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Enhancement of solubility and permeability of cefpodoxime proxetil by self-micro-emulsifying drug delivery system

Naveen Kumar C, Latha K *, Keerthi G, Nithila P and Padmavathi R

G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Telangana, India.

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Abstract

The goal of this study was to design Cefpodoxime Proxetil SMEDDS (self-microemulsifying drug delivery system), to improve solubility and permeability which could improve therapeutic performance and drug loading capacity. Castor oil, Tween 80, PEG 400 were used as the oil, surfactant, and, co-surfactant respectively. A ternary phase diagram was used to choose the best formulations. Selected formulations were evaluated for various parameters. According to the findings, all SMEDDS formulations had nano-sized globules, good stability, and rapid dispersibility of microemulsions, which were clear and slightly bluish in colour, and no symptoms of phase separation, creaming or, cracking Intestinal permeability studies of SMEDDS formulations show that the drug diffused through a biological membrane is more when given in form of SMEDDS. The present investigation has shown that it is possible to enhance the solubility and permeability of poorly soluble drugs.

Keywords: Cefpodoxime Proxetil; SMEDDS; Ternary phase diagram; Solubility; Permeability; TWEEN 80; PEG 400; Castor oil; Microemulsion; SMEDDS

1. Introduction

Lipid-based formulation techniques, particularly the self-microemulsifying drug delivery system (SMEDDS), have been extensively studied for their potential as alternate strategies for delivery of poorly soluble drugs, with poor absorption and low oral bioavailability[1]. SMEDDS formulations are isotropic mixtures of oil, surfactant, cosurfactant and, a drug. These systems are capable of forming fine oil-in-water (o/w) microemulsions with gentle agitation and dilution by aqueous phases[2]. Similarly,[3] the agitation required for *invivo* self-emulsification in the gut lumen is provided by the digestive motility of the stomach and intestine [4–6]. The drug remains solubilized form due to the spontaneous formation of an emulsion in the gastrointestinal tract, and the small size of the formed droplet provides a wide surface area for drug dissolution and absorption. In addition to solubilization, the presence of lipid in the formulation further improves bioavailability by enhancing the drug permeation through the biological membrane [7,8]. The solubility of the drug in various components and the droplet size distribution of resultant emulsion on self-emulsifying regions determined from the phase diagram are used to screen self-emulsifying formulations [9–11].

Cefpodoxime proxetil (CFP) is a broad spectrum, third generation cephalosporin ester, administered orally for the treatment of upper respiratory tract and urinary tract infections. This prodrug is hydrolyzed *in vivo* to its active metabolite, cefpodoxime. Bioavailability in humans is about 50%. The low bioavailability of CFP is mainly claimed due to the degradation of its ester side chain by cholinesterases present in the intestinal lumen[12,13]. Furthermore, it has a low water solubility (400 g/ml), which may contribute to its poor bioavailability, as dissolution is a rate-limiting factor in intestinal absorption of weakly water soluble drugs [14]. A method, which will increase drug solubility and protect

* Corresponding author: Latha K
G.Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Telangana, India.

from degradation by cholinesterase in the intestinal lumen is highly required for optimizing the therapeutic performance of CFP [15,16].

So, the present study was planned to develop and evaluate an optimal SMEDDS formulation of Cefpodoxime Proxetil, to enhance solubility, permeability which may improve therapeutic performance and drug loading capacity.

2. Material and methods

2.1. Materials

Micro labs, Banglore provided Cefpodoximeproxetil and Labrosol as a gift sample. Castor oil, Olive oil were obtained from Aceites Agro Sevilla, S.A.U; Coconut oil was obtained from Marico limited; Oleic acid from Thomas bakers(chemicals) Pvt.Ltd., was a Gift sample from Micro labs, Banglore; Tween 80, Span 20, PEG 400, Propylene glycol, Hydrochloric acid were obtained from S.D fine chemicals Ltd; Distilled water from In house source.

2.2. Methods

2.2.1. Determination of absorption maxima (λ_{max}) and standard graph for CFP

On a double beam spectrophotometer, cefpodoxime proxetil was scanned against solution as a blank and a standard graph was created in the range of 5 - 30 g/ml.

2.2.2. Determination of the solubility of CFP in oils, surfactants, and co-surfactants

To select the best combination of oils, surfactants, and co-surfactants for SMEDDS formulation, the component which shown a maximum solubility for CFP was selected. Different oils, surfactants, co-surfactants were used to study the solubility of CFP. 2ml of different oils, surfactants, and co-surfactants were taken separately in a small vial and an excess amount of the drug was added to each vial. The vials were tightly closed and were stirred continuously for 72 hrs using a mechanical shaker at 25^0C. Then oils, surfactants, and co-surfactants were centrifuged at 10000 rpm for 10 min to separate un-dissolved drug. The supernatant was filtered and the sample was diluted with 0.1N HCl and solubility was quantified with UV-spectroscopy at 264.2 nm[17].

2.2.3. Selection of Surfactants and Co-Surfactants

Various surfactants and co-surfactants were selected from the solubility study and screened for SMEDDS formation. The chosen amounts of surfactant and co-surfactant mixtures were combined with the chosen oil phase and analysed. [18].

2.2.4. Drug-excipient compatibility studies

This experiment was carried out to confirm that additives and CFP were compatible. Fourier transform infrared spectra (FTIR) were obtained from Shimadzu 8400S for pure drug fluconazole and liquids. FT-IR studies were carried out for the prepared formulation and their compatibility was checked. The spectrum of the drug was obtained exploitation the restrainer disc methodology. The pellet was prepared using dry samples by applying 10tons/inch^2 pressure[19].

2.2.5. Construction of pseudo ternary phase diagram for cefpodoxime proxetil

Table 1 Batches selected for construction of pseudo ternary phase diagram

Batch No.	Oil	Surfactant	Co-surfactant
I	Castor oil	Tween 80	PEG 400
II	Castor oil	Span 20	n-butanol
III	Castor oil	Labrosol	PEG 400
IV	Olive oil	Labrosol	Propylene glycol
V	Olive oil	Span 20	n-butanol
VI	Oleic acid	Tween 80	PEG 400

From solubility studies, the screening and selection of surfactants and co-surfactants were carried out. For the preparation of stable SMEDDS, the microemulsion region was identified by constructing a pseudo ternary phase diagram containing a different proportion of surfactant: co-surfactant ratios S/Co (1:1, 2:1, 3:1, 4:1), oil, and water. Smix and oil were mixed at a ratio of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 in a pre-weighed test tube. To the above mixtures, water was added dropwise till the first sign of turbidity was observed to identify the endpoint. Water addition was continued till the system becomes clear. The concentrations of the components were observed and recorded to complete the pseudo ternary phase diagrams. Then the contents of oil, surfactant, co-surfactant, and water at an appropriate weight ratio were selected based on these results **(Table 1)**. To prepare SMEDDS, the microemulsion region from the phase diagram was selected, the region where the solution remains clear even on infinite dilution[20–22].

2.2.6. Preparation of SMEDDS formulation

Drug and co-surfactant were mixed and oil was added by stirring, then it was heated at 60°C and cooled. After attaining room temperature, surfactant was added slowly in a dropwise manner with gradual stirring to obtain SMEDDS[23]. Formulations are tabulated in Table 2.

Table 2 Formulations of (microemulsions) SMEDDS

Formulations	Smix ratio	Oil: smix	Oils		Surfactants			Co-surfactants		
			Castor oil	Olive oil	Tween 80	Span 20	Labrosol	PEG 400	Propylene glycol	n-butanol
F1	1:1	4:6	4	-	1	-	-	1	-	-
F2	2:1	4:6	4	-	2	-	-	1	-	-
F3	3:1	4:6	4	-	3	-	-	1	-	-
F4	4:1	4:6	4	-	4	-	-	1	-	-
F5	3:2	4:6	4	-	3	-	-	2	-	-
F6	3:3	4:6	4	-	3	-	-	3	-	-
F7	1:1	6:4	6	-	-	1	-	-	-	1
F8	2:1	6:4	6	-	-	2	-	-	-	1
F9	3:1	6:4	6	-	-	3	-	-	-	1
F10	4:1	6:4	6	-	-	4	-	-	-	1
F11	2:2	6:4	6	-	-	2	-	-	-	2
F12	2:3	6:4	6	-	-	2	-	-	-	3
F13	1:1	2:8	2	-	-	-	1	1	-	-
F14	2:1	2:8	2	-	-	-	2	1	-	-
F15	3:1	2:8	2	-	-	-	3	1	-	-
F16	4:1	2:8	2	-	-	-	4	1	-	-
F17	1:2	2:8	2	-	-	-	1	2	-	-
F18	1:3	2:8	2	-	-	-	1	3	-	-
F19	1:1	3:7	-	3	-	-	1	-	1	-
F20	2:1	3:7	-	3	-	-	2	-	1	-
F21	3:1	3:7	-	3	-	-	3	-	1	-
F22	4:1	3:7	-	3	-	-	4	-	1	-
F23	3:2	3:7	-	3	-	-	3	-	2	-
F24	3:3	3:7	-	3	-	-	3	-	3	-

2.2.7. Thermodynamic stability studies

This study was carried out to determine phase separation and temperature effects on SMEDDS formulations. SMEDDS were diluted 100 times with distilled water and centrifuged for 20 minutes at 10,000 rpm, with phase separation noted visually. To see how temperature affects the liquid SMEDDS formulations, they were exposed to 4°C for 2 days and then

45°C for 2 days. The formulations were diluted and centrifuged as stated above at the end of the cycle, and phase separation was assessed. [24,25].

2.2.8. Robustness to dilution

It was determined by diluting liquid SMEDDS with water and 0.1N HCl solution 50, 100, and 1000 times. Any phase separation and drug precipitation were detected [26].

2.2.9. Evaluation of self-emulsification efficiency

Dispersibility test

A standard USP XXII type II apparatus was used to test it. At 37.50C and 50 rpm, 1ml of each prepared formulation was added to 500ml of water. [18,27].

Self-emulsification time

It was determined by adding 2.1ml of each formulation dropwise to 500 ml of purified water at 37^0C using a USP type I dissolution device. A basic stainless steel dissolving paddle revolving at 50rpm offered gentle agitation. The time it took to emulsify was measured visually [28].

Visual observation for Phase separation

Each SMEDDS formulation was placed into 200ml of distilled water in a beaker, which was kept at 37°C, and the diluted solution was vortexed for 1 minute. After storing this mixture for 24 hours, phase separation and precipitation was observed visually. Further studies were conducted on mixtures that showed negligible phase separation during a 24-hour period. It provides information about the stability and viability of the fashioned tiny emulsion [28].

Measurement of Droplet size

A Malvern Zeta Sizer was used to determine the droplet size and poly dispersity index (PDI) of SMEDDS. The PDI indicates the width of a particle distribution. The samples were diluted to an acceptable scattering intensity using double distilled water prior to testing [29,30].

Zeta potential (ZP)

It is a measure of the electric charge on the surface of the particles that reflects colloidal systems' physical stability. A Zeta Sizer was used to determine ZP. Each sample was suitably diluted and placed in a disposable zeta cell using double distilled filtered water. The particle electrophoretic mobility was used to determine the ZP values. The Helmholtz–Smoluchowski equation was used to restore electrophoretic quality to the ZP. All measurements were done in triplicate. [26].

Transmission electron microscopy (TEM)

SMEDDS was diluted in distilled water and gently blended together. The copper grids were exposed for sixty seconds on the sample obtained after dilution was deposited. After removing excess fluid using filter paper, the grid was stained for 30 seconds in a 1 percent phosphotungstic acid solution. SMEDDS microstructure and morphology can be studied using transmission electron microscopy [29].

2.2.10. In vitro Drug release studies

The USP dissolution apparatus type II was used to conduct *invitro* drug release assessment. The dissolution vessel was filled with 900 mL of water and 0.1N HCl, then the SMEDDS formulation was added to the dissolution medium and agitated at 50rpm at 37°C. 5ml of samples were taken at pre-determined intervals of 5 min, 10 min, 15 min, 30 mi, 1 hr, 2 hrs, 3 hrs, 4 hrs, and 5 hrs. Every time the withdrawn volume was refilled, a new dissolution media was used. A UV spectrophotometer was used to determine the medication concentration [29].

2.2.11. Permeability studies

The permeability were conducted using sheep intestine that had been washed with phosphate buffered saline and Ringer solution, filled with the formulation by sealing one end and then sealing the other end, and then placed in a dissolution type II apparatus with 900 ml of water and 0.1N HCl and stirred at 50rpm at 37°C. At specific time intervals of 5, 10, 15, 30, 60, 120, 180, 240, 300, and 360 minutes 5ml of samples were withdrawn and the drug concentration

was measured using a UV spectrophotometer. The withdrawn volume was replaced by a fresh dissolution medium every time [29].

3. Results and discussion

3.1. Drug-excipient compatibility study by FTIR

Cefpodoxime proxetil compatibility with excipients was done by FTIR

(A)
(B)

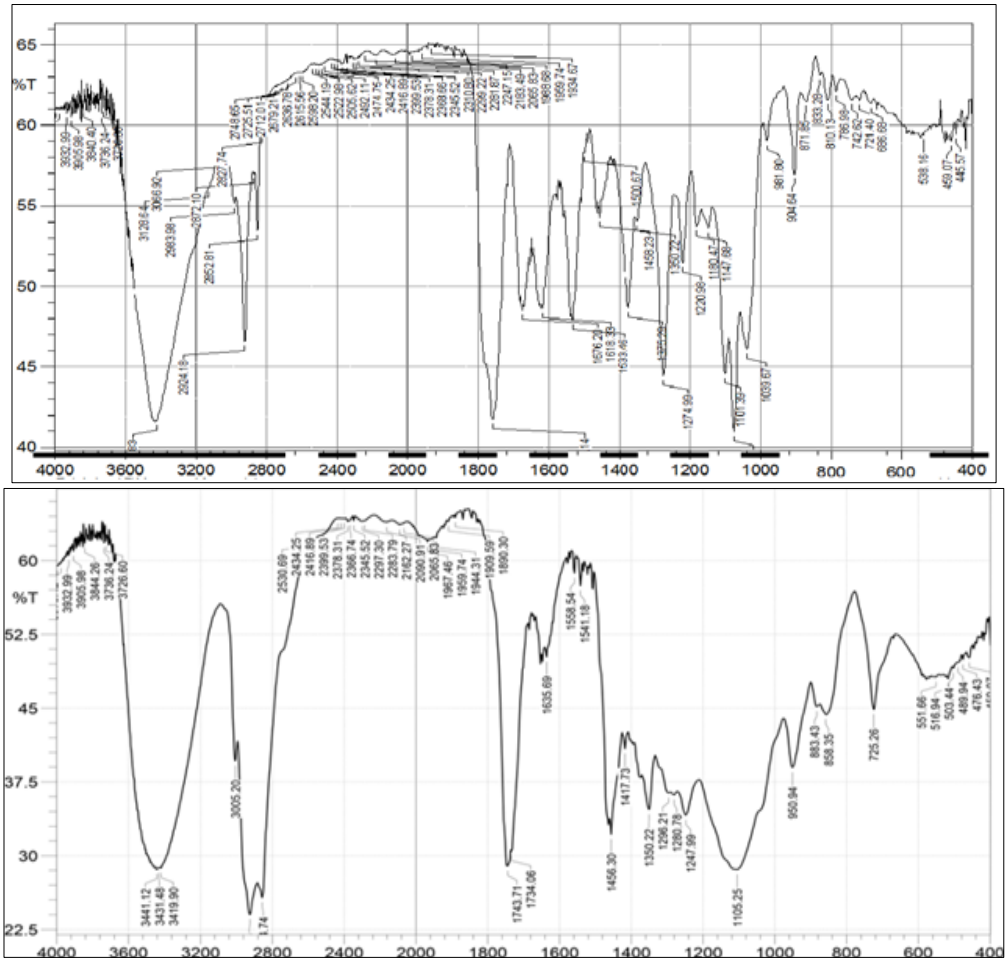

Figure 1 FTIR of cefpodoxime proxetil (A) Pure drug, (B) SMEDDS formulation containing drug

From the IR spectra **(Figure1**) the peaks representing the pure drug were found to be similar and retained following the formation of micro-emulsion using different excipients, implying that there is no interaction. The functional peaks were found to be unaltered, implying that the pure drug was not functionally altered. As a result, there is no drug-excipient interaction. It means the drug remained stable and compatible with other excipients throughout the manufacturing process.

3.2. Solubility of cefpodoxime proxetil in oils, surfactants, and co-surfactants

Results of solubility studies show that cefpodoxime proxetil was more soluble in oils (castor oil, olive oil), surfactants (labrosol, Tween 80 and span 20), and co-surfactants (propylene glycol, n-butanol and, PEG 400)as shown in **Table 3.** Hence castor oil, olive oil selected as oil phase and labrosol, tween 80 and span 20 as surfactants and propylene glycol, PEG 400 and n-butanol were selected as co-surfactants for further studies due to their emulsification ability for optimum SMEDDS with improved drug loading capabilities.

Table 3 Solubility of cefpodoximeproxetil in oils, surfactants, and co-surfactants

Excipient	Amount of drug (mg/ml)
Oils	
Castor oil	3.39
Coconut oil	0.163
Olive oil	1.33
Oleic acid	0.693
Surfactants	
Tween 80	17.87
Span 20	4.7
Labrosol	10.21
Co-solvents	
Propylene glycol	12.242
PEG 400	20.42
n-butanol	12.39

3.3. Construction of pseudo ternary phase diagram

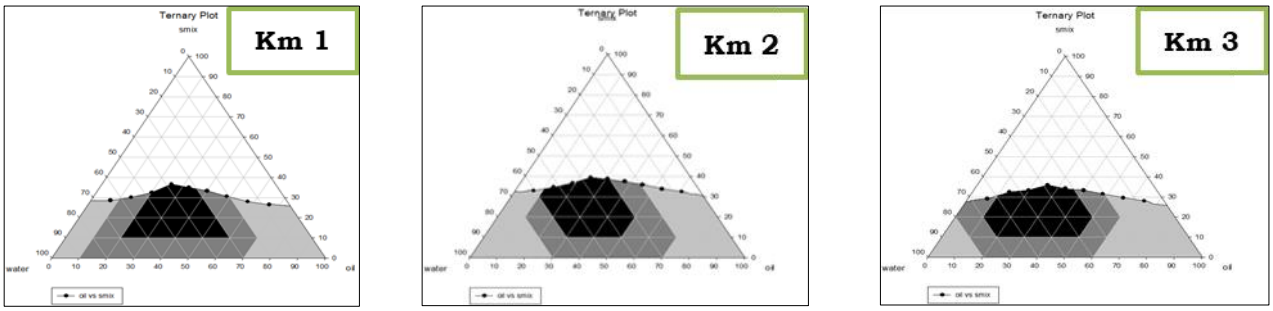

Figure 2 Ternary phase diagrams of castor oil, Tween 80 and PEG 400 and water at km values 1(3:1), 2(4:1), 3(3:4)

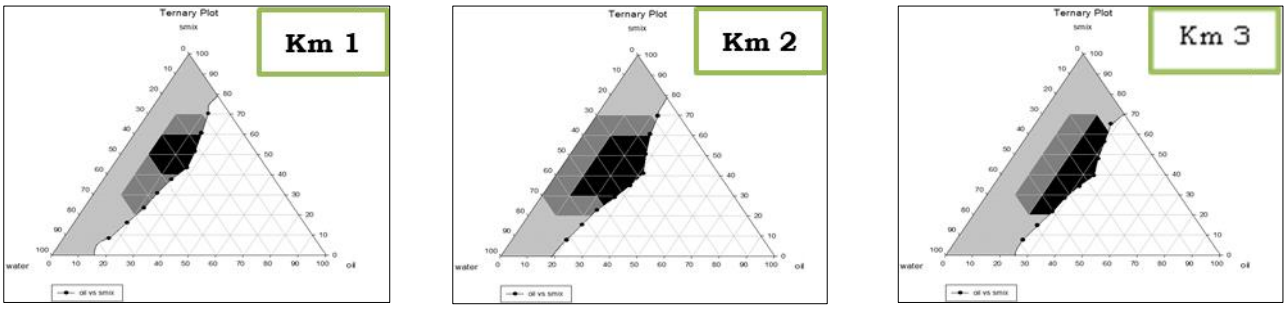

Figure 3 Ternary phase diagrams of castor oil, span 20 and n-butanol and water at km values 1(2:1), 2(3:1), 3(2:3)

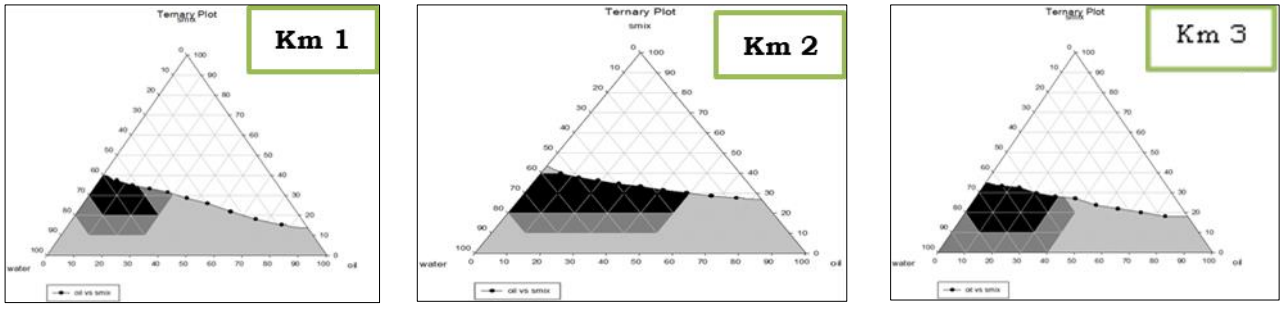

Figure 4 Ternary phase diagrams of castor oil, labrosol and PEG 400 and water at km values 1(1:1), 2(2:1), 3(1:3)

The pseudo ternary phase diagrams were initially produced with S/CoS (km) ratios of 1:1, 2:1, 3:1, and 4:1, then verified for emulsion formation and the surfactant ratio was fixed. Then, while keeping the amount of surfactant constant, it was tested by adjusting the co-surfactant ratios and evaluating the best formulations, with the concentration of oil taken at 90% and the amount of S/CoS at 10%. Oil concentration was decreased gradually with increased S/CoS. It was found that a high concentration of oil makes a poor emulsion with very little water required for dilution, and that as the concentration of S/CoS increases, the anticipated time to generate microemulsion decreases.

Figure 2-4 shows a series of microemulsions made with various oil and S/CoS concentrations. The amount of oil in the mixture was found to be a rate-limiting element, with a high amount of oil resulting in a poor emulsion region. The microemulsion area is enclosed by a black barrier. When the solution is diluted past this barrier, the microemulsion that was produced initially becomes turbid. The formulations of Table 4 are more stable, resulted in fine emulsion and, are further subjected to evaluation studies.

Table 4 Composition of formulations optimized from the ternary phase diagram.Note: In all formulations drug is 100 mg

Formulation	Smix ratio	Oil: Smix ratio	Oils		Surfactants		Co-surfactants	
			Name	Amount (gm)	Name	Amount (gm)	Name	Amount (gm)
F3	3:1	4:6	Castor oil	4	Tween 80	4.5	PEG 400	1.5
F4	4:1	4:6	Castor oil	4	Tween 80	4.8	PEG 400	1.2
F6	3:4	4:6	Castor oil	4	Tween 80	2.57	PEG 400	3.42
F8	2:1	6:4	Castor oil	6	Span 20	2.66	n-butanol	1.33
F9	3:1	6:4	Castor oil	6	Span 20	3	n-butanol	1
F12	2:3	6:4	Castor oil	6	Span 20	1.6	n-butanol	2.4
F13	1:1	2:8	Castor oil	2	labrosol	4	PEG 400	4
F14	2:1	2:8	Castor oil	2	labrosol	5.33	PEG 400	2.67
F18	1:3	2:8	Castor oil	2	labrosol	2	PEG 400	6
F21	3:1	3:7	Olive oil	3	labrosol	5.25	Propylene glycol	1.75
F22	4:1	3:7	Olive oil	3	labrosol	5.6	Propylene glycol	1.4
F23	3:2	3:7	Olive oil	3	labrosol	4.2	Propylene glycol	2.8

3.4. Evaluation parameters

3.4.1. Thermodynamic stability studies

Heating-cooling cycles and centrifugation tests were used to investigate thermodynamic stability. The heating-cooling cycle and centrifugation test were passed by formulations (F3, F4, F6, F8, F9, F12, F14, F18, F21, and F22) **(Table 5)**. After tests, it was observed that SMEDDS had good stability with no phase separation, creaming, or cracking. When subjected to high temperatures, the formulations (F13 and F23) separated and became unstable.

Table 5 Evaluation parameters of the prepared SMEDDS formulations

Formulation Code	Heating Cooling Cycle	Centrifugation	Robustness	Dispersibility test	Emulsification Time (Sec)	Inference
F3				Grade A	90	Passes
F4				Grade D	210	Failed
F6				Grade A	70	Passes
F8				Grade A	60	Passes
F9				Grade A	95	Passes
F12			x	Grade D	182	Failed
F13	x	x	x	Grade D	190	Failed
F14				Grade A	90	Passes
F18				Grade B	110	Passes
F21				Grade A	70	Passes
F22				Grade B	80	Passes
F23	x	x	x	Grade D	170	Failed

3.4.2. Robustness to dilution

The findings of the robustness of the dilution studies revealed that formulations F3, F6, F8, F9, F14, F18, F21, and F22 showed no signs of phase separation or drug precipitation, and they were further tested for dispersibility (Table 5).

3.4.3. Dispersibility test for the efficiency of self-emulsification

According to the findings of the self-emulsification efficiency study, the formulation quickly generated a micro-emulsion within 1 minute that was clear and slightly bluish in appearance. As per grade A, formulations F3, F6, F8, F9, F14, and F21 rapidly formed, slightly less clear emulsion with a bluish-white appearance and as per grade B formulation F18, F22 slowly forming, and F4, F12, F13, and F23 formulations that exhibit poor or minimal emulsification with large oils droplets present on the surface as per grade D formulations F4, F12, F13, and F23 formulations that exhibit poor or minimal. According to the results of the preceding tests, the majority of SMEDDS formulations are stable, with good dispersibility and a short self-emulsification time (Table 5).

3.4.4. Zeta potential (F_3 formulation)

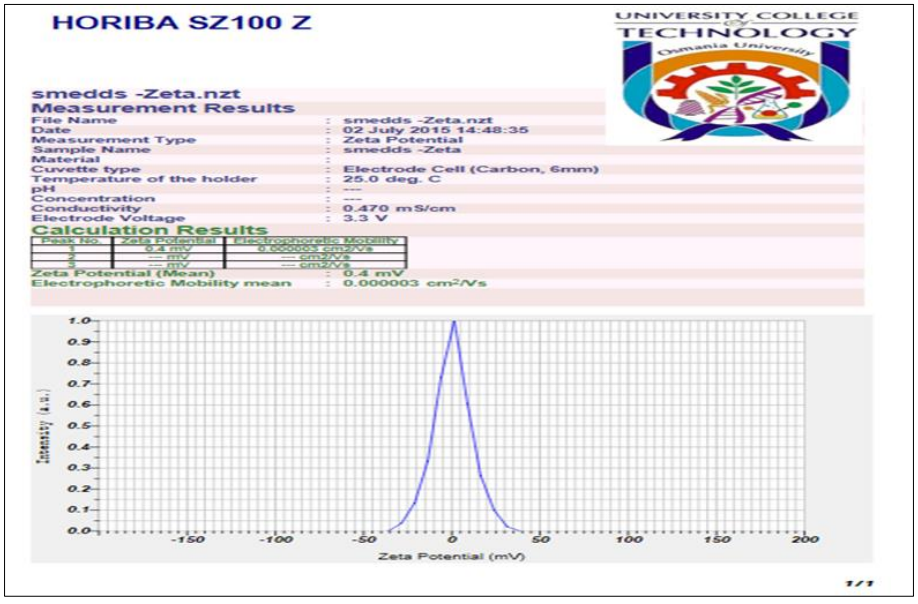

Figure 5 Measurement of Zeta potential of optimized formulation F3

The average particle size was 144.9 nm. The size distribution of the formulation was found to be 0.399, indicating that it is mono-dispersed. The zeta potential of the formulation was 0.4 mV. (Figure 5).

3.4.5. Transmission electron microscopy (F_3 formulation)

TEM was used to evaluate the morphology and size of the optimised SMEDDS (F3) formulation. Photographs of the formulation F3 demonstrate a uniform molecular distribution of the drug in the globules. The globules have a smooth surface and are shaped like spherical outlines of microemulsion droplets. (Figure 6).

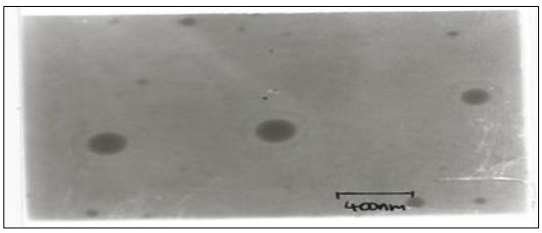

Figure 6 TEM photographs of optimized formulation F3

3.4.6. Drug release studies of selected formulations using dialysis membrane in 0.1N HCl and distilled water

In vitro drug release studies were carried out using USP dissolution apparatus type II with 900ml of 0.1N HCl and distilled water as dissolution media.

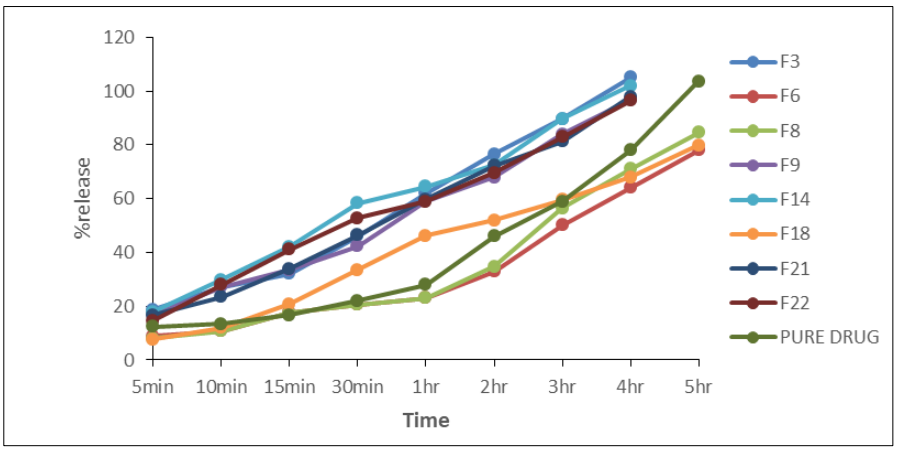

Figure 7 Drug release profiles of formulations using dialysis membrane using 0.1N HCl

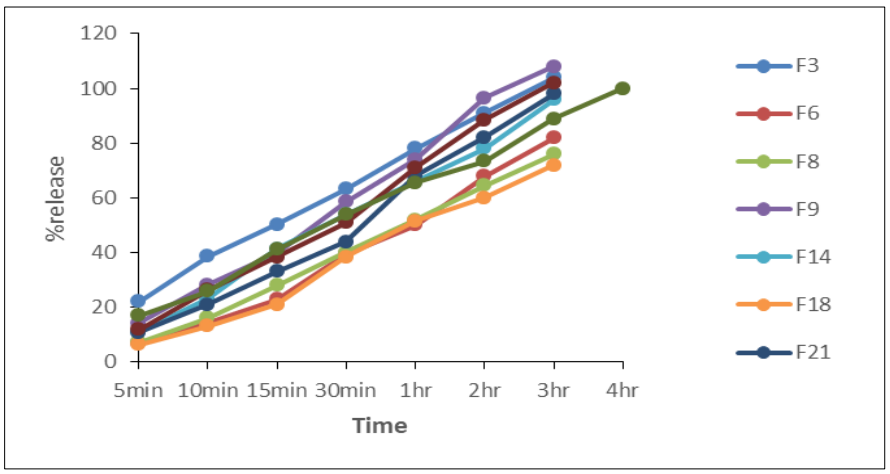

Figure 8 Drug release profiles of formulations using dialysis membrane using distilled water

The dialysis bag method was used to conduct *invitro* drug release studies. Equal amounts of SMEDDS formulations(F3, F6, F8, F9, F14, F18, F21, F22) and suspension of pure dug formulations were placed in each dialysis bag and subjected to dissolution at 50rpm at ±37°C using 0.1N HCl as dissolution medium. Rapid release up to 27.2% (F3)occurred for SMEDDS for the first 10min whereas only 13% of the pure drug was released from the suspension in the same time period (Figure 7). The accumulated amount of drug release from SMEDDS was 105% (F3)for 4hrs,78.8% (F6) for 5 hrs, 84.5%(F8) for 5hrs,96.8%(F9)for 4hrs, 102%(F14) for 4hrs,79.9%(F18) for 5hrs,98%(F21) for 4hrs, 96.4%(F22) for 4hrsand from suspension was only 78% release for 4hrs. The results showed a superior faster release of SMEDDS in comparison with the suspension containing the pure drug. The development of a microemulsion with microscopic droplets on its own may have resulted in a faster drug release. (Figure 8). *Invitro* drug release studies using distilled water showed more amount of drug release from SMEDDS i.e. 104% (F3)for 3hrs, 82% (F6) for 3hrs, 76%(F8) for 3hrs, 108%(F9) for 3hrs, 96%(F14) for 3hrs, 72.1%(F18) for 3hrs, 98%(F21) for 3hrs, 102%(F22) for 3hrs and from suspension was only 89% release for 3hrs period (Figure 9).

3.4.7. Permeation studies of selected formulations using intestine with 0.1N HCl and distilled water

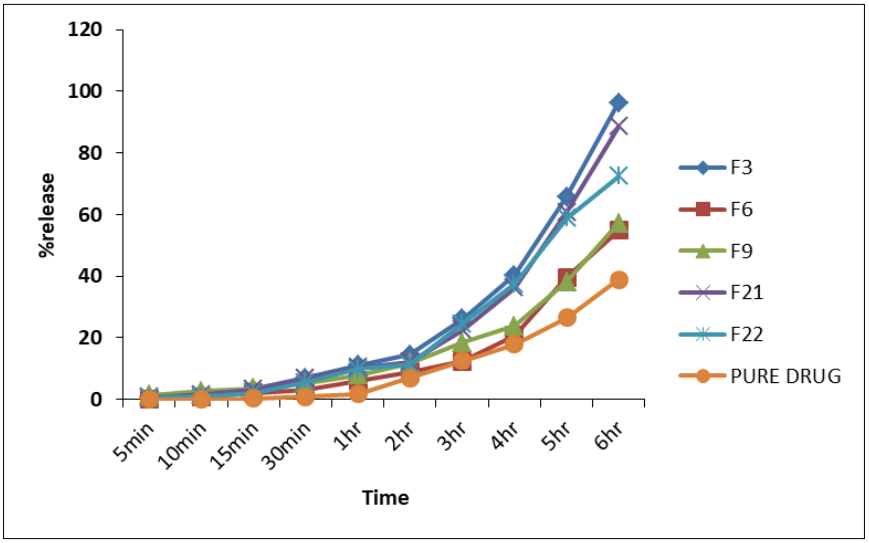

Figure 9 Drug release profiles of formulations through the intestine in 0.1NHCl

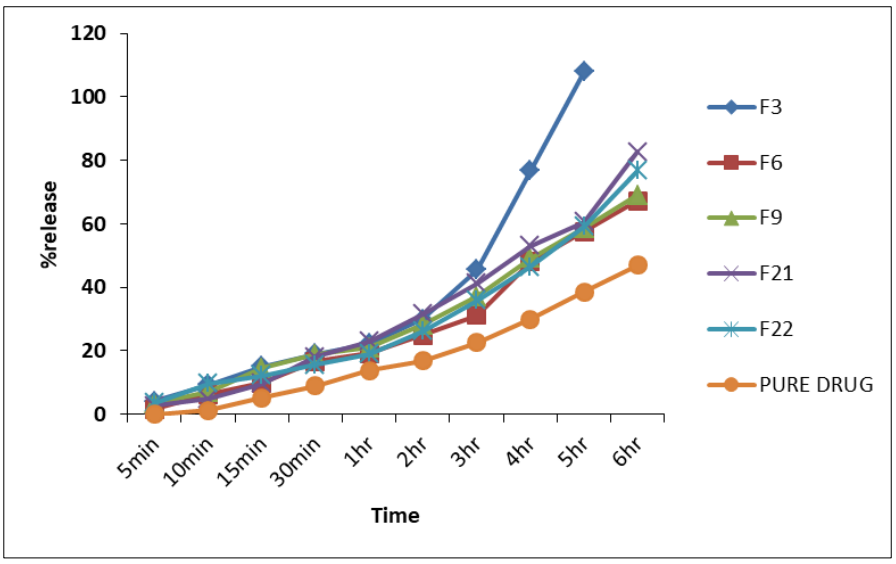

Figure 10 Drug release profiles of formulations through the intestine in distilled water

Permeability tests were carried out using intestine (isolated from sheep) in 0.1N HCl medium. When compared to pure drug suspension, the amount of drug permeated through the intestine from the formulation has exhibited a modest increase in the first 10 minutes of 2 percent (F3). When compared to the pure drug, total drug release was seen in 6

hours at 96.2 percent, which is considerably greater. F3 (castor oil, Tween 80, PEG 400) exhibits the highest cumulative percent drug release of all the formulations (ratio 4:6, km value 3:1). As a result, as compared to pure drug suspension, the formulation appears to have a greater amount of release. (Figure10).

Permeability studies were done using the intestine (isolated from sheep) with distilled water as media. When comparing the amount of permeation via the intestine, formulation F3 exhibited higher permeability (108 percent for 5 hours) than the pure drug (38.5 percent for 5 hours). (Figure 11).

In comparison to the other formulations, formulation F3 has exhibited higher release in permeability experiments. F3 formulation is further subjected for the evaluation of zeta potential and transmission electron microscopy.

4. Conclusion

- SMEDDS of cefpodoxime proxetil, a cephalosporin class antibiotic, can be designed to improve solubility and permeability.
- SMEDDS have been prepared using castor oil, olive oil, Tween 80, Labrosol, PEG 400, and propylene glycol.
- Among all the formulations F3 containing castor oil, Tween 80, PEG 400 has shown a better dissolution profile i.e. 96.2% in 6hrs.
- Hence F3 formulation has been selected as the final optimized formulation.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Author contribution

Dr. K. Latha was the research guide. Naveen Kumar and Nithila under the guidance of Dr. K. Latha collected the content, performed the literature review and experimental work. Keerthi and Padmavathi designed the work and made necessary corrections and, revisions in the manuscript. All the authors drafted the final manuscript.

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