Research Article

Design and Evaluation of Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) of Cefuroxime Axetil

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ABSTRACT

Cefuroxime axetil (CA) is poorly soluble in water and exhibits low and variable bio availability on oral administration. In this work an attempt was made to develop self-micro emulsifying drug delivery system of cefuroxime to increase the solubility to overcome its variable and poor bio availability to enhance the patient compliance. Saturation solubility of CA in various oils, co solvents, surfactants and co-surfactants was studied and ternary phase diagram was drawn to identify the micro emulsification region. Based on the solubility and emulsification data the prototype formulations were prepared with different ratios of surfactants, co surfactants and solvents but without oils. These formulations are reported to be belonging to type IV lipid formulation. The formulations were characterized for self-emulsification properties and tested for *in-vitro* dissolution. Based on the study results, optimized formulation was selected. The optimized formulation was analyzed for globule size, thermal stability. On comparing the *in-vitro* dissolution of the formulation with the marketed product and pure drug, it was found that the dissolution of the SMEDDS was complete and rapid. The prepared SMEDDS preparation produced nanoemulsion on addition to water and no marked changes in the physical and emulsification property of was observed on stability.

Keywords: Cefuroxime axetil, Co-solvents, Oil free SMEDDS, Ternary phase diagram.

INTRODUCTION

Cefuroxime (C) is a broad-spectrum, lactamase-stable cephalosporin having well-defined pharmacokinetics on intramuscular and intravenous administration in the form of sodium salt. When given by oral route, its absorption was lower than 1% of the administered dose, which restricts its use to the parenteral route. The prodrug, 1-acetyloxyethyl (axetil) ester of C known as Cefuroxime axetil (CA) is used in oral dosage forms. The CA is used in treatment of wide range of infections, but exhibits poor and variable bioavailability and thus it is difficult to establish the optimal oral dosage schedule.[1]

The prodrug CA undergoes de-esterification on absorption in mucosal cells, portal blood and liver and only C circulates systemically. CA esterases an enzyme hydrolyse CA to C in the gut lumen, the later one is non-absorbable. CA is reported to have bioavailability of 30% to 40% when taken on fasting and 5% to 60% when taken after food, rate and extent of bioavailability is varies with the dosage forms.[2] Poor solubility of CA and enzymatic conversion to Cat the gut lumen are the main reasons for incomplete bioavailability. The formulation technique which increases drug solubility and prevent enzymatic conversion to C is highly desirable for increasing the bio availability.

SMEDDS are isotropic and thermodynamically stable preparations consisting of oil, surfactants and co-surfactants that spontaneously form oil-in-water micro emulsions when mixed with water under gentle stirring. On oral administration, digestive motility of stomach and intestine provides agitation required for self-emulsification.[3] Advantages of these systems are improved drug solubilisation and improved absorption due to drug present in dissolved form and its large interfacial surface area. The SMEDDS form transparent micro emulsion with droplet size of less than 100 nm.[4-5]

The lipid formulations were classified in to four types; type I to type IV. The prepared SMEDDS formulation in this work is belonging to type IV. This type of formulations contains mixture of surfactants and co solvents but no oil component. Co solvent present in the formulation provides good solubility and facilitate dispersion of the surfactant which reduces variability and irritancy caused by high concentrations of surfactant.[6-9] Use of long chain triglycerides in the SMEDDS formulation improves lymphatic absorption and promotes lipoprotein synthesis.[10]

Nieves Ruiz-Balaguer Guer et al., reported that bioavailability of CA could be improved through the co-administration of substances containing hydrolyzable ethyl esters preferably triglycerides and recommends the use of combination of medium chain triglycerides and polyglycolyzed glycerides as surfactants to overcome the poor bio availability.[11]

The commercially available CA dosage forms are exhibiting low and variable bioavailability, leading to side effects and frequent dosing. The literature survey showed that limited work is done on CA to increase bio availability to overcome patient in-compliance. In this study an

attempt was made to increase the solubility of CA by formulating in to SMEDDS.

MATERIALS AND METHODS

Materials

CA was received from Indoco Remedies, Mumbai. Labrasol and Gelucire were received from Gattefosse and PEG 400 (Lutrol E-400) from Signet. Hard gelatine capsules were received from Associated Capsules, Mumbai, India and other reagents were purchased from SD fine chemicals. All the excipients and reagents were used as received. Double distilled water was prepared freshly and used whenever required.

Cefix- 125 mg tablet, a marketed product was used in comparative *in-vitro* dissolution testing.

Methods

Saturation solubility studies

Saturation solubility of CA in various oils, surfactants, co-surfactants and co-solvents was determined by shake flask method. In this study, an excess amount of CA (approximately 500mg) was added to 2 ml of each vehicle in to screw-capped glass vials. The mixture was mixed using cyclo mixer to get uniform slurry. The vials were fixed in to flask shaker and stirred for 72 hrs. The samples were taken out at 72 hrs and centrifuged at 3,000 rpm for 10 min to separate the supernatant. Aliquots of supernatant were taken, filtered through syringe filter, filtrate was suitably diluted with Methanol and drug content was quantified by measuring absorbance at 282 nm using UV spectroscopy.

Construction of ternary phase diagram

A series of self-emulsifying systems were prepared with varying concentrations of co solvents at 10 to 90% w/w, surfactant and co surfactant concentration at 5 to 45%. In any mixture, total of surfactant, co surfactant and co solvent concentrations were added to 100%. In the first experiment the first mixture consisted of 90% co solvent (PEG 400) 5% each of surfactant (Labrasol) and co-surfactant (Gelucire 44/14). In the next trials the co solvent concentration was decreased by 10% on reaching up to 10%, whereas the surfactant and co surfactant concentration were increased by 5% each on reaching up to 45%. Likewise 11 such mixtures were prepared.

Mixtures were evaluated for formation of emulsion by adding 0.2 ml of mixture in to 250 ml of distilled water in a glass beaker and contents were shaken gently with glass rod. The formation of clear solution indicates the self-emulsification and formation of hazy and turbid solution indicates non-emulsification. Trials were repeated thrice, with similar observations being made between repetitions were taken as final reading. The ternary phase diagrams were drawn by taking the percentage of surfactant, co-surfactant and co solvent at three sides of a triangle. The percentage of co solvent, surfactants and co surfactants resulted in emulsion was denoted by dark vertical and horizontal lines whereas non emulsification area was marked by dotted lines.[12]

Prototype SMEDDS formulation

Totally 10 formulations were prepared by using co solvent, surfactant and co surfactant levels within the micro emulsion region. The formula composition is mentioned in table 2. The co solvent concentration was used between 27 to 81%, surfactant between 7 to 50% and co surfactant between 7 to 36%. For each mixture drug loading capacity was determined by adding excess CA to the mixture, stirred well and filtered the solution. The filtered solution was suitably diluted and measured the absorbance at 282 nm using UV-Visible spectroscopy. Based on the drug loading capacity the minimum amount of CA to be added to each mixture was calculated. The prototype formulations were prepared by adding calculated amount of CA to each mixture. The prepared liquid SMEDDS was filled in to hard gelatine capsules and tested for *in vitro* dissolution and subjected for stability.

Self-emulsification property and self-emulsification time

Few ml of prototype formulation (approximately 1 ml) was added to 250 ml of purified water, stirred gently and checked for clarity of the solution.[13]

Self-emulsification time of formulation was determined using USP II dissolution apparatus. 1 ml of formulation was added drop wise to 250 ml purified water at 37°C, gentle agitation was provided by dissolution paddle rotating at 50 rpm/min. Time taken for formation of clear solution was noted as self-emulsification time, the target time was fixed at 1 minute.

In-vitro dissolution

Based on drug content of prototype formulations, the amount of SMEDDS preparation containing 125 mg of C was filled into hard gelatine capsules. The USP dissolution apparatus-II (make: Lab India, Mumbai) was used for dissolution studies with dissolution medium of 900 ml of 0.07 N HCl, temperature was maintained at 37 ± 0.5^{0}C and speed of the paddle at 100 rpm. At predetermined time intervals of 5, 10, 15, 30, 45 and 60 min an aliquot (3 ml) of the sample was collected, filtered and analyzed for content of CA by measuring absorbance at 282 nm using UV spectroscopy[14] (make: Shimadzu corporation, Japan. Model: 1700). An equivalent volume (3 ml) of fresh dissolution medium was added at each sampling time to compensate for the sampled volume.

Globule size analysis

1mL of optimum formulation was added to 250 ml of water, stirred and analysed for the particle size of emulsion using Zeta Nano S90 (Make : Malvern Instruments, UK, Model: ZetasizerVer 6.2) dynamic light scattering particle size analyzer by measuring wavelength at 635 nm at the scattering angle of 90^0 at 25°C.[15]

Stability

The hard gelatine capsules of optimised formulation containing 125 mg of C was subjected for stability study by keeping them in stability chambers maintained at 40˚C, 25˚C, 2– 8˚C (refrigerator). The samples were withdrawn at 1M, 2M, 3M and observed for any physical changes like capsule leaking, colour change, shrinkage and contents were checked for clarity, phase separation, flocculation or precipitation and self-emulsification property.

RESULTS AND DISCUSSION

Saturation Solubility studies

Identifying the suitable vehicles is the first step in the lipid formulation. The saturation solubility of CA in various oils, surfactants co-surfactants and co solvents are tabulated in table 1. Among the surfactants, Transcutol was shown good solubility followed by Labrasol. As reported in literature, long chain triglycerids improves bio availability by enhancing the lymphatic absorption, Labrasol a long chain triglyceride was selected as surfactant instead of Transcutol. Among the co surfactants, Gelucire showed good solubility; hence it was selected as co surfactant. Among the co solvents, PEG 400 showed good solubility; hence it was selected as co solvent. Solubility of drug in oils was less than 10 mg/mL, hence no oils were selected for the prototype formulations.

Table 1: Saturation solubility of CA in various vehicles

Name of the vehicle	Solubility in mg/mL ± SD
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
Solvents	
PEG 400 (Lutrol E400)	167 ± 19.01
Propylene glycol	34 ± 7.25

Construction of ternary phase diagram

The ternary phase diagram of Labrasol, Gelucire 44/14 and PEG 400 was drawn as shown in figure 1. The emulsification area is denoted by closely drawn rectangles and non-emulsification area is by broadly drawn vertical and horizontal lines. The graphs showed that percentage of each component is important in forming the emulsion.

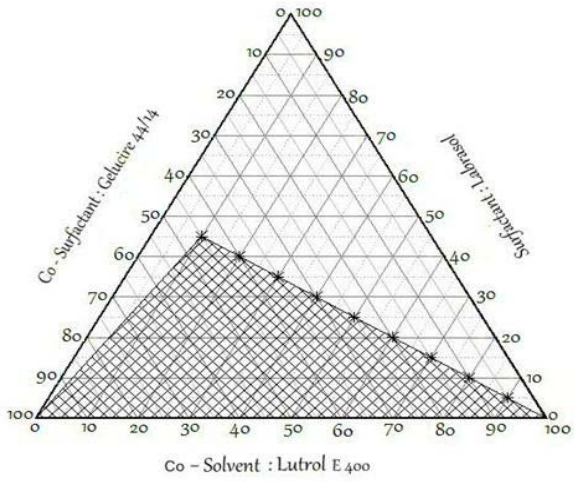

Figure 1: Ternary phase diagram

Prototype formulation

Totally 10 prototype formulations were prepared by varying the concentration of the different components. The formulations were clear and moderately viscous.

Table 2: Formula composition of prototype formulation

Formulation code	Luterol E 400 (ml)	Labrasol (ml)	Gelucire 44/14 (ml)
F1	0.82	0.09	0.09
F2	0.52	0.24	0.24
F3	0.6	0.2	0.2
F4	0.54	0.23	0.23
F5	0.64	0.28	0.08
F6	0.37	0.5	0.13
F7	0.28	0.37	0.36
F8	0.54	0.23	0.23
F9	0.37	0.13	0.5
F10	0.64	0.08	0.28

Self-emulsification property and emulsification time

All the prototype formulations produced clear solution on addition to water. Time taken for formation of clear solution on addition to water was noted. The target time was fixed as 1 min. All the prototype formulations formed clear solution within a minute. The drug loading capacity of formulation coded with No. F-10 was 152 mg/ml and was highest as compared to other formulations.

In-vitro dissolution

In-vitro dissolution prototype formulations were rapid and complete. No marked difference in dissolution profile

was observed between the formulations. At 15 minutes of dissolution, nearly 100% of drug was released.

Based on self-emulsification property, drug loading capacity and *in-vitro* dissolution of prototype formulations the formulation code No. 10 was selected as optimum formulation. This formula was used in globule size analysis and stability study.

Comparative *in-vitro* dissolution profile of optimum SMEDDS formulation, marketed formulation and pure drug are shown in figure 2. Dissolution of SMEDDS formulation was rapid and completed within 10 minutes whereas marketed product released only 70% at 60 minutes and dissolution of pure CA was very less.

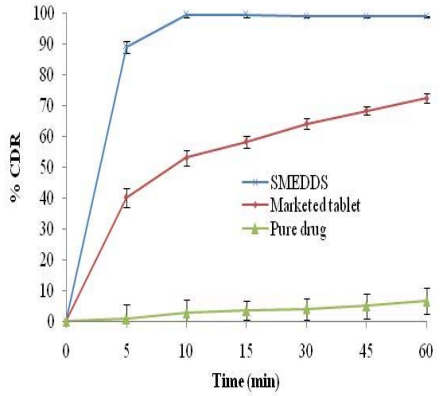

Figure 2: Comparative in-vitro dissolution of SMEDDS, marketed tablet and pure drug

Globule size analysis

The droplet size of optimum formulation on addition to water was determined using Zeta Nano S90 instrument. The average droplet size range of self-emulsified system was 74.03 nm, the graph is shown in figure 3. The result indicates that SMEDDS produced nanoemulsion.

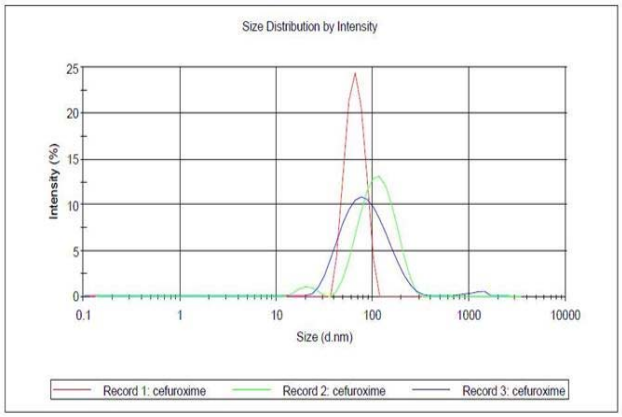

Figure 3: Globule size analysis report of SMEDDS by intensity

Stability

No evidence of phase separation or any flocculation or precipitation was observed and formulation retained the self-emulsification properties on stability up to three months at all stability conditions.

CONCLUSION

The study demonstrates the development of oil free SMEDDS for enhancing the solubility and *in vitro* dissolution of poorly soluble CA. The use of long chain triglycerides as surfactants played the role in formation of clear transparent micro emulsion and also helps in enhancing the bio availability by enhancing the lymphatic absorption. The optimum formulation exhibited all the property of self-emulsion in terms of self-emulsification, rapid and complete dissolution and produced nanoemulsion. Stability study showed that the optimum formulation retained the self-emulsification property and physically stable.

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