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Cashew oil: A novel excipient for self-micro emulsifying drug delivery system using cefixime trihydrate as a model drug

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ABSTRACT

Improvement of bio-availability of poor water soluble drugs presents one of the furthermost challenges in drug formulations. One of the most admired and commercially viable formulation approaches for this challenge is self-micro emulsifying drug delivery system (SMEDDS). Hence, the aim of present study was to develop SMEDDS of poor water soluble drug Cefixime (CEF) using a combination of cashew and corn oil as the oil phase carrier. Liquid SMEDDS was prepared using combination of cashew and corn oil, Labrafil M 1944 CS and Transcutol as oil, surfactant and co-surfactant respectively. Prepared SMEDDS was evaluated for particle size, zeta potential, water dispersion properties and in-vitro drug release. Dilution study by visual observation showed that there was spontaneous micro emulsification and no sign of phase separation. Study concluded that SMEDDS can effectively be formulated with enhanced dissolution rate and bioavailability. A successful attempt was made to incorporate CEF in cashew kernel oil which has be proven to be naturally compatible with the body and laden with anti- inflammatory and anti-pyretic properties.

INTRODUCTION

Poor bioavailability is a trouble, frequently faced in the drug development process. Enhancement of bioavailability of poor water soluble drugs becomes farthest challenge for pharmaceutical scientist. Most of new drug candidates reveal low solubility in water, which leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality. Various approaches should use to improve the dissolution rate of the drug. Among them, Self micro emulsifying drug delivery systems (SMEDDS) have shown great pledge for enhancing bioavailability of poorly soluble compounds.

Cefixime trihydrate is a third generation cephalosporin antibiotic. It acts by inhibiting the synthesis of cell wall of the bacteria. It is clinically used in the treatment of susceptible infections including gonorrhoea, otitis media, pharyngitis, lower respiratory-tract infections such as bronchitis, and urinary-tract infections. Oral absorption of several poorly water soluble drugs was enhanced by SMEDDS. SMEDDS is the mixture of oil, surfactant and co-surfactant having poorly water soluble drug. It forms the fine dispersion of oil in water in the range of 1-100 nm when comes in contact with the water in stomach.[1]

In this study the SMEDDS of cefixime containing the oil, surfactant, and co-surfactant were developed and physicochemical characteristics were evaluated and release profile was determined by *in-vitro*. The solubility of cefixime in various oils, surfactants and co-surfactants were determined. The formulated SMEDDS of cefixime were characterized for Zeta potential, Particle size analysis, Assay and Thermodynamic stability were investigated. [2]Cefixime SMEDDS were encapsulated in hard gelatin capsules were evaluated using USP dissolution apparatus II in 0.1 N HCl and the release of cefixime SMEDDS compared with the release of cefixime from conventional tablet. The oral bioavailability of cefixime from SMEDDS is higher than the release of cefixime from conventional tablet.

MATERIALS AND METHODS

Materials used

Cefixime Trihydrate was obtained as a gift sample from Aristo Pharmaceuticals Ltd. Maisine 35-1, Peceol, Labrafil M 1944 CS and Transcutol P was acquired from Gattefosse India. Cremophor EL and Cremophor RH40 were obtained as a gift sample from BASF India, Mumbai. Cashew oil, Corn oil, Olive oil, Tween 20, Propylene glycol, PEG 400 and ethanol were obtained from the local suppliers.

Table 1. : Formulation composition of Cefixime SMEDDS.

Formulation	S: CoS ratio	Oil (mg)	Surfactant (mg)	Co-surfactant (mg)
F1	1:1	100	450	450
F2	1:1	200	400	400
F3	1.5:1	100	540	360
F4	2:1	100	600	300

Solubility analysis

Preformulation solubility analysis was done to select the vehicle in which drug is more soluble and suitable for formulation of SMEDDS. The solubility of cefixime in various oils, surfactants and co-surfactants was determined by adding excess amount of cefixime into 1 ml of each vehicle in a centrifuge tube, followed by mixing at around 200 rpm in an orbital shaker at room temperature for 24 h. [3-5] The samples were centrifuged at 3000 rpm for 10 m to remove the excess cefixime after which the concentration of cefixime in the supernatant was measured by UV Spectrophotometry (Shimadzu UV Spectrophotometer 1800) after appropriate dilution with methanol. [3, 4]

Preparation of SMEDDS of cefixime

A series of SMEDDS formulation were carried out by using Labrafil M 1944 CS and Transcutol P as S/CoS combination and Cashew and corn oil in the ratio of 1:1 as oil. In all formulations the level of cefixime was kept constant (i.e. 80mg) and the varying ratio of oil, surfactant and co-surfactant were added. Then the components were mixed by gentle stirring and sonication and were heated at 40ºC on a magnetic stirrer until cefixime was perfectly dissolved. [6]The mixture was stored at room temperature until further use. The various formulation ratios are given in Table 1.

Saturation solubility

The solubility of cefixime SMEDDS and pure drug in various buffers (0.1N HCL pH 1.2 and Phosphate buffer pH 7.2) and distilled water was determined by adding a fixed dose of cefixime (i.e. 80mg) into 1 ml of each vehicle in a centrifuge tube, followed by mixing at around 200 rpm in an orbital shaker at room temperature for 24 h. The samples were centrifuged at 3000 rpm for 5 min to remove the excess cefixime after which the concentration of cefixime in the supernatant was measured by UV Spectrophotometry (Shimadzu UV Spectrophotometer 1800) after appropriate dilution with the required solvent.

Characterisation and evaluation

Freeze thawing

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at 5 °C for 24 h followed by

Table 2. : Visual Assessment of Efficiency of Self-Micro emulsification

Grade	Dispersibility	Time for self-emulsification (min)
A	Rapidly forming clear or bluish appearance	<1
B	Rapidly forming but has less clear bluish white appearance	1-2
C	Bright white milky appearance	2-3
D	Dull greyish white emulsion with slightly oily appearance	>3
E	Poor emulsification with large oil droplets on the surface	>3

Table 3. : Saturation solubility comparison between cefixime pure drug and SMEDDS

Sr. No.	Buffers used	Solubility in mg/ml	
		Cefixime pure drug	Cefixime SMEDDS
1.	0.1N HCl pH 1.2	15.58	76.99
2.	Phosphate Buffer pH 7.2	14.27	62.15
3.	Water	10.51	57.65

Table 4. : Particle size and zeta potential determination of cefixime SMEDDS

Parameters	Formulation	
	F1	F2
Polydispersity index	0.619	0.712
Particle size (nm)	10.80	15.6
Dispersion time (min)	<1	1-2
Zeta potential (mV)	83.17	79.92

thawing at 40 °C for 24 h. Centrifugation was performed at 3000 rpm for 5 min. The formulations were then observed for phase separation or precipitation. Only formulations that were stable to phase separation were selected for further studies.

Determination of particle size and zeta potential

Globule size and polydispersity index of the cefixime SMEDDS were determined by particle size analyser. Data analysis was conducted using the software package provided by manufacturer. [7]

The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SMEDDS formulation was measured using a Zetasizer instrument. The SMEDDS were diluted with a ratio of 1:10 v/v with distilled water and mixed for 1 m using a cyclomixer.

Self-emulsification and precipitation assessment

Evaluation of the self-emulsifying properties of SMEDDS formulations was performed by visual assessed using the grading system given in Table 2. In brief, different compositions were categorized on speed of emulsification, clarity and apparent stability of the resultant emulsion. Visual assessment was performed by drop wise addition of the cefixime (SMEDDS) into 250 ml of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred magnetically at ~100 rpm. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 h.

In- vitro drug release studies

The In-vitro dissolution studies were carried out by using paddle type USP dissolution apparatus II. Dissolution tests were done separately for marketed drug Tablet and SMEDDS capsules containing the equivalent drug to 80 mg of pure drug were used for dissolution studies. Dissolution was carried out in 900 ml 0.1 N HCl at 50rpm at temperature of 37 ± 0.5 °C. Sample aliquots (10 ml) of dissolution medium were withdrawn at different time intervals. The samples were assayed spectrometrically at 289 nm. [8]

RESULTS

Solubility studies

Results from solubility studies are reported in Figure 1, 2 and 3 as seen, combination of cashew and corn oil (1:1), Labrafil M 1944 CS and Transcutol P showed the highest solubilization capacity for cefixime which were selected as oil, surfactant and co- surfactant, respectively.

Saturation solubility

Solubility of pure drug and SMEDDS were evaluated and cefixime SMEDDS showed considerable enhancement in solubility as compared to the pure drug. The results are depicted in Table 3.

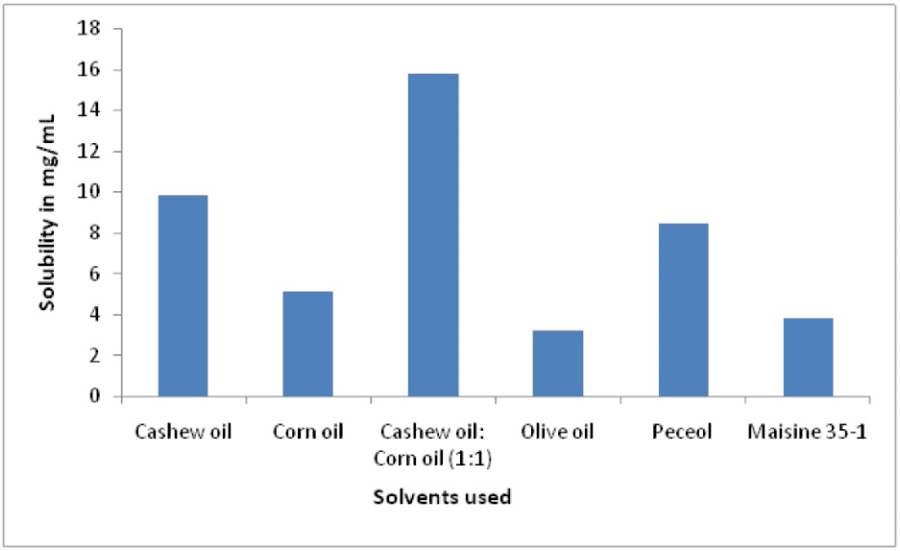

Figure 1 : Solubility in oil

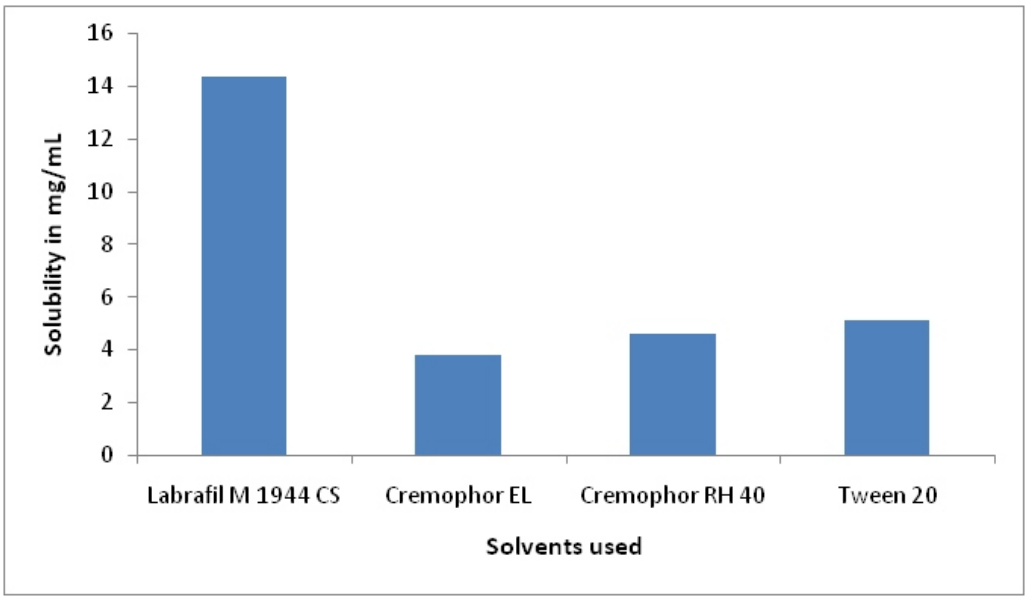

Figure 2 : Solubility in surfactant

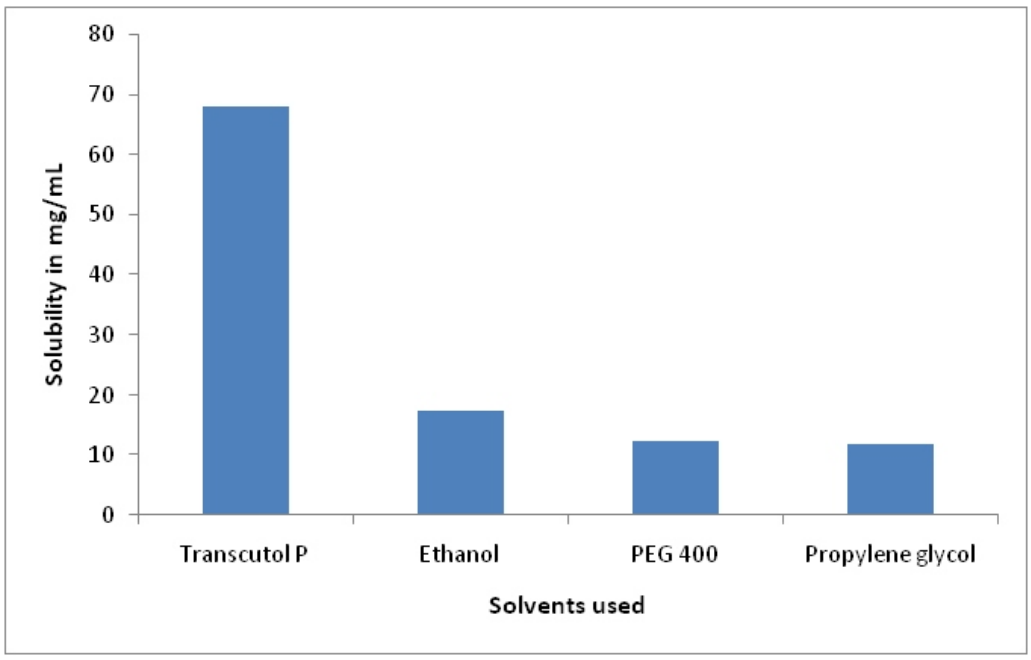

Figure 3 : Solubility in co- surfactant

Characterisation and evaluation

Freeze thawing

Freeze thawing was carried out to evaluate the stability of formulation. It was observed that in formulations F3 and F4, there was turbidity and drug precipitation. Hence these formulations were excluded for further studies.

Particle size and zeta potential determination

The droplet size distribution of various formulations is given in Table 4. It was observed that formulation F1 having highest proportion of surfactant (450 mg) and co-surfactant (450 mg) and oil (100 mg) shows the lowest mean particle diameter, where formulation F2 having lowest proportion of surfactants shows higher mean particle size.

The values of *Zeta potential and Drug content (%)* of formulations are shown in Table 4.Formulation F1 and F2 have zeta potential 83.17 mV and 79.92 mV respectively.

Self-emulsification and precipitation studies

The results of self-emulsification and precipitation studies are given in Table 4.The S/CoS ratio of 1:1 was kept constant for the initial formulation study. Transcutol P when added as a co-surfactant seems to increase the solubilization capacity of the vehicle (Cashew: corn oil).

In- vitro drug release studies

The *in-vitro* drug release studies were performed and the % drug release graph was plotted against time. A comparison of *in-vitro*drug release profile of pure drug, marketed formulation and

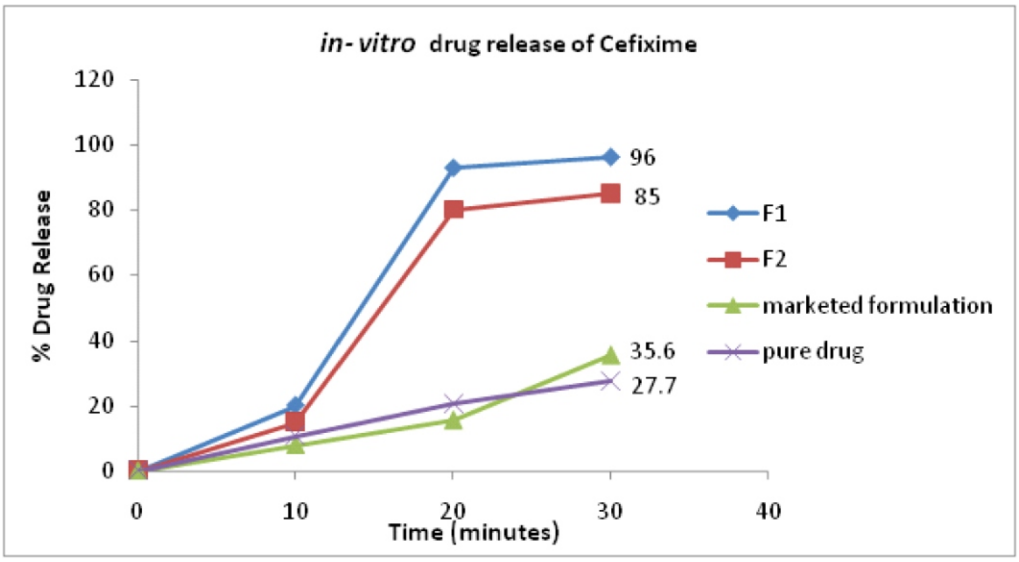

Figure 4 : In-vitrodrug release of Cefixime SMEDDS in comparison to Marketed Formulation

SMEDDS formulation (F1 and F2) are given in Figure 4. Based on drug release comparison studies, it was observed that the drug release from SMEDDS was found to be significantly higher when compared with conventional marketed formulation. There was 96% release of drug from formulation F1 in 30 m.

DISCUSSION

Solubility studies

Solubilisation studies are carried out as to find out the component which solubilizes maximum amount of the drug so as to provide the optimum dose required for the therapeutic activity in the least amount of volume possible. The components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion and therefore avoiding precipitation of drug on dilution therefore ensuring that the drug reaches its therapeutic level of activity.

Saturation solubility

These studies are carried out in order to determine the in-vitroenhancement in solubility. The enhancement in solubility of SMEDDS formulation as compared to that of the pure drug proves that the bioavailability in considerably more. This in turn results in a lower amount of dose required to show the therapeutic effects in the body. This also reduces the time taken to reach the therapeutic effect and also reduces the potential risks associated with the drug.

Characterisation and evaluation

Freeze thawing

Freeze thawing pushes the formulation to the extreme in terms of stability therefore not limiting its application and potentially reducing the effects oftemperature on the formulation. This test is necessary to evaluate the stability of the formulation and also to notice the precipitation and any other such chemical or physical degradation of the drug.

Particle size and zeta potential determination

An increase in the oil phase resulted in proportional increase in particle size because of simultaneous decrease in the S/CoS proportion. Addition of surfactants to the microemulsion system causes the interfacial film to stabilize and condense, while the addition of co-surfactant causes the film to expand.

Zeta potential value of more than ± 60 indicates excellent stability of the formulation. The zeta potential indicates that there is no flocculation of particles and thus the microemulsion was stable.

Self-emulsification and precipitation studies

It was seen that an increase in the proportion of Labrafil M 1944 CS in the composition resulted in decreasing self-emulsification time. The decrease in self- emulsification time can be assumed to be due the relative increase in surfactant concentration, leading to decreased viscosity of the formulation. However, with an increase in the surfactant ratio, it was found that the resultant dispersion showed precipitation and thus was not stable. Based on these studies, an optimum amount of all the vehicles were selected for the formulation of SMEDDS.

In- vitro drug release studies

It was suggested that the SMEDDS formulation resulted in spontaneous formation of a microemulsion with small droplet size which permitted a faster rate of drug release into the aqueous phase, much faster than conventional marketed cefixime formulation. Thus, this greater availability of dissolved cefixime from the SMEDDS formulation could lead to higher absorption and oral bioavailability.

Poor water solubility and less absorption is a major limitation with many drugs despite their good therapeutic efficacy. SMEDDS provides an opportunity for the improvement in the *in-vitro* and *in- vivo* performance of poor water soluble drugs and thus serve as an ideal carrier for the delivery of drugs belonging to BCS classes II and IV. The current study was performed to define the role of self- micro emulsifying formulations to enhance the bioavailability of cefixime. SMEDDS represent a possible alternative to the more traditional oral formulations for lipophilic compounds. It has isotropic mixture of oil, surfactants, and co-surfactants. This mixture should be clear, monophasic liquid at ambient room temperature. SMEDDS self-emulsifies rapidly in the aqueous contents of the stomach under gentle digestive motility in the gastrointestinal tract to present the drug in solution

in small droplets of oil (<100 nm). It is considered that the excipients in SMEDDS increase the dissolution and permeability of drug by significantly decreasing droplet size. The use of SMEDDS for the delivery of cefixime could improve its solubility and permeability through the mucous membranes significantly.

In the present work, we have prepared the cefixime SMEDDS formulations and assessed the particle size, zeta potential, thermodynamic stability and dissolution *in- vitro*. The choice of excipients to prepare SMEDDS depends on its drug dissolving capacity.

Carbamazepine possesses the highest solubility in Cashew and corn oil (1:1 ratio) hence; we selected Cashew and corn oil (1:1 ratio) as oil phase forcefixime SMEDDS formulation. The selection of surfactant and co- surfactant in this study was governed by their emulsification efficiency rather than their ability to solubilize drug. The efficiency of self-microemulsification is much more related to the hydrophiliclipophilic balance (HLB) value of the surfactant. Surfactants with HLB value >10 are greatly superior at providing fine, uniform microemulsion droplets. Safety is the main determining factor in choosing a surfactant. Non-ionic surfactants are less toxic and less affected by pH and ionic strength than ionic surfactants. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsion.

SMEDDS shows the 85- 96 % release in 30 m as compared with marketed formulation which shows a limited dissolution rate between 27- 35 %. Thus the study confirmed that SMEDDS formulation can be used as possible alternative to traditional oral formulation of cefixime to improve its solubility and oral bioavailability.

CONCLUSION

An optimized cefixime loaded formulation consisting of 1:1 ratio of Cashew: Corn oil (100 mg), Labrafil M 1944 CS (450 mg) and Transcutol P (450 mg) offers the advantage of good clarity systems at high oil content and thus should offer good solubilization of cefixime trihydrate. Thus our studies conformed that SMEDDS can be used as a possible alternative to conventional oral formulation of cefixime. Results further conclude that cashew oil can be used to formulate SMEDDS and incorporate lipophilic drugs and can be a mode to formulating more natural and system compatible pharmaceuticals given that it can be also used as an anti- inflammatory and anti-pyretic agent and therefore can be explored as a potential drug carrier for dissolution enhancement of cefixime and other lipophilic drug.

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