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Original Article

FORMULATION AND EVALUATION OF ORAL SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM OF CANDESARTAN CILEXETIL

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ABSTRACT

Objective: The objective of our investigation was to formulate a liquid self micro emulsifying drug delivery system (SMEDDS) of candesartan cilexetil that could improve its solubility, stability, and oral bioavailability.

Methods: The prepared SMEDDS was the concentrate of drug, oil, surfactant, cosurfactant. The formulation was evaluated for various tests like solubility, Drug-surfactant compatibility, particle size, zeta potential, *in vitro* dissolution, etc.

Results: The optimized formulation C7IIB showed drug release (99.91%), droplet size (9.15 nm), Zeta potential (-23.2), viscosity (0. 8824 cP) and infinite dilution capability. *In vitro* drug release of the C7IIB was highly significant ($p<0.05$) as compared to marketed conventional tablet (M).

Conclusion: The present investigation shows that candesartan cilexetil Self microemulsifying drug delivery system can be formulated as unit dosage form. The C7IIB can be further used for the preparation of various Solid SMEDDS(S-SMEDDS) formulations.

Keywords: Self microemulsifying drug delivery system, Candesartan cilexetil, Drug release, Stability study, Bioavailability

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INTRODUCTION

Candesartan cilexetil is an esterified prodrug of candesartan, a nonpeptide angiotensin II type 1(AT_1) receptor antagonist used in the treatment of hypertension. Based on its solubility across physiological relevant pH conditions and absorption characteristic, candesartan cilexetil is classified in the Biopharmaceutical classification system as a class II dug. Low solubility of candesartan cilexetil across the physiological pH range is reported to result in incomplete absorption from the GI tract and hence is reported to have an oral bioavailability of about 15%. candesartan cilexetil is a highly lipophilic compound and has good solubility in tri and diglyceride oils.

Thus,a novel oral formulation of candesartan cilexetil can be developed which increases its solubility and enhances permeability across the biological membrane to overcome its poor bioavailability.

Lipid-based formulation approaches, particularly the self-microemulsifying drug delivery system (SMEDDS), are well known for their potential as alternative strategies for delivery of hydrophobic drugs [1], which are associated with poor water solubility and low oral bioavailability[2, 3]. SMEDDS formulations are isotropic mixtures of an oil, a surfactant, a co surfactant (or solubilizer), and a drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases (i.e., the digestive motility of the stomach and intestine provide the agitation required for self-emulsification *in vivo* in the lumen of the gut)[4].

This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption [5]. Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption [1]. Selection of a suitable self-emulsifying formulation depends upon the assessment of (i) the solubility of the drug in various components, (ii) the area of the self-emulsifying region as obtained in the phase diagram, and (iii) the droplet size distribution of the resultant emulsion following self-emulsification [6].

The objective of this study was to develop and characterize liquid SMEDDS of candesartan cilexetil for increasing solubility and permeability across the biological membrane to improve the bioavailability, dosing frequency, *in vitro* dissolution as well as enhance patient compliance.

MATERIALS AND METHODS

Materials for component selection

Candesartan cilexetil was obtained as a gift sample from Alembic Pharma Ltd, Baroda, Gujarat. Transcutol P, Capryol 90, Plurol Oleique, Labrasol, Labrafil 1944 CS, Peceol were obtained as a gift sample from Gattefosse, France. Captex 500, Capmul MCM (C8), Captex 200, Captex 200 P, Captex 355 were kindly gifted by Abitec Corporation, Janesville, USA. Polyethylene Glycol 400 was purchased from Suvidhinath Chemicals. The other chemicals used were of the analytical grades. Double-distilled water was used throughout the study.

Screening of components

The most important criterion for the screening of components for SMEDDS is the solubility of poorly soluble drug in oils, surfactants and co-surfactants. Since the aim of this study is to develop an oral formulation, therefore, solubility of drug in oils is more important as the ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oil phase. In this study excess amount of drug was added to 2 ml of each vehicle separately in screw capped glass vial and mixture was heated to 60 °C in water bath under continuous stirring using a vortex mixture to facilitate drug solubilization. The vials were then kept at 25±1.0 °C in an isothermal shaker for 72 h to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 2000 rpm for 10 min. The supernatant was taken, filtered and diluted with methanol. The concentration of candesartan cilexetil was determined for various vehicles using HPLC technique [13, 14, 16].

Preparation of candesartan cilexetil SMEDDS

A series of SMEDDS formulations were prepared using various oils, Surfactants and Co-surfactants as shown in table 1. In all the

formulations, the level of Candesartan cilexetil was kept constant (i.e. 32 mg). The amount of oil should be such that it should solubilize the drug (single dose) completely. Candesartan cilexetil was added in the oil phase and solubilized. Then the mixture of surfactant and co-surfactant (Smix) was added in the oil phase, mixed by gentle stirring, vortex mixing and heating at 37±0.5 °C. The mixture was stored at room temperature until used. Thus, the prepared SMEDDS was the concentrate of oil, surfactant, cosurfactant and drug. Total 96 liquid formulations were prepared using various surfactants and cosurfactant concentrations.

Table 1(a): Various formulations of candesartan cilexetil SMEDDS

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8
Candesartan cilexetil	√	√	√	√	√	√	√	√
Capryol 90	√	√	√	√	√	√	√	√
Labrasol				√	√		√	√
Peceol	√							
Plurol Oleique	√							
Transcutol P		√	√					
Tween 80						√		
Lauroglycol		√	√					
Capmul MCM (C8)				√				
Capmul MCM (EP)					√			
Acconon cc-6						√		√
Captex 500							√	

Table 1(b): Various concentrations of oil and S/CoS

Code	Amount of oil (%)	Code	Ratio of S/CoS
I	5	A	1:1
II	10	B	2:1
III	15	C	1:2
		D	3:1

Drug and surfactant compatibility study

Physical compatibility of the water-insoluble drug with surfactants should be used in surfactant selection procedure. Physical compatibility may include precipitation/crystallization, phase separation and color change in the drug–surfactant solution during course study. Chemical compatibility is primarily regarded as the chemical stability of the drug in a surfactant solution. A surfactant was considered for further development only if it was physically and chemically compatible with drug [15].

Pseudoternary phase diagram

The existence of microemulsions regions was determined by using pseudo-ternary phase diagrams. SMEDDS were diluted under agitation conditions using water titration method [17]. The mixture of oil and Smix at certain weight ratios were diluted with water in a dropwise manner. Phase diagrams were constructed in the presence of drug to obtain the optimum concentrations of oil, surfactant and co-surfactant. SMEDDS form fine oil-water emulsion upon addition to an aqueous media under gentle agitation. Distill water was used as an aqueous phase for the construction of phase diagrams. As the free energy required for forming an emulsion is very low, the formation is thermodynamically spontaneous. The surfactants used in formulation form a layer around the emulsion droplets thus reducing the interfacial energy and providing a mechanical barrier. The spontaneity was measured by visual observations. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the Smix ratio [17].

Thermodynamic stability

Heating cooling cycle

Six cycles between refrigerator temperature 4 °C and 45 °C with storage at each temperature of not less than 48hr was studied. Those formulations, which were stable at these temperatures, were subjected to centrifugation test.

Centrifugation

Passed formulations were centrifuged at 3500 rpm for 30 min. Those formulations that did not show any phase separation were taken for the freeze-thaw stress test.

Freeze-thaw cycle

Three freeze-thaw cycles between-21 °C and+25 °C with storage at each temperature for not less than 48hr was done for the formulations. Those formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility test for assessing the efficiency of self-emulsification. The formulations were observed visually for any phase separation or color change.

Dispersibility test

The efficiency of self-emulsification of oral SMEDDS was assessed using a standard USP XXII dissolution apparatus 2[18]. 1 ml of each formulation was added to 500 ml of water at 37±0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in vitro* performance of the formulations was visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) microemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear microemulsion, having a bluish-white appearance.

Grade C: Fine milky microemulsion that formed within 2 min.

Characterization of smedds of candesartan cilexetil

Viscosity and pH

The viscosities were measured to determine rheological properties of formulations. Brookfield LVDV 111+CP viscometer at 30 °C with a CPE 42 spindle at 5 rpm was used to serve this purpose. The pH of the formulations was measured using pH meter.

Globule size and ζ-potential analysis

One gram of SMEDDS was dispersed in 100 ml distilled water and 0.1 mol/l HCl, at 37±0.5 °C. The resultant emulsions were prepared by gentle agitation for 10 min using a magnetic stirrer. The globule size and ζ-potential of the resulting microemulsions was determined using Malvern zeta sizer.

% Transmittance

The % transmittance of various formulations was measured at 254 nm using UV spectrophotometer keeping methanol as a blank.

Polydispersibility index

The procedure for preparation of the sample is same as for globule size and zeta potential. The poly dispersibility index is measured using the Malvern zeta sizer.

***In vitro* diffusion study**

In vitro drug diffusion study was carried out by using dialysis bag method. Dialysis bag was soaked overnight in 0.1 N HCl for saturation purpose and then it was further used for experimental procedure.1 ml of candesartan cilexetil SMEDDS diluted with aqueous phase was instilled in dialysis bag and one end was tied with thread and was placed in 900 ml of 0.02% Tween 20 in 0.1 N HCl as dissolution medium at 37±0.5 °C temperature. The revolution speed of paddle was maintained at a rate of 50 rpm [19]. An aliquot of 5 ml was withdrawn at regular time intervals of 0, 5, 10, 20, 30, 45 and 60 min. The SMEDDS formulation was compared with the conventional marketed tablet formulation (Atacand 32 mg tablet) and the suspension of pure drug. The samples were analyzed for the drug content using HPLC method at 254 nm.

RESULTS AND DISCUSSION

Screening of components

One important consideration when formulating a self-micro emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen *in vivo*. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results from solubility studies are reported in table 2. The solubility of candesartan cilexetil was found to be highest in Capryol 90 (80.12±4.04 mg/ml) as compared to other oils while in water it was 0.09±0.01 mg/ml. This may be attributed to the polarity of the poorly water soluble drugs that favor their solubilization in small/medium molecular volume oils such as medium chain triglycerides or mono-or diglycerides [30]. Thus, Capryol 90 was selected as the oil phase for the development of the formulation.

Table 2: Solubility study of candesartan cilexetil in various vehicles (oils, surfactants, Co surfactants and distill water) at 25 °C

Solvent	Solubility
Transcutol P	253.1±0.27
Plurol oleique	169.21±2.19
Labrasol	159.7±3.53
Capryol 90	80.12±4.04
Labrafil 1944 CS	49.76±1.13
Captex 200	5.67±0.68
Captex 200 P	7.29±0.94
Captex 355	10.31±1.02
Capmul MCM	35.02±1.32
Tween 80	261.09±2.85
PEG 400	108.13±3.22
IPM	22.54±0.29
Lauroglycol FCC	177.05±1.54
Capmul MCM (C8)	198.70±2.13
Acconon CC-6	181±1.76
Captex 500	191.35±2.78
Capmul MCM EP	173.64±1.19
Distill water	0.09±0.01

*mean±SD, n=3

Drug and surfactant compatibility study

Physical and chemical compatibility of the water-insoluble drug candesartan cilexetil with various surfactants and co-surfactants was carried out to check the physical as well as chemical compatibility. As shown in table 3, all the formulations passed the physical as well as chemical compatibility tests. The formulations did not show any changes during the compatibility studies and were found to be stable. Further studies were carried out using these formulations [30].

Table 3: Drug surfactant compatibility study

Formulation	Precipitation	Crystallization	Phase separation	Color change
C1	√	√	√	√
C 2	√	√	√	√
C 3	√	√	√	√
C 4	√	√	√	√
C 5	√	√	√	√
C6	√	√	√	√
C7	√	√	√	√
C8	√	√	√	√

Where, √-Passed and ×-Failed

Pseudoternary phase diagram

Self-micro emulsifying systems from fine oil-water emulsions with only gentle agitation, upon their introduction into aqueous media. Surfactant and co-surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the microemulsion formulation [9, 10]. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion.

In the present study capryol 90 was tested for phase behavior studies with labrasol and Captex 500 as the S/CoS mixture. As seen from the ternary plot C7IIB gave a wider microemulsion region at all S/CoS ratios. The microemulsion area increased as the S/Cos ratios increased. However, it was observed that increasing the surfactant ratio resulted in a loss of flowability. Thus, an S/CoS ratio 10% 2:1 was selected for the formulation study.

Viscosity and pH

The viscosity of microemulsion systems can be monitored by standard rheological techniques. All the formulation has a viscosity which is highly similar to that of water i.e.1.0. Thus, it shows that SMEDDS forms o/w microemulsion and water remains as external phase. The results of viscosity are as shown in table 4.

The excipients used in the formulation decide the pH of the final preparation. The change in the pH may affect the zeta potential of the formulation which in turn can affect the stability of preparation. All the formulations showed similar pH values in the range of 5.1 to 6.0. Thus, pH is not affecting stability. Therefore, it can be assumed that drug is not diffusing in the external phase and remains in the oil phase. Since water is the external phase entire system showed pH of water. Candesartan cilexetil is unstable in alkaline pH. Here the formulations show acidic to neutral pH which is suitable for the stability of Candesartan cilexetil.

Table 4: Viscosity and pH of various SMEDDS formulations

Formulation code	Viscosity (cp)	pH
C 4III D	0.8865	5.12
C7III D	0.8887	5.57
C4 II B	0.8812	5.88
C7 II B	0.8824	5.14

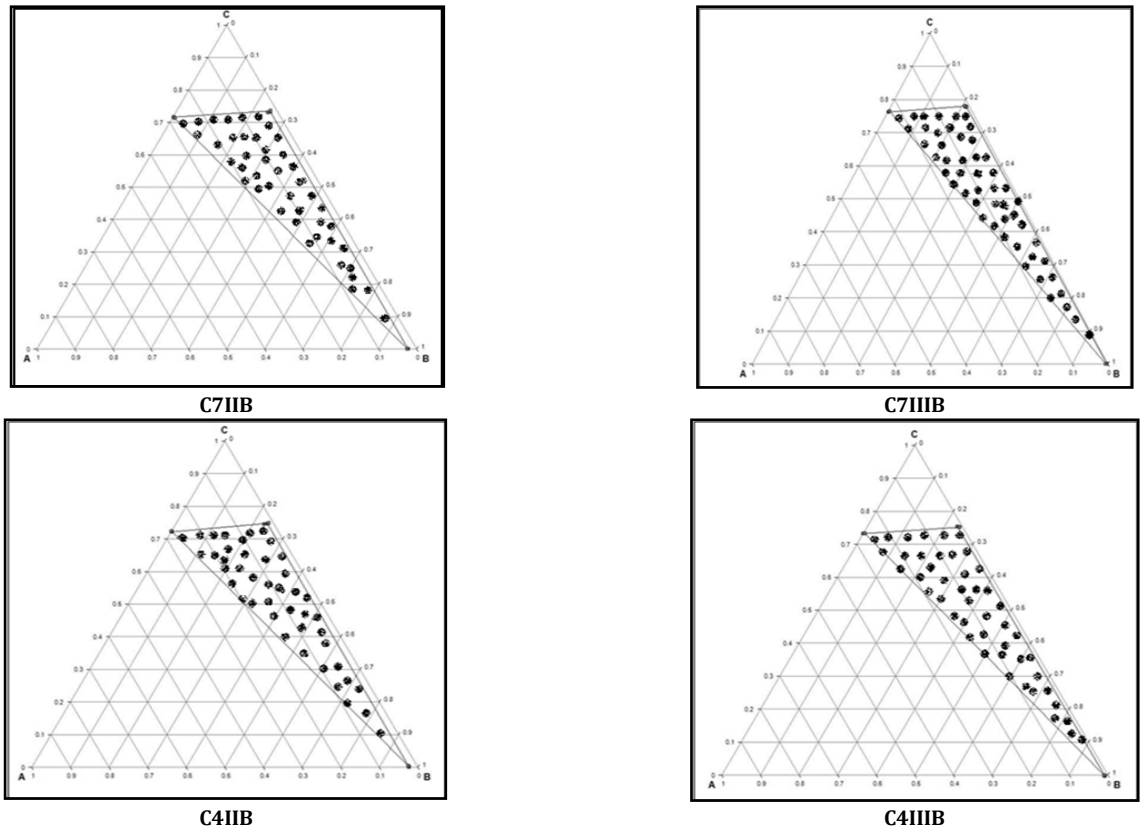

Fig. 1: Phase diagrams for various liquid SMEDDs formulations

Dispersibility and thermodynamic stability

In the present study, we used distilled water as a dispersion medium because it is well reported that there is no significant difference in the microemulsions prepared using nonionic surfactants, dispersed in either water or simulated gastric or intestinal fluid [32]. Keeping the criteria of increasing oil concentration and minimum amount of surfactant used for its solubilization, one formulation for each percent of oil (5%, 10% and 15%) was selected irrespective of the Smix ratio used for that percent of oil. The results for the dispersibility test are as shown in table 5.

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. Thus, the selected formulations were subjected to different thermodynamic stability by using heating-cooling cycle, centrifugation, and freeze-thaw cycle stress tests. Those formulations, which survived thermodynamic stability tests, were taken for dispersibility test. It was observed that formulation prepared from Capryol 90 as oil; Labrasol as surfactant whereas Captex 500 and Capmul MCM (C8) as co surfactant pass the thermodynamic stress tests and thus were used for further study. The results are as shown in table 5.

Table 5: Thermodynamic stability and dispersibility test of different formulations

Formulation code	A	B	C	D
C2I	Xx	xx	Xx	Xx
C2II	Xx	xx	Xx	+
C2III	Xx	xx	Xx	+
C4I	+	+	X	+
C4II	+	+	+	+
C4III	+	+	+	+
C7I	+	+	+	+
C7II	+	+	+	+
C7III	+	+	+	+
C8I	+	+	+	+
C8II	+	+	+	+
C8III	+	+	+	+

Where; I-5%; II-10% and III-15% oil concentration. Also, Whitish-XX; Slightly whitish-X and clear-+is visual appearance.

Globule size and ζ-potential analysis

The globule size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as drug absorption. Also, it has been reported that the smaller globule size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability [34].

Fig. 2 shows the particle size distribution of candesartan cilexetil SMEDDS diluted with water and 0.1 mol/l HCl, respectively. The optimal batch was C7IIB with mean globule size 9.15 nm in water.

SMEDDS produced a resultant emulsion with a small mean globule size and a narrow globule size distribution regardless of the dispersion medium. The blank SMEDDS formulation exhibited

almost no charged emulsion whereas a negatively charged emulsion was obtained with drug-loaded SMEDDS. This may be because the emulsifier used in the formulation was a nonionic surfactant. The optimal batch C7IIB has the least zeta potential i.e.-23.2 mV which highest zeta potential towards the negative side. The zeta potential governs the stability of microemulsion; it is important to measure its value for the stability of samples. A negative force means a negative potential between the droplets.

Table 6: Particle size and zeta potential of the optimized batch C7IIB of candesartan cilexetil SMEDDS

Formulation code	Avg. particle size (nm)		Zeta potential
	Water	HCL	
C7II B	9.15	24.5	-23.2

n=3

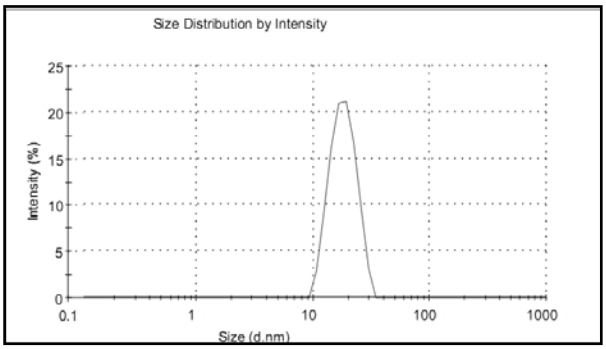

Fig. 2(a): Particle size of formulation C7IIB in 0.1 N HCL

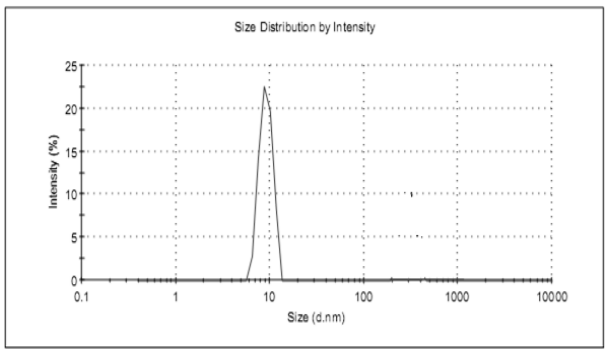

Fig. 2(b): Particle size of formulation C7IIB in water

% Transmittance

The clarity of microemulsions was checked by transparency, measured in terms of transmittance (%T). SMEDDS forms o/w microemulsion since water is an external phase. Formulation C7 has % transmittance value greater than 99%. These results indicate the high clarity of microemulsion. The results of %T are as shown in table 7.

Table 7: % Transmittance for C7IIB formulation

Period (mo)	%T	
	25˚C	40˚C
0	99.7±0.2	99.6±0.3
1	99.6±0.5	99.4±0.2
2	99.4±0.3	99.2±0.5
3	99.3±0.6	95.4±0.7
6	99.1±0.2	80.3±0.6

mean±SD, n=3

Polydispersibility index (PDI)

Polydispersibility, which determines size range of particles in the system, is measured by;

$$\frac{\text{No. of particles having size greater than 100 nm}}{\text{No. of particles having size less than 100 nm}} \quad \text{---------- (1)}$$

It is expressed in terms of poly dispersibility index (PDI). An ideal SMEDDS should be widely distributed with particles less than 100 nm and so PDI should be less than 0.3 or in other words, particles having size more than 100 nm should be maximum up to 23%. The data are as shown in table 8. The results show that formulations C3ID and C3IB does not pass the test as they have PDI more than 0.3 whereas remaining all formulations pass the test as they have PDI less than 0.3.

Table 8: Polydispersibility index of candesartan cilexetil SMEDDS formulations

Formulation code	PDI
C4 II D	0.136
C4II B	0.096
C7 II D	0.246
C7II B	0.221

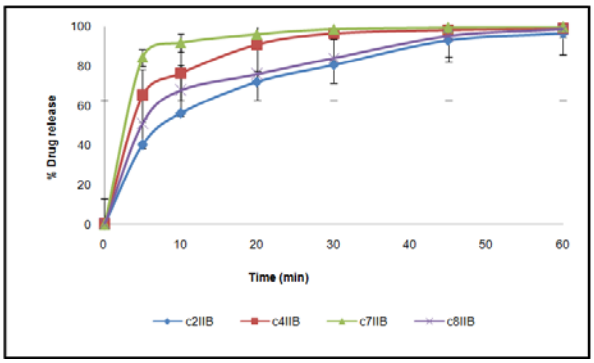

Fig. 3(a): *In vitro* diffusion study of various SMEDDS formulation

In vitro diffusion study

Sink conditions are often violated when using conventional release methods for dispersed systems. So, methods must be developed for SMEDDS to separate the dissolved drugs from micro emulsion-associated drugs before their determination. It has been reported that a dialysis method and an ultrafiltration method have been applied to candesartan SMEDDS, and a relatively high release rate was obtained using the latter. In this study, a bulk-equilibrium reverse dialysis bag method was developed to allow an increase in the membrane surface area available for transport from the donor to the receiver phases and, hence, to maintain sink conditions in the donor phase by infinite dilution of the emulsion in the outer vessel.

In the dissolution media, 0.02% of tween 20 was added since it provided better discrimation between the formulations. The faster dissolution from SMEDDS may be attributed to the fact that in this formulation, the drug is a solubilized form and upon exposure to dissolution medium results in small droplets that can dissolve rapidly in the dissolution medium.

The dissolution profile for formulations C2II B, C4II B, C7II B and C8II B is as shown in the fig. 3. The formulation C7IIB showed

highest release rate among all the liquid SMEDDS formulations i.e. 92.01% in 10 min which is highest among all batches. In this case, the drug was present in the form of micro globules of microemulsion and water was an aqueous phase. Due to low size of microemulsion particles, they easily diffuse through the dialysis membrane [19]. The results indicate that candesartan cilexetil SMEDDS can be diluted previously with aqueous phase before performing the *in vitro* release test in dialysis bag. Thus, *in vitro* study concludes that release of candesartan cilexetil was greatly enhanced by SMEDDS formulation. The batch C7IIB was thus taken for further studies and comparison.

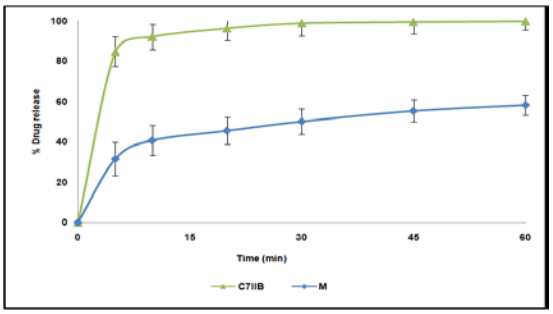

Fig. 3(b): *In vitro* diffusion study of C7IIB and M

CONCLUSION

A SMEDDS formulation of a poorly water soluble drug, candesartan cilexetil was formulated for oral administration. The formulation C7IIB was found to be the optimized formulation on the base of results of pseudo ternary phase diagram, *in vitro* drug release, droplet size and zeta potential. The optimized formulation showed rapid self-emulsification in aqueous media. *In vitro* drug release of the C7IIB was highly significant ($p<0.05$) as compared to conventional marketed tablet (M). The results from the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like candesartan cilexetil.

CONFLICT OF INTERESTS

Declared none

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