5)	1:1	1:2	2:1	3:1	300	No phase separation
PF6 (4:6)	1:1	1:2	2:1	3:1	300	No phase separation
PF7 (3:7)	1:1	1:2	2:1	3:1	300	No phase separation
PF8 (2:8)	1:1	1:2	2:1	3:1	300	No phase separation
PF9 (1:9)	1:1	1:2	2:1	3:1	300	No phase separation

After 24 h of storage, the formulations did not show phase separation and turbidity.

Ternary phase diagram: The ternary phase diagram was constructed using various surfactant and co-surfactant to understand the nature of resultant dispersion such as phase separation, coarse emulsion and emulsification region [34]. A pseudo ternary phase diagram was designed using various surfactant and co-surfactant weight ratios of 1:1, 1:2, 2:1 and 3:1 ratio. The self-emulsifying region (red and yellow area) at each ratio of SCOS mix was determined (Figs. 2 and 3). Among all four weight ratios of SCOS mix, a 1:1 ratio was selected as a best ratio due to its greater self-emulsifying region.

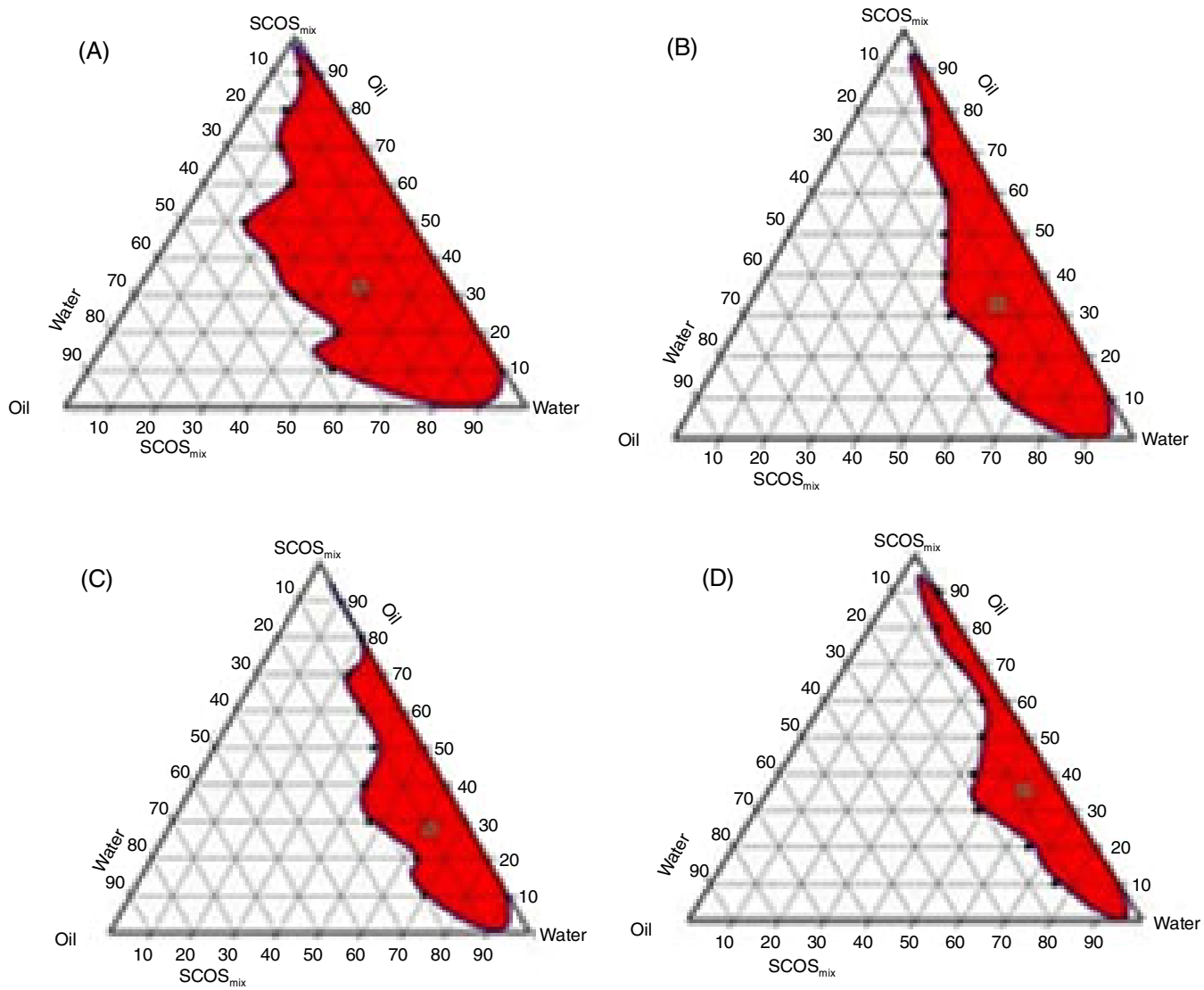

Fig. 2. Pseudo ternary phase diagram of SMEDDS formulations containing oleic acid(oil), Tween 80 (surfactant) and PEG 400 (cosurfactant) at 1:1 (A), 1:2 (B), 2:1 (C) and 3:1 (D) of SCOS mix (surfactant: cosurfactant)

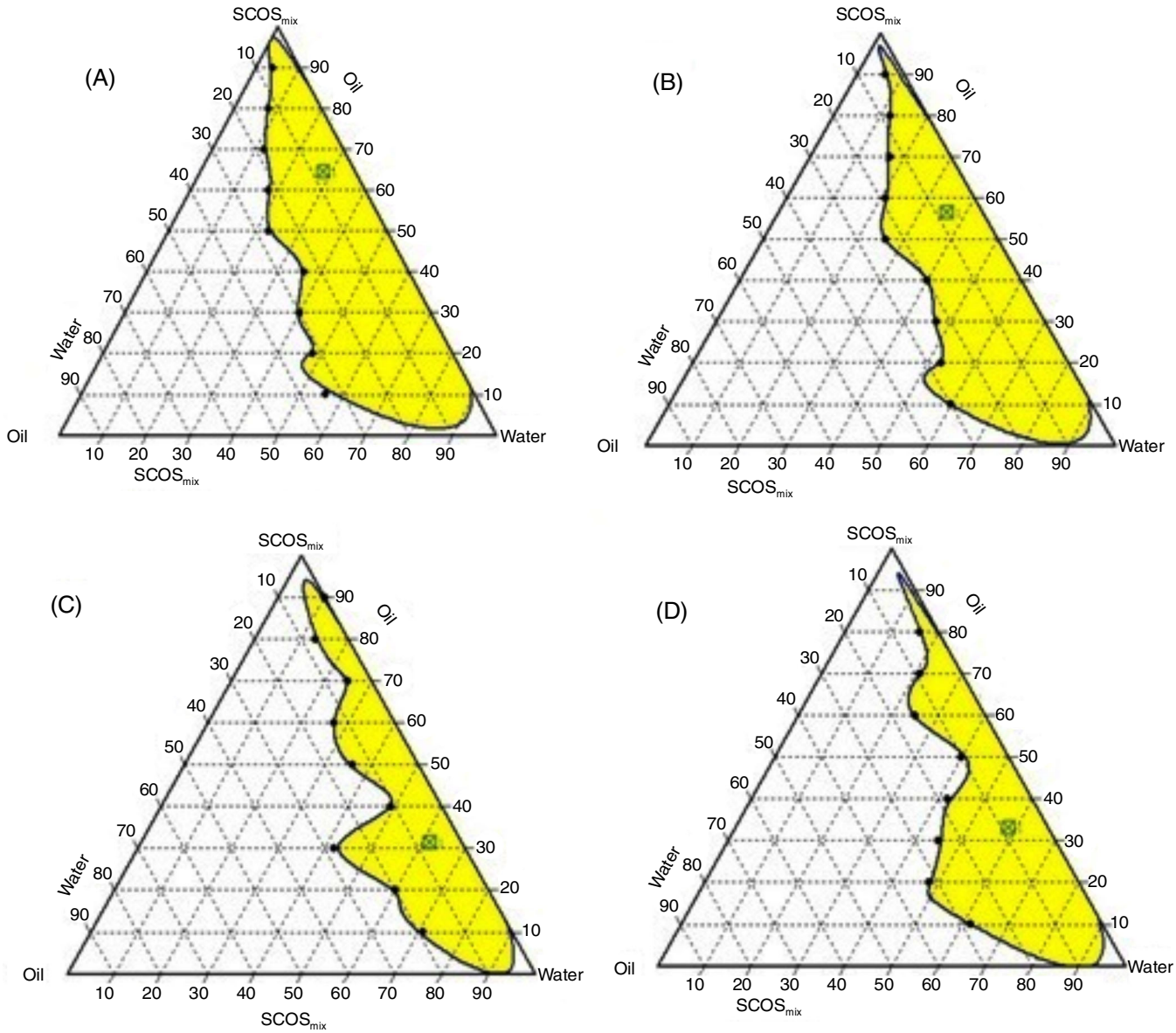

Fig. 3. Pseudo ternary phase diagram of SMEDDS formulations containing peppermint oil (oil), Tween 80 (surfactant) and PEG 400 (co surfactant) at 1:1 (A), 1:2 (B), 2:1 (C) and 3:1 (D) of SCOSmix (surfactant: cosurfactant)

It was shown that same ratio of surfactant and co-surfactant in mixture provided an increase in the emulsifying region in both the oils (oleic acid and pippermint oil). Based on the observation in the phase diagram, a series of SMEDDS containing EPM was prepared and characterized by further studies.

Thermodynamic stability analysis: Thermodynamic stability of formulations confers that formulation doesn't undergo any precipitation, appearance of creaming or cracking under any change in temperature and pressure [25]. Poor stability of formulations having can cause phase separation. The prepared SMEDDS formulations of both the oils were tested for centrifugation stress test; heating-cooling cycle, freeze-thaw stress test and eight formulations stable were found after centrifugation test, heating cooling cycle and freeze-thaw stress test. Among oleic acid containing SMEDDS (OF), the formulations having more oil concentration (50-90%) showed physical instability, which leads to phase separation. And in case of pippermint oil, the formulation having oil concentrations from 20-40% produced milky emulsion and shown instability. Insufficient concentration of surfactant system causes physical instability leading to interfacial tension between the oil and aqueous phase.

Self-emulsification time: Self-emulsification efficiency was determined by the amount of oil, surfactant and cosurfactant [25]. It is observed that few formulations had high emulsification-time because of high concentration of oil requiring more time for self-emulsification. The SMEDDSOF9 with 10% oil concentration showed less self-emulsification time (30 s); the SMEDDSOF6 with higher oil concentration (40%) showed high emulsification time (85 s). Likewise, the SMEDDSPF5 with 50% oil concentration showed less self-emulsification time (38 s) while the SMEDDSPF2 with 80% oil concentration showed high emulsification time (70 s). According to visual grading system, the emulsification time of OF9 and PF5 was

less than 1 min, which suggested that the formulations were formed as clear and bluish emulsion rapidly upon dilution (Table-3). Thus, it can be said that the spontaneity of emulsification was more when the surfactant proportion system in the formulation was high.

Cloud point measurement: Cloud point indicates the temperature above which precipitation of drug and phase separation cause cloudiness. Decrease in solubilization of drug and stability of emulsion leads to drug precipitation and phase-separation. Above 37 ºC, cloud point temperature was preferable. In all SMEDDS formulations, the cloud point temperature was found to be higher than 65 ºC. Cloud point temperature of OF9 and PF5 was highest *i.e.* 90 ºC and 85 ºC, in comparison to other formulations (Table-3). In present study, all the formulations had higher cloud point temperature with OF9 showing highest suggesting maximum solubility of drug; optimized SCOS mix ratio and higher HLB value of surfactant in this formulation [35].

Transmittance: Transmittance was in the range of 85% to 97% for all the formulations. SMEDDSOF9 showed highest percent transmittance (97%) and SMEDDSPF2 showed lowest percent transmittance (94%) (Table-3). It was observed that with decreasing proportion of oil, clarity significantly increased.

Rheological determination: From the rheological study, the viscosity of PF2, PF3, PF4 and PF5 was low than OF6, OF7, OF8 and OF9. The viscosity of SMEDDSPF2was also found to be less than PF3, PF4 and PF5 (Table-3). Rheological study indicated that few formulations with peppermint showed less viscosity than those with oleic acid. This might be due to the fact that viscosity of pippermint oil is low than oleic acid which produced less viscous formulations. Moreover, it was also observed in case of formulations with peppermint oil that the high proportion of surfactant to cosurfactant (PF3, PF4 and PF5) resulted in increased viscosity and more viscous formulations.

Drug content analysis: Drug content of all eight formulations was in the range of 71.00% to 90.54%. The maximum drug content was found in OF9 and PF5 in comparison to other formulations (Table-3). All the formulations had high drug content with OF9 and PF5 showing maximum, which might be due to presence of high amount of surfactant and cosurfactant which solubilized more drug.

Determination of droplet size and zeta potential: Both rate and extent of drug absorption are determined by droplet size of emulsion [36]. Rapid absorption and improved bioavailability is favoured by small particle size of emulsions. The average particle size of oleic acid containing SMEDDSs was in the range of 132.9 to 180.7 nm and pippermint oil containing formulations was in the range of 218.5 to 248.3 nm. Sample OF9 from oleic acid containing formulation and another sample PF5 from pippermint oil containing formulation had the smaller droplet size *i.e.* 132.9 and 218.5 nm, respectively (Fig. 4).

Zeta potential is another important factor determining the stability of microemulsions. High zeta potential value of a microemulsion indicates that aggregation between the molecules is prevented conferring better stability to formulations. Oil and surfactant molecules charge could have contributed to negative zeta potential value of SMEDDS formulations. Zeta potential of all formulations fitted with the requirement of zeta potential for stability indicating that the formulations had good stability. Free fatty acids in oil contribute to charge on SMEDDS

TABLE-3
SELF EMULSIFICATION TIME, VISUAL GRADES, CLOUD POINT MEASUREMENT, % TRANSMITTANCE, VISCOSITY AND % DRUG CONTENT OF PREPARED SMEDDS FORMULATIONS

Formulation batch	Self emulsification time (s)	Visual observation based on grades	Cloud point (°C)	Transmittance (%)	Viscosity (cp)	Drug content (%)
OF6	85 ± 0.21	B	75 ± 0.23	90.75 ± 0.35	110.60 ± 0.23	73.05 ± 0.68
OF7	71 ± 0.36	B	80 ± 0.19	92.06 ± 0.51	113.51 ± 0.51	79.45 ± 0.55
OF8	40 ± 0.45	A	85 ± 0.14	94.30 ± 0.41	116.46 ± 0.18	84.28 ± 0.15
0F9	30 ± 0.22	A	90 ± 0.11	97.00 ± 0.23	120.31 ± 0.11	90.54 ± 0.26
PF2	70 ± 0.21	B	68 ± 0.16	85.00 ± 0.19	41.19 ± 0.13	71.00 ± 0.21
PF3	88 ± 0.25	B	74 ± 0.25	88.00 ± 0.26	44.24 ± 0.22	74.00 ± 0.42
PF4	52 ± 0.38	A	77 ± 0.28	91.00 ± 0.32	46.47 ± 0.14	81.00 ± 0.19
PF5	38 ± 0.29	A	85 ± 0.12	94.00 ± 0.25	49.11 ± 0.21	89.00 ± 0.31

Data expressed as mean ± SD (n = 3)

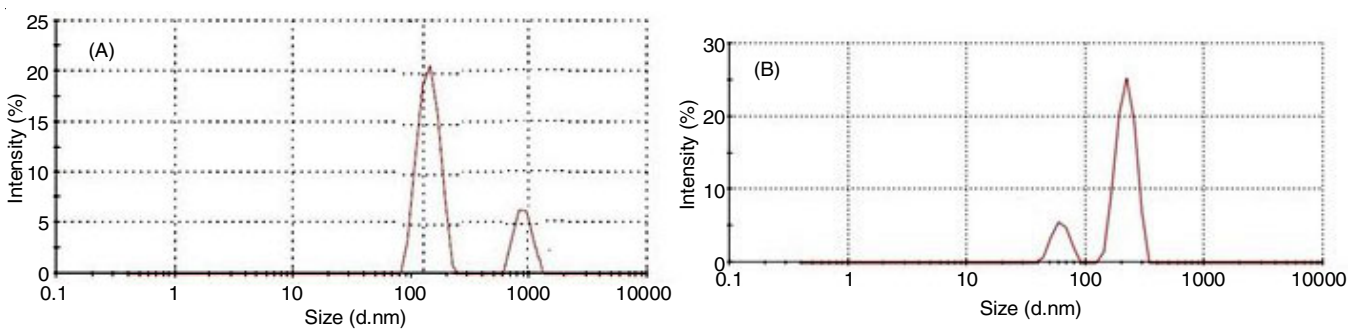

Fig. 4. Particle size of SMEDDSOF9 (A) and SMEDDSPF5 (B)

formulations leading to high zeta potential [25,29]. It was evident from drug release studies *in vitro* that in pH 7.4, the drug release of all SMEDDS was higher as comparison in pH 1.2. This was due to the fact that increased pH results in increased solubility [17]. The zeta potential of all SMEDDS was in the range of -16.9 to -32.2 mV (Fig. 5). The SMEDDS formulations *i.e.* OF9 and PF5 showed the highest release.

***in vitro* Dissolution study:** At pH 1.2 buffer, the drug release of OF6, OF7, OF8 and OF9 was from 73.47% to 85.92% and PF2, PF3, PF4 and PF5 was from 73.21% to 84.25%. But in phosphate buffer pH 7.4, the drug release of OF6, OF7, OF8 and OF9 was from 81.15% to 98.56% and PF2, PF3, PF4 and PF5 was from 83.92% to 95.59%. SMEDDS formulations OF9 and PF5 showed the highest release of 98.57% and 95.59% respectively whereas plain drug showed drug release of 42% at 2 h in pH 7.4 (Fig. 6). Thus, the drug release from OF9 and PF5 formulation was significantly higher than the pure drug ($p < 0.01$) (Table-4).

TABLE-4
PROVIDES THE TUKEY HSD RESULT OF PAIR OF TREATMENTS IS SHOWING *p*-VALUE IS LESS THAN 0.01. A: OF9; B: PF5: C: PURE DRUG

Treatment pair	Tukey HSD Q statistic	Tukey HSD *p*-value	Tukey HSD inference
A *vs.* C	120.5979	0.0010053	$^{**}p < 0.01$
B *vs.* C	102.3368	0.0010053	$^{**}p < 0.01$

***in vitro* Diffusion study:** *in vitro* Diffusion study was performed using formulations OF9 and PF5 due to their highest percentage of drug release in 2 h. After 6 h of diffusion experiment, 93.71% of drug was diffused from OF9, while 90.27% of drug was diffused from PF5 whereas plain drug suspensions diffused only 38.01% at the entire time (Fig. 7). Diffusion experiments indicated that OF9 and PF5 diffused drug in higher amount than plain drug formulation. This suggests that both formulated SMEDDS improved the solubilization of EPM. Both formulations OF9 and PF5 diffused higher percentage of drug using goat intestine as compared to plain drug indicating that drug diffusion from the intestine is enhanced with SMEDDS. This could be because of microemulsion droplets formation in micron rampresence of surfactants reducing the interfacial tension of formulation.

***ex vivo* Intestinal permeability study:** After 6 h of diffusion, 74.22% of drug was diffused from OF9 formulation and 72.23% of drug released from PF5 formulation whereas the plain drug suspension was diffused only 33.17%. The *ex vivo* release study of both the formulation was fitted to the first order kinetic model due to their highest R^2 value ($R^2 = 0.9920$ and 0.9951). It was indicated that the release kinetic of both the formulation were concentration dependent and the release mechanism followed non-fickian diffusional release kinetics due to n values in korsemeyer peppas model observed from SMEDDS formulation OF9 (0.509) and PF5 (0.595). But the observed n

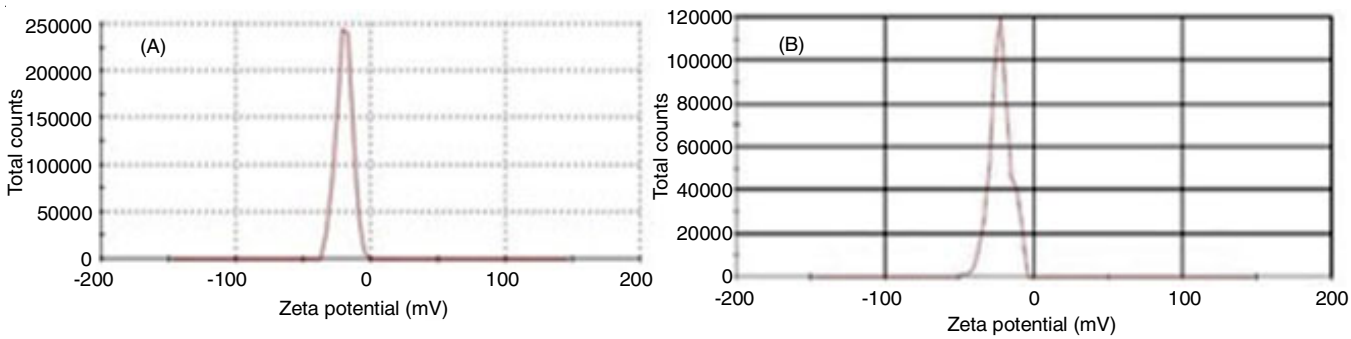

Fig. 5. Zeta potential of SMEDDSOF9 (A) and SMEDDSPF5 (B)

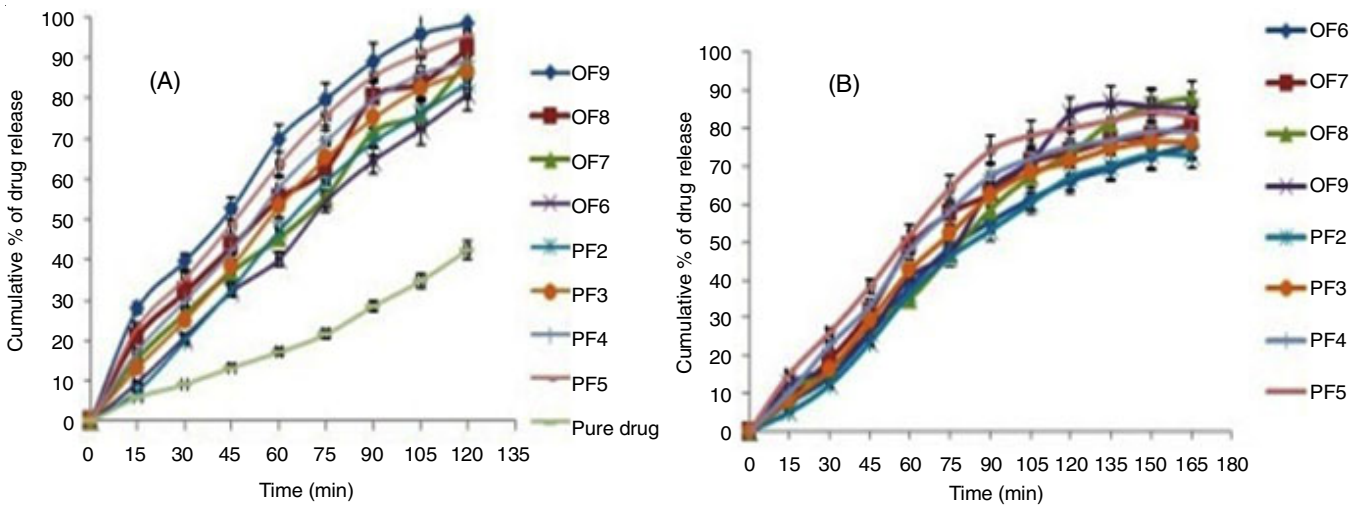

Fig. 6. *in vitro* Dissolution profile of SMEDDS formulations and pure drug at pH 1.2 (A) and pH 7.4 (B). (n = 3; Mean ± SD)

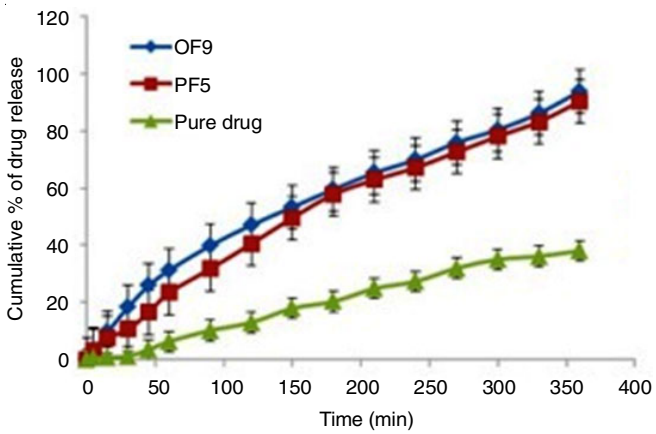

Fig. 7. *in vitro* Diffusion profile of SMEDDS formulations (OF9 and PF5) and compared with plain drug suspension. (n = 3; Mean ± SD)

values were close to the 0.45, which can be said that the release mechanism was fickian diffusional release kinetic (Fig. 8).

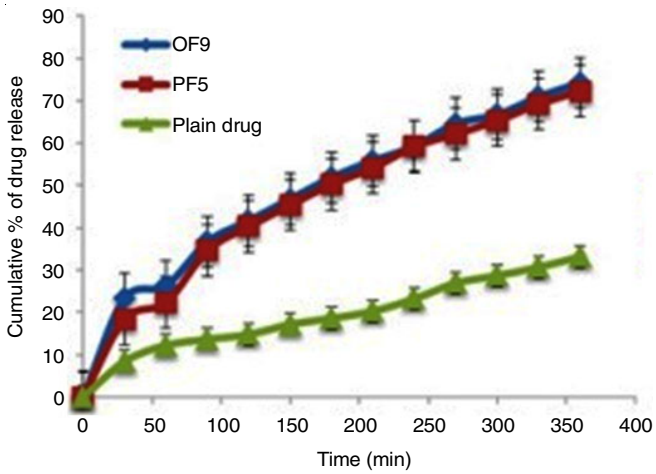

Fig. 8. *ex vivo* Intestinal permeation profile of SMEDDS formulations (OF9 and PF5) and compared with plain drug. (n = 3; Mean ± SD)

FTIR study: Eprosartan powder exhibits a C=O (carboxylic acid) stretching vibration at 1714.41 cm^{-1}, C=O (carboxylate ion) stretching vibration at 1648.84 cm^{-1}, C-H stretching vibration at 1540.85 cm^{-1}, C=C (aromatic ring) stretching vibration at 1614.13 cm^{-1}, CH_2 (mesylate group) stretching vibration at 2956.34 cm^{-1}, O-H stretching vibration at 3479.92 cm^{-1}, C-N (imidazole) stretching vibration at 1049.09 cm^{-1}, SO_2 (symmetrical) sulphonic acid stretching vibration at 1163.83 cm^{-1} and sulphonic acid (asymmetrical) stretching vibration at 1418.39 cm^{-1}. All the above mentioned characteristic peaks of eprosartan were also present in spectra of OF9 and PF5 (Fig. 9). From all above the data from different analysis it was confirmed that SMEDDSOF9 was found to be best formulation than SMEDDSPF5.

Conclusion

In this study, SMEDDS was formulated using oleic acid, peppermint oil, Tween 80 as surfactant and PEG 400 as co-surfactant. Thermodynamic stability along with good self-emulsification efficiency, highest drug content along with droplet size in the micrometer range was obtained in all the prepared SMEDDSs. Significantly higher dissolution rate and *in vitro* diffusion rate were shown by SMEDDSs containing eprosartan mesylate in comparison to plain drug suspensions. Higher drug diffusion of both the SMEDDS across the intestinal membrane was observed in *ex vivo* studies as compared to plain drug suspensions. The release kinetic of both the formulation followed Fickian diffusional release kinetics. FTIR analysis confirmed that drug and excipients did not interact. Stability of SMEDDS was indicated by cloud point measurement and formulations did not show any precipitation with increase in temperature. Thus, from these observations, SMEDDSOF9 showed best effect on solubility and intestinal permeability of Eprosartan mesylate. Therefore, it is concluded that SMEDDS using vegetable oil (oleic acid) is a promising and an efficient drug delivery system for drugs with less water solubility and systemic bioavailability, offering a therapeutic advantage.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

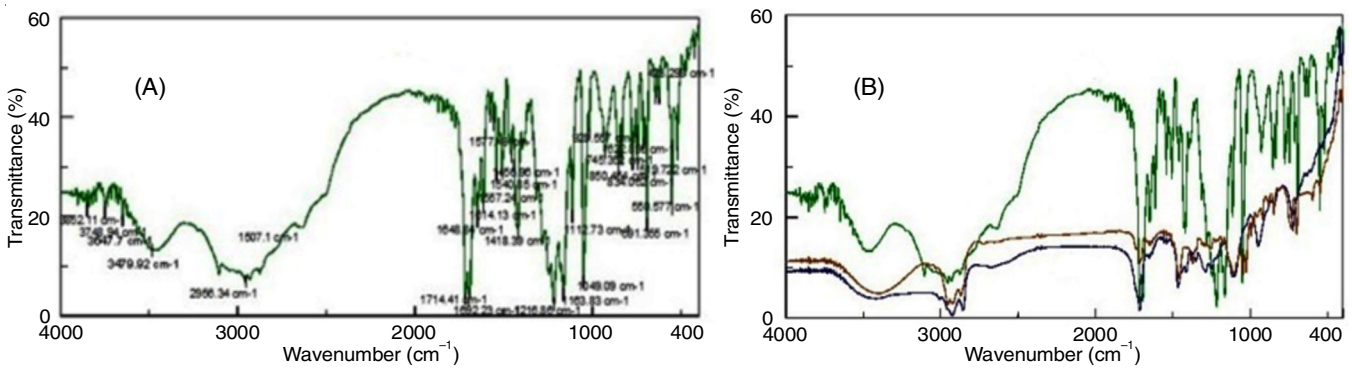

Fig. 9. Fourier transform infrared spectra of plain drug (A) and (B) represents FTIR spectra of plain drug (A), OF9 (B) and PF5 (C)

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