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A Novel Self – Microemulsifying Formulation To Enhance The Solubility of Cefuroxime Axetil

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ABSTRACT

Poorly, water soluble drugs such as cefuroxime axetil offer challenges in developing a drug product with adequate bioavailability. The main objective of present study was to prepare a lipid based self-microemulsifying drug delivery system to improve the oral bioavailability of cefuroxime axetil. The liquid self - microemulsifying drug delivery system consisted of cefuroxime axetil, Lutrol E 400, Labrasol and Gelucire 44/14. Initially liquid self - microemulsifying drug delivery system were characterized for clarity, rate of emulsification and drug loading capacity. The optimized formulation characterized for the zeta particle sizer, Differential scanning calorimetrystudies. In vitro results of self - microemulsifying drug delivery system and cefuroxime axetil were shown that the rate of drug dissolution from lipid based self-microemulsifying drug delivery system was significantly higher than commercial tablet and as well as pure drug. The results demonstrate the potential use of self - microemulsifying drug delivery system as a means of improving solubility, dissolution thereby it may enhance the bioavailability of cefuroxime axetil.

Keywords: Cefuroxime axetil, lipid based formulation, Self – microemulsifying drug delivery system.

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INTRODUCTION

Most of the new drug candidates in development today are sparingly soluble and associated with poor bioavailability. There were various formulation strategies reported to address these problems; these include the use of surfactants, cyclodextrins, drug nanoparticles, solid dispersions, micronization, lipids, and permeation enhancers. Majority of these approaches have resulted in limited success because of the need for specialized equipments, complicated manufacturing process, longer processing time, and regulatory complexity[1]. In recent years, an area that is gaining popularity with formulation scientists is using lipid-based careers to develop self-emulsifying drug delivery systems (SEDDS) to improve oral bioavailability of many lipophilic drugs[2].

Self- microemulsifying drug delivery systems (SMEDDS) are isotropic and thermodynamically stable solutions consisting of an oil, surfactant, cosurfactant and drug mixtures that spontaneously forms oil-in-water microemulsions when mixed with water under gentle stirring. The digestive motility of stomach and intestine provides the agitation required for self-emulsification *in vivo*. The advantages of these systems include not only improved drug solubilization but also enhanced release and absorption properties, due to the already dissolved form of drug in formulation and the resulting small droplet size thus providing a large interfacial surface area. The SEDDS formulation typically produce emulsions with a droplet size between 100 and 300 nm, while SMEDDS form transparent microemulsions with a droplet size that is less than 100 nm. The droplet size of the emulsion is a critical factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are relatively easy to manufacture[3].

In the present study, an attempt was made to enhance the solubility and *in vitro*dissolution of Cefuroxime axetil by formulating it as SMEDDS for filling into hard gelatin capsules. Cefuroxime axetil is a prodrug, 1-acetyoxy ethyl ester of Cefuroxime. Based on its solubility across physiologically relevant pH conditions and absorption characteristics, Cefuroxime axetil is classified in the Biopharmaceutics Classification System as a class II drug. Low solubility of Cefuroxime axetil across the physiological pH range is reported to result in incomplete absorption from the gastrointestinal(GI) tract and hence is reported to have a poor oral bioavailability. This paper provides the first instance at developing a SMEDDS formulation of Cefuroxime Axetil using a combination of medium chain triglycerides and polyglycolyzed glycerides as surfactants. The formulation was characterized for its ability to form

microemulsions based on droplet size, zeta potential, and dissolution characteristics[4].

MATERIALS AND METHODS

Materials

Cefuroxime axetil drug, Polyglycolyzedglyserides (Labrafac, Labrasol, Gelucire 44/14, Transcutiol and Plurololique) were obtained from Gattefosse and J&J Pvt ltd -Mumbai.

Excipient Screening – Saturation Solubility studies

The Saturation solubility of Cefuroxime axetil was evaluated in various oils, surfactants, co-surfactants and co-solvents. In this study, an excess amount of Cefuroxime axetil (approximately 500mg) was added to 2ml of each of vehicle in screw- capped glass vials and the mixture heated to 60^0C in a water bath under continuous stirring using vortex mixture to facilitate drug solubilization. The mixture was kept at ambient temperature for 72 hr's to attain equilibrium. The equilibrated sample was centrifuged at 3,000 rpm for 10 min to remove the undissolved drug. Aliquots of supernatant were diluted with methanol and drug content was quantified using an UV spectrometer at λ_{max}282 nm (Table 1).

Table 1: Solubility of Cefuroxime axetil in various vehicles

Name of the vehicles	Solubility of Cefuroxime axetil (mg/ml)
Surfactants	
Labrasol	42.6 ± 2.31
Transcutol P	96.1 ± 1.67
Tween 20	>20
Tween 80	>20
Co-Surfactants	
Gelucire 44/14	150 ± 12.38
Labrafil	8 ± 2.01
Plurololecuate	4 ± 15.7
Span 20	>20
Span 80	>20
Oils	
Sunflower oil	>10
Castor oil	>10
Cotton seed oil	>10
Sesam oil	>10
Co-Solvents	
Lutrol E 400	167 ± 19.01
Propylene glycol	34 ± 7.25

Construction of Ternary phase diagram

The existence of self-emulsifying formulation fields that could self-emulsify under dilution and gentle agitation was identified from ternary phase diagrams of systems containing surfactant-

cosurfactant and co-solvent. A series of self-emulsifying systems were prepared in the formula with varying concentrations of Lutrol E 400 (40-95% v/v), Labrasol (5–40% v/v), Gelucire 44/14 (0–25%v/v) and 100–150 mg/ml of Cefuroxime axetil (10–30% w/v).A formulation (0.2 ml) was introduced into 300 ml of water in a glass beaker at 37^0C and the contents were mixed gently with a magnetic stir bar. The tendency to emulsify spontaneously formation was observed. The apparent spontaneity of emulsion formation was measured by visually after infinite dilution using purified water, wherein a series of SMEDDS formulations were prepared and self-emulsifying properties observed visually. All studies were repeated thrice, with similar observations being made between repeats. After identifying the microemulsion region in the phase diagrams, formulation were selected at desired ratio of component based on its ability to form microemulsion[5].

Design of SMEDDS formulation

The formulation was prepared by dissolving the formulation amount of Cefuroxime axetilin the mixture of surfactant, cosurfactant and cosolvents at 25^0C (Table 2). The final mixture was vortexed for 1hr to get fine emulsification then filled into hard gelatin capsules.

Table 2: Composition of optimize liquid SMEDDS formulation

S.No	Name of Ingredients	Content to be taken
1.	Cefuroxime axetil(w/w)	150.36
2.	Luterol E 400(%)	64
3.	Labrasol(%)	8
4.	Gelucire 44/14 (%)	28

EVALUATION OF SMEDDS

SMEDDS (100 µl) were added to a volumetric flask containing 15 ml of distilled water. The flask was inverted and shaken gently to form a fine emulsion and was kept for 12 hr at room temperature.

Droplet size of emulsions

The particle size of emulsion was determined by Zeta Nano S90 (Malvern Instruments, UK) dynamic light scattering particle size analyzer at a wavelength of 635 nm at a scattering angle at 90^0C at 25^0C.

Visual assessment of Self Microemulsification

SMEDDS concentration (approximately 0.2 ml) was diluted with purified water (100 ml) and gently stirred with magnetic stirrer. Temperature should be 37˚C.

Determination of Self Microemulsification time

The emulsification time of SMEDDS was determined according to USP 22, dissolution apparatus 2. 300 mg of formulation was added drop wise to 500 ml purified water at 37˚C. Gentle agitation was provided by standard stainless steel dissolution paddle rotating at 50 r/min. Emulsification time were assessed visually.

Transmission test

The optimized microemulsion formulation with respect to dilution was checked by measuring transmittance through UV spectrophotometer (UV-1700, Shimadzu). Transmittance of samples was measured at650 nm and for each sample three replicate assays were performed.

Differential scanning calorimetry

Samples of 2–8 mg of 1:1 physical mixture of optimized formulation was accurately weighed and kept in sample pan holder of a DSC 60. The samples were heated in an atmosphere of nitrogen over a temperature range from 50 to 300˚C with a constant heating rate of 10˚C/min. Thermo grams were obtained by the DSC 60 thermal analyzer program and recorded at constant chart speed of 1 inch/min. The thermogram, transition temperature range, the onset of peak transition and the maximum peak of transition were recorded.

Stability

Shelf life as a function of time and storage temperature was evaluated by visual inspection of the SMEDDS system at different time period. SMEDDS was diluted with purified distilled water and to check the temperature stability of samples, they were kept at two different temperature range (2˚C–8˚C (refrigerator), room temperature) and observed for any evidences of phase separation, flocculation or precipitation. In order to estimate metastable systems, the optimized SMEDDS formulation was diluted with purified distilled water. Then microemulsion was centrifuged (Remi Laboratories, Mumbai, India) at1000 r/min for 15 min at 37˚C and observed for any change in homogeneity of microemulsions.

In vitro drug release studies

Drug release studies from SMEDDS (equivalentto 125 mg of Cefuroxime) were performed using USP dissolution apparatus-I with 900 ml of 0.07 N HCL as a medium at 37 ± 0.5^0C. The speed of the paddle was adjusted to 100 rpm. 125 mg of powder Cefuroxime and Marketed product of the cefuroxime (cefix- 125 mg) were placed in a dissolution tester (Shinseang Instrument Co., South Korea). At predetermined time intervals 5, 10, 15, 30, 45 and 60 min; an aliquot (3 ml) of the sample was collected, filtered and analyzed for the content of Cefuroxime axetil by UV Spectroscopy. An equivalent volume (3 ml) of fresh dissolution medium was added to compensate for the loss due to sampling.

RESULTS AND DISCUSSION

Excipients Screening – Saturation Solubility studies

The drug substances showed good solubility in surfactants – Labrasol, Transcutol P and Co-surfactant Gelucire 44/14. Among Co-solvents Lutrol E 400 showed desirable solubility for dosage form development. Based on the solubility and safety aspects of dosage form delivery, Labrasol were selected as surfactant and Gelucire 44/14 were selected as Co-surfactant, Lutrol E 400 selected as a Co-solvent for further development.

Construction of Ternary phase diagram

A series of SMEDDS were prepared and their self-emulsifying properties were observed visually. It was reported that the drug incorporated in the SMEDDS might have some effect on the self-emulsifying performance. Thus, pseudo-ternary phase diagrams were constructed in the presence of 100–300 mg of Cefuroxime axetil(10–30% w/v) to identify the self-emulsifying regions with maximum drug loading and to optimize the concentration of cosolvent, surfactant and cosurfactant in the SMEDDS formulations. Lutrol E 400 showed significant difference with different amounts of drug incorporation, it was observed that with increased drug loading, self-emulsification region and efficiency of the self emulsification process decreased. Thus, the formulation was optimized to 20% w/v of drug incorporation. The phase diagram of the system containing Luterol E 400 as a cosolvent, Labrasol as a surfactant and Gelucire 44/14 as a co-surfactant with 20% w/v drug loading is shown in (Figure 1). In this system, the formulations surrounding the good self-emulsifying region in the phase diagram exhibited poor emulsion-forming ability.

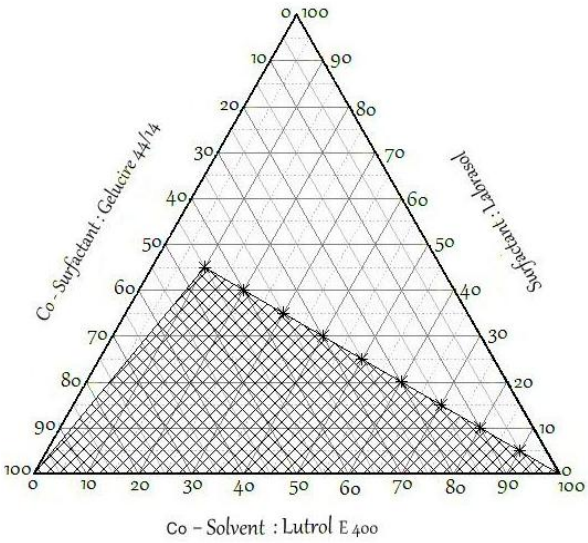

Figure 1: Pseudo-ternary phase diagram

Droplet size of emulsions

The SMEDDS had the mean particle size of 74.03 nm with Pdi of 0.031 shown in (Figure 2).

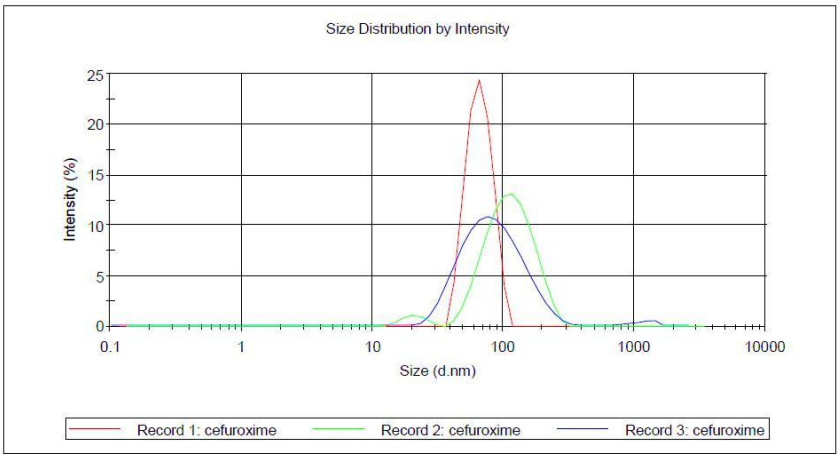

Figure 2: Liquid SMEDDS Zeta size distribution report by intensity

Visual assessment of self Microemulsification

The formulation was showing Rapid forming microemulsion which is clear in appearance (Figure 3).

Figure 3: Visual assessment of self Microemulsification before diluted with water and after dilution with water

Determination of self-Microemulsification time

It was shown that self-emulsification of formulation required less than 1 min for emulsification.

Transmission test

Transmittance of light from optimized SMEDDS formulation as well as its 50 times and 100 times dilution with water and 0.07 N HCl were checked at 650 nm. The percentages of transmittance for these dilutions were shown the 99.29±0.01%, 99.38±0.04%, 99.31±0.02% and

99.56±0.05% respectively. The results of transmission analysis are shown that the formulation is clear and transparent and dosen't effect even diluted with 0.07 NHCl.

Differential scanning calorimetry

DSC enables the quantitative detection of all processes in which energy is required or produced (*i.e.*,endothermic or exothermic phase transformations). The thermo grams of Cefuroxime axetil and SMEDDS formulation are presented in (Figure 4 and Figure 5). The Cefuroxime axetil has shown an endothermic peak at 85.92˚C in DSC thermo gram and midpoint at 246˚C.This endotherm does not change much larger after physical mixing with cosolvents, surfactant and co-surfactant indicates compatibility of cosolvents, surfactant and co-surfactant with drug.

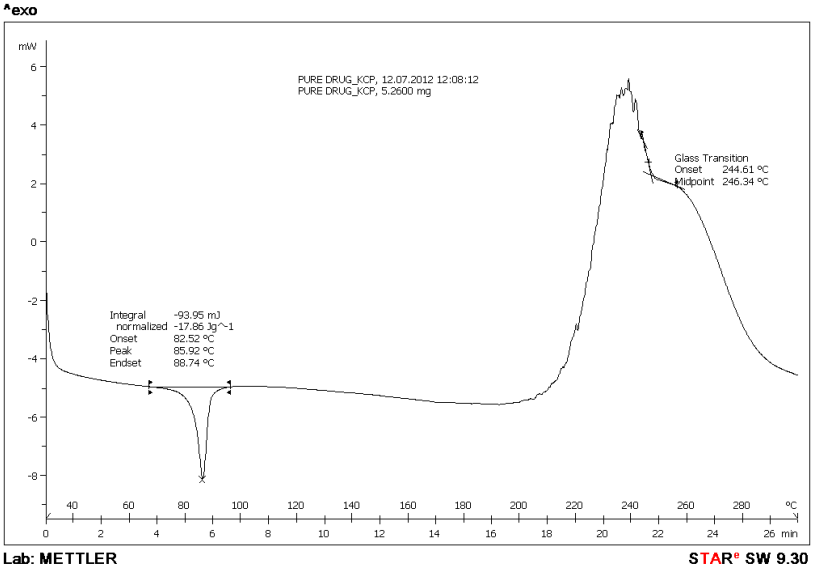

Figure 4: Differential scanning calorimetric thermogram of Cefuroxime axetil

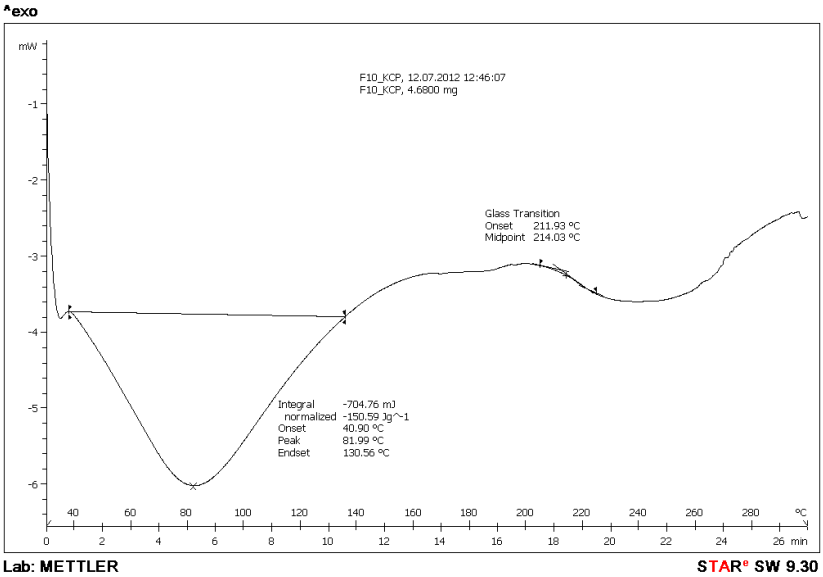

Figure 5: Differential scanning calorimetric thermogram of Liquid SMEDDS

Stability

Stability studies of the SMEDDS samples were carried out by subjecting them to temperature stability and centrifugation. The temperature stability study was carried out by keeping the microemulsion sample at two different temperatures (2–8˚C and room temperature)for two months and visual as well as particle size measurements inspection was carried out by drawing samples at monthly intervals for the subsequent months. No evidence of phase separation or any flocculation or precipitation was observed in SMEDDS formulation. Thus, it was concluded that SMEDDS formulation was stable thermally as well as under stressful conditions.

In vitro drug release studies

The comparative in vitro drug release profile of cefuroxime axetil (pure drug) with Liquid-SMEDDS and marketed formulation were carried out by using 0.07 N HCL as dissolution media (Figure 6). The percentage drug release in 60 min was found to be 99.13%, 72.48% and 6.54% from Liquid- SMEDDS, marketed formulation and pure drug respectively.

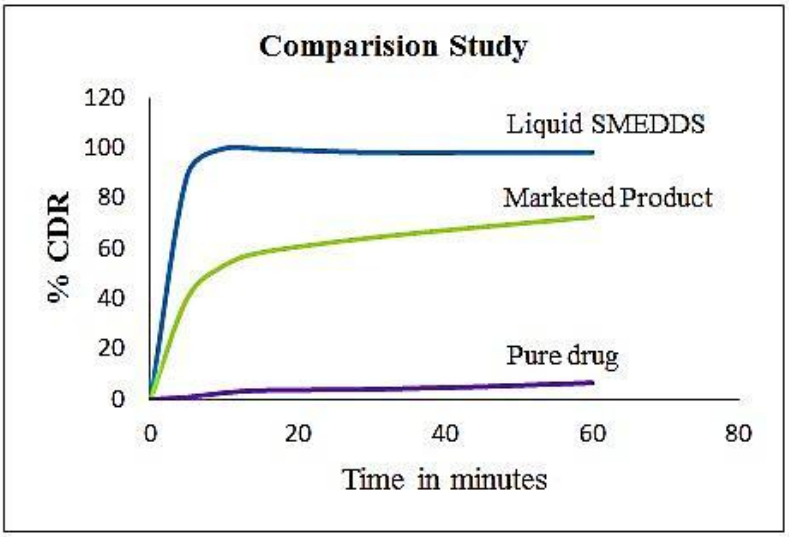

Figure 6: Dissolution profile of liquid SMEDDS, marketed product and pure drug in 0.07N HCl.

CONCLUSION

In this study, the liquid SMEDDS of cefuroxime axetil was formulated for direct filling into hard gelatin capsules for oral administration. The formula composition of SMEDDS for capsule filling was obtained based on solubility evaluation, pseudoternary phase diagram. The optimized formulation showed rapid self-Microemulsification in an aqueous media, droplet size range in Nano range and *in vitro* results shown the rate of drug dissolution from lipid based self-microemulsifying drug delivery system was significantly higher than commercial tablet and as

well as pure drug. It demonstrates the potential use of self - microemulsifying drug delivery system as a means of improving solubility, dissolution thereby it may enhance the bioavailability of cefuroxime axetil. Such formulations are easier to manufacture does not give much formulation challenges, it improves patient compliance. So, this technology can be widely used for stable formulation aspects where the 40% of drug are in hydrophobic in nature.

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