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Research Article

FORMULATION AND EVALUATION OF SELF MICRO EMULSIFYING SYSTEM OF CANDESARTAN CILEXETIL

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ABSTRACT

The present work was aimed at formulating a SMEDDS (self-microemulsifying drug delivery system) of candesartan cilexetil and evaluating its *in vitro* and *in vivo* potential. The solubility of candesartan cilexetil was determined in various vehicles. Pseudoternary phase diagrams were used to evaluate the microemulsification existence area, and the release rate of candesartan cilexetil was investigated using an *in vitro* dissolution test. SMEDDS formulations were tested for microemulsifying properties, and the resultant microemulsions were evaluated for various evaluation parameters. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsions. The optimized formulation was composed of Transcutol P as oil, Capryol 90 as surfactant and Plurol Oleique as co surfactant. The SMEDDS formulation showed complete release in 60 minutes .Thus, the study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of Candesartan cilexetil to improve its bioavailability.

Keywords: Candesartan cilexetil, Particle size, Self emulsification, Bioavailability, Pseudoternary phase diagrams.

INTRODUCTION

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. [2-4]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).[5] 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. [6] 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 (1) the solubility of the drug in various components, (2) the area of the self-emulsifying region as obtained in the phase diagram, and (3) the droplet size distribution of the resultant emulsion following self-emulsification. [7]

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. These factors, may contribute toward absorption via the lymphatic route. The aim of our present study was to develop a SMEDDS formulation of candesartan cilexetil and characterize for its ability to form a microemulsion based on its particle size, zeta potential and in-vitro dissolution studies.

MATERIALS

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. Capmul MCM, Captex 200, Captex 200 P, captex 355 were kindly gifted by Abitec Corporation, Janesville, USA.The other chemicals used were of the analytical grades.

METHODS

Solubility studies

The saturation solubility of candesartan cilexetil was determined in various oils, surfactants and co-surfactants. The excess amount of drug was added to each screw capped glass vials containing 2 ml of vehicle in a water bath with constant stirring using a vortex mixture to facilitate drug solubilization. The mixture was kept at ambient temperature for 72 hr. to attain equilibrium. The samples were than centrifuged at 2000 rpm for 15 min and then the supernatant was taken. The aliquots of supernatant were diluted and drug assay was performed.

Pseudoternary phase diagrams

Pseudoternary phase diagrams of oil, surfactant/ co surfactant (S/CoS), and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a dropwise manner. For each phase diagram at a specific ratio of S/CoS (i.e., 1:1,1:2, 2:1, 3:1, and 4:1 wt/wt), a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 minutes. Then each mixture was titrated with water and visually observed for phase clarity and flowability. 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 S/CoS mixing ratio. To determine the effect of drug addition on the microemulsion boundary, phase diagrams were also constructed in the presence of drug using drug-enriched oil as the hydrophobic component. Phase diagrams were then constructed using Ternary phase diagram software.

Preparation of SMEDDS formulations

A series of SMEDDS formulations were prepared using Capryol 90 and Plurol Oleique CC 497 as the S/CoS combination and Transcutol P as the oil (Table 1). In all the formulations, the level of candesartan cilexetil was kept constant. Briefly, accurately weighed candesartan cilexetil was placed in a glass vial, and oil, surfactant, and co surfactant were added. Then the components were mixed by gentle stirring and vortex mixing and were heated at 40ºC on a magnetic stirrer, until candesartan cilexetil was perfectly dissolved. The mixture was stored at room temperature until further use.

Table 1: Formulations of SMEDDS of candesartan cilexetil

Component	Formulation A	Formulation B	Formulation C	Formulation D
Oil	Transcutol P	Transcutol P	Transcutol P	Transcutol P
Surfactant	Capryol 90	Labrasol	Peceol	Peceol
Co-surfactant	Plurol Oleique	PEG 400	Plurol Oleique	PEG 600

Particle size distribution (PSD) and ζ-potential analysis

One gram of SMEDDS was dispersed in 100 ml of 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. In addition, the PSD and ζ-potential of the final microemulsions were determined immediately using, a Malvern Mastersizer. All studies were repeated in triplicate, with good agreement being found between measurements.

Thermodynamic stability

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

Centrifugation: Passed formulations were centrifuged at 3500 rpm for 30min. 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 48h 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.

Dispensability test

The efficiency of self-emulsification of oral SMEDDS was assessed using a standard USP XXII dissolution apparatus 2. [8] One milliliter of each formulation was added to 900 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.

***In vitro* drug release**

The *in vitro* release of liquid SMEDDS filled in hard gelatin capsule was performed in 900 ml of 0.02% Tween 20 in 0.05 M phosphate buffer, and the temperature was maintained at 37˚ C with paddle operated at 50 rpm.An aliquot of 5 ml was withdrawn at predetermined intervals of 5, 10,15,30,45 and 60 min. Aliquot were analyzed after filtration through Whatman filter paper (No.41), spectrophotometrically at 254 nm.

RESULT AND DISCUSSION

Solubility studies

One important consideration when formulating a self-microemulsifying 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. As seen from the table 2, Transcutol P and Tween 80 showed the highest solubilization capacity for candesartan cilexetil, followed by Plurol Oleique. Thus, for our study we selected Transcutol P as oil and Capryol 90 and Plurol Oleique as surfactant and cosurfactant, respectively.[8]

Table 2: Solubility study of Drug in Oils, Surfactants and Co-surfactants

Vehicle	Solubility (mg/g), mean±SD
Transcutol P	253.1±20.23
Plurol Oleique	169.21±1.54
Labrasol	159.7±2.98
Capryol 90	80.12±0.87
Labrafil 1944 CS	49.76±0.43
Captex 200	5.67±2.76
Captex 200 P	7.29±4.11
Captex 355	10.31±9.81
Capmul MCM	35.02±1.32
	261.09±21.76
PEG 400	108.13±2.34
Iso propyl myristate	22.54±2.77

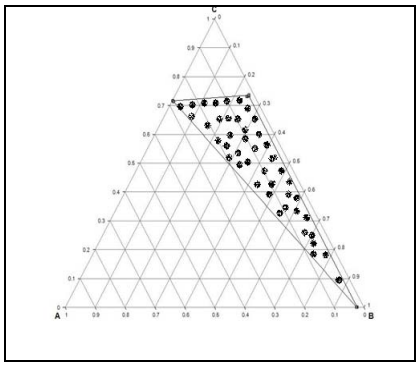
Pseudoternary phase diagrams

Self-microemulsifying systems form 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.

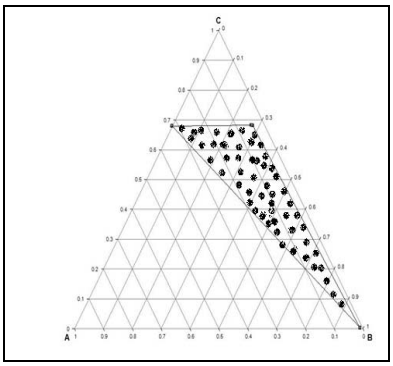
In the present study Transcutol P was tested for phase behavior studies with capryol 90 and Plurol Oleique as the S/CoS mixture. As seen from the ternary plot (Figures 1), Transcutol P gave a wider microemulsion region at all S/CoS ratios. The microemulsion area increased as the S/Cos ratios increased. 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.

Particle size distribution (PSD) and ζ-potential analysis

The droplet size of the emulsion is a crucial factor 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 particle size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. Table 3 shows the particle size of candesartan SMEDDS diluted with water and 0.1 mol/l HCl. All emulsions exhibited a singlet peak in their volume-weighted particle size distribution obtained by the particle size analyzer. The mean particle size of candesartan SMEDDS was 20.5 ± 1.87 nm and 12.3 ±0 .13 nm. These results indicate that the optimal candesartan SMEDDS produced a resultant emulsion with a small mean size and a narrow particle size distribution [11].



S/Cos - 2:1



S/CoS - 3:1

Fig. 1: Pseudoternary phase diagram with following components: Transcutol P (oil), capryol 90 (Surfactant) and Plurol Oleique (co-surfcatant). The dark area indicates the microemulsion region.

Table 3: The particle size and Zeta potential of optimized formulations

Formulation Code	Average droplet size(nm)	Average zeta potential
A	12.3±0.13	-27.9
B	20.5±1.87	-21.3

Thermodynamic stability

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and Co surfactant, with no phase separation, creaming or cracking. It is the thermostability which differentiates nano-or microemulsion from emulsions that have kinetic stability and will eventually phase separate. [13] 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 C and D did not pass the thermodynamic stress tests and thus were dropped for further study. The results are as shown in Table 4.

Dispersibility test:

When infinite dilution is done to formulation, there is every possibility of it to phase separate, as microemulsions are formed at a particular concentration of oil, surfactant and water. For oral formulations the process of dilution by the GI fluids will result in the gradual desorption of surfactant located at the globule interface. The process is thermodynamically driven by the requirement of the surfactant to maintain an aqueous phase concentration equivalent to its CMC.[13]

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 formulations prepared using nonionic surfactants, dispersed in either water or simulated gastric or intestinal fluid.Formulations A and B passed the thermodynamic stability tests whereas formulation C and D did not passed the test. The results are as shown in table 4.

Table 4: Thermodynamic stability and dispersibility test of the formulations

Formulation code	H/C	Cent.	Freeze thaw.	Disperse. grade	Inference
A	√	√	√	A	Passed
B	√	√	√	A	Passed
C	×	×	×	B	Failed
D	×	×	×	C	Passed

Where, H/C-Heating cooling cycle, cent.-centrifugation test, Freeze Thaw.-Freeze thaw cycle and Disperse.-Dispersibility test

***In vitro* drug release 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 microemulsion-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 .The release of candesartan from the SMEDDS in release media is presented in Fig. 2.

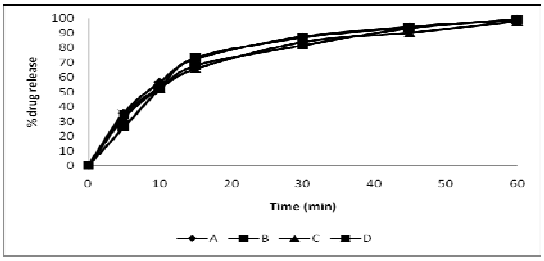


Fig. 2: Release profile of candesartan from SMEDDS in various release medium at 37˚C.

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 release from SMEDDS formulation a with (12.3±0.13) was faster than SMEDDS formulation b with (20.5±1.87) indicating influence of droplet size on the rate of drug dissolution[12].

CONCLUSION

A SMEDDS formulation of a poorly water soluble drug, candesartan cilexetil was formulated for directly filling in hard gelatin capsules for oral administartaion.The formulation A was found to be the optimized formulation on the base of results of pseudoternary phase diagram ,*in vitro* drug release ,droplet size and zeta potential. The optimized formulation showed rapid self emulsification in an aqueous media. The results from the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like candesartan.

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