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Development and *In Vitro* Characterization of a Cefixime Trihydrate-loaded Self-Microemulsifying Drug Delivery System for Enhanced Dissolution

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Abstract

Background: Cefixime trihydrate is a poorly water-soluble drug with limitations in dissolution and oral bioavailability. Self-microemulsifying drug delivery systems (SMEDDS) are lipid-based formulations that can improve drug solubilization and dissolution by spontaneously forming fine oil-in-water microemulsions upon dilution in aqueous media. **Objective:** The present study aimed to develop and evaluate an optimized SMEDDS formulation of Cefixime trihydrate and to compare its *in vitro* performance with the marketed formulation, ZAKTER 200 DT. **Materials and Methods:** Solubility studies of Cefixime trihydrate were performed in various oils, surfactants, and cosolvents. Based on the solubility results, Oleic acid, Tween 80, and polyethylene glycol (PEG) 400 were selected as oil, surfactant, and cosurfactant, respectively. Pseudoternary phase diagrams were constructed using different surfactant-to-cosurfactant (S/CoS) ratios of 1:1, 2:1, and 3:1. Ten SMEDDS formulations (F1–F10) were prepared by varying the oil-to-surfactant ratio while maintaining the drug concentration at 50 mg/mL. The formulations were evaluated for thermodynamic stability, self-emulsification time, *in vitro* dissolution, droplet size, polydispersity index (PDI), zeta potential, and drug-excipient compatibility. **Results:** PEG 400 showed the highest solubilization capacity for Cefixime trihydrate. The S/CoS ratio of 2:1 produced a clear and transparent microemulsion region and was selected for further optimization. All formulations passed the thermodynamic stability studies, showing no significant changes following freeze-thaw, heating-cooling, and centrifugation tests. Formulations F1, F2, F3, F5, F6, and F9 produced clear dispersions without drug precipitation. Among the formulations, F2 showed a self-emulsification time of 1.32 ± 0.0189 min and was selected as the optimized formulation. F2 produced a mean droplet size of 125.0 nm with a PDI of 0.128 and a zeta potential of −8.78 mV. The *in vitro* dissolution study demonstrated an improved dissolution profile of F2 SMEDDS compared with the marketed ZAKTER 200 DT formulation. Drug-excipient compatibility studies showed no visible changes in the appearance of Cefixime trihydrate with Tween 80, PEG 400, or Oleic acid during the 90-day observation period. **Conclusion:** The optimized Cefixime trihydrate SMEDDS containing Oleic acid, Tween 80, and PEG 400 demonstrated satisfactory self-emulsification characteristics, nanosized droplets, good physical stability, and improved *in vitro* dissolution compared with the marketed formulation. The developed SMEDDS therefore represents a potential lipid-based approach for improving the dissolution and oral delivery performance of Cefixime trihydrate.

Key words: Cefixime trihydrate, dissolution, droplet size, oleic acid, polyethylene glycol 400, self-microemulsifying drug delivery system, Tween 80, zeta potential

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INTRODUCTION

Self-microemulsifying drug delivery systems (SMEDDS) are well-established lipid-based drug delivery systems that have attracted considerable attention as alternative approaches for the oral delivery of poorly water-soluble drugs. Poor aqueous solubility is one of the major challenges encountered during the development of oral dosage forms because inadequate dissolution of a drug in gastrointestinal fluids can result in incomplete, delayed, or variable absorption and consequently may limit its oral bioavailability. In conventional oral formulations, the drug must undergo dissolution before it becomes available for absorption. Therefore, enhancement of drug solubility and dissolution is an important consideration in the formulation of drugs exhibiting poor aqueous solubility. SMEDDS provide a promising approach to overcome these limitations by incorporating the drug into an isotropic lipid-based formulation capable of undergoing spontaneous emulsification following contact with an aqueous medium.[1]

SMEDDS are generally composed of an isotropic mixture of an oil, a surfactant, a co-surfactant or solubilizer, and the drug. The basic principle of SMEDDS is their ability to form a fine oil-in-water microemulsion when subjected to mild agitation followed by dilution with an aqueous medium, such as gastrointestinal fluids. After oral administration, the formulation comes into contact with the aqueous environment of the gastrointestinal tract and undergoes spontaneous self-emulsification. This process results in the formation of fine droplets in which the drug is maintained in a solubilized or finely dispersed state. The formation of small droplets produces a large interfacial surface area, which may facilitate drug release and interaction with the gastrointestinal absorptive surface. Consequently, SMEDDS can reduce the dependence of drug absorption on the dissolution of the original drug particles and may improve the *in vitro* dissolution characteristics of poorly water-soluble drugs.[2]

The performance of a SMEDDS formulation depends substantially on the selection and proportion of its individual components. The oil phase plays an important role in solubilizing the drug and provides the lipidic environment required for formulation of the self-emulsifying system. The surfactant reduces the interfacial tension between the oil and aqueous phases and promotes spontaneous emulsification, whereas the co-surfactant or solubilizer can improve drug solubilization and facilitate the formation of a stable and homogeneous dispersion. The appropriate combination and concentration of these components are therefore essential for obtaining a formulation with rapid self-emulsification, good drug solubilization, and suitable physicochemical characteristics.[3]

Selection of a suitable self-emulsifying formulation involves systematic assessment of several critical formulation parameters. Initially, the solubility of the drug in different oils, surfactants, and co-surfactants or solubilizers is determined to identify components capable of dissolving an adequate amount of drug. Subsequently, the self-emulsifying region can be investigated using pseudoternary phase diagrams. These phase diagrams provide useful information regarding the proportions of oil, surfactant, and co-surfactant that can produce a clear and stable microemulsion following aqueous dilution. The size and characteristics of the self-emulsifying region are therefore important considerations during formulation optimization. In addition, the droplet size distribution of the resultant emulsion following self-emulsification provides important information about the quality and uniformity of the formed dispersion. Thus, drug solubility in formulation components, the extent of the self-emulsifying region, and the droplet size distribution are important parameters in the development and optimization of SMEDDS.[4]

Cefixime trihydrate is an orally administered cephalosporin antibacterial drug. In the present study, cefixime trihydrate is considered a biopharmaceutical classification system Class IV drug with a high dose number. The poor oral bioavailability of cefixime trihydrate may therefore be associated with its solubility and dissolution limitations. Inadequate aqueous solubility can restrict the amount of drug available in the gastrointestinal fluids for dissolution and subsequent absorption. Consequently, improvement of the solubility and dissolution characteristics of cefixime trihydrate represents an important formulation objective. Various approaches have been investigated for enhancing the pharmaceutical performance of poorly soluble drugs, including complexation with cyclodextrins, solid dispersion, suspension, co-precipitation, micronization, salt formation, emulsification, use of micelles, and co-grinding.[5]

Although these conventional formulation approaches can improve the dissolution characteristics of poorly soluble drugs, their effectiveness may vary according to the physicochemical properties of the drug and the formulation method employed. Lipid-based systems such as SMEDDS provide an alternative strategy in which the drug is incorporated into a formulation containing suitable lipidic and surface-active excipients. Following dilution in gastrointestinal fluids, the formulation spontaneously generates a fine dispersion and may maintain the drug in a solubilized state. This characteristic makes SMEDDS particularly attractive for investigating the *in vitro* dissolution enhancement of drugs whose performance is limited by poor aqueous solubility.[6]

Furthermore, it has been reported that the absorption of cefixime trihydrate is increased by approximately 35% when it is administered with food rather than in a fasting state. The influence of food on drug absorption suggests that changes in the gastrointestinal environment and the availability of the drug in a solubilized state may influence its oral absorption characteristics. This observation provides an additional rationale for investigating formulation strategies capable

of improving drug solubilization and dissolution under gastrointestinal conditions.[7]

Cefixime trihydrate is available in various strengths, including 50 mg, 100 mg, 200 mg, and 500 mg. In the present study, 200 mg was selected as the working dose in order to limit the total formulation volume while providing a suitable drug quantity for the development and evaluation of the SMEDDS formulation. The selection of an appropriate drug concentration is important during SMEDDS development because the formulation should possess adequate drug-loading capacity while retaining its ability to undergo rapid and complete self-emulsification following dilution.

For the development of cefixime trihydrate SMEDDS, suitable excipients were selected based on their ability to solubilize the drug and facilitate spontaneous emulsification. In the present study, oleic acid was investigated as the oil phase, Tween 80 as the surfactant, and polyethylene glycol (PEG) 400 as the co-surfactant/solubilizer. Preliminary solubility studies were performed to determine the suitability of individual formulation components for cefixime trihydrate. The selected components were subsequently evaluated at different surfactant-to-co-surfactant ratios using pseudo ternary phase diagrams to identify an appropriate self-emulsifying region. The optimized composition was then selected on the basis of its physical appearance, self-emulsification behavior, and ability to produce a clear dispersion on dilution.

The developed formulations were further subjected to thermodynamic stability studies to evaluate their physical stability under different stress conditions. Self-emulsification time was determined to assess the ability of the formulations to spontaneously form an emulsion on dilution with an aqueous medium. The optimized formulation was subsequently characterized by *in vitro* dissolution studies and evaluated for droplet size, polydispersity index, and zeta potential. These characterization parameters provide important information regarding the performance and physicochemical properties of the SMEDDS after dilution.

Therefore, the present study was undertaken with the main objective of developing and evaluating an optimized SMEDDS containing cefixime trihydrate and comparing its *in vitro* dissolution performance with the marketed formulation ZAKTER 200 DT. The study involved systematic selection of formulation components, construction of pseudoternary phase diagrams, optimization of the oil-surfactant-co-surfactant ratio, evaluation of thermodynamic stability and self-emulsification characteristics, and physicochemical characterization of the optimized formulation. The *in vitro* dissolution behavior of the optimized cefixime trihydrate SMEDDS was subsequently compared with the marketed formulation to assess its potential as an alternative formulation approach for improving the dissolution performance of cefixime trihydrate.

MATERIALS AND METHODS

Materials

A gift sample of Cefixime trihydrate was obtained from FDC Mumbai (Mumbai, India). PEG 600, PEG 400, Tween 80 (polyoxyethylene sorbitan monooleate), Tween 60, Oleic acid, and Transcutol were purchased from Lobachem, Pvt. Ltd., Mumbai. HPLC-grade acetonitrile, methanol, ethanol, and hydrochloric acid (HCL) were used for the present study.

Methods

Solubility study

The drug was added in excess amount into 5 mL of each component in vials and stirred for 24 h at 25 ± 0.5°C on a magnetic stirrer (Remilab, India), and equilibrated samples were removed from the stirrer and centrifuged at 3000 rpm for 15 min to remove the excess drug. The supernatant was taken and filtered through a 0.45 µm membrane filter, after which the concentration of drug in the supernatant was measured by ultraviolet (JASCO V-630) spectrophotometric method after appropriate dilution with methanol. Then drug solubility (mg/mL) was calculated.[8]

Pseudo ternary phase diagram

SMEDDS forms a microemulsion when titrated with water under agitation condition. The lipid mixtures with different surfactant, cosurfactant, and oil ratios lead to the formation of SMEDDS with different properties. Since surfactant and cosurfactant adsorb at the interface and providing mechanical barrier to coalescence, the selection of oil, surfactant, and cosurfactant and the mixing ratio to surfactant/cosurfactant play an important role in microemulsion formation. Several formulations were prepared using oleic acid, Tween 80, and PEG 400 with seven different S/CoS ratios of 1:1, 2:1, and 3:1 and titrated with water to get Microemulsion regions. Microemulsion regions were observed visually and graded as transparent with good flow: oil/water microemulsion; transparent gel with medium flow: microemulsion gel; milky or cloudy with good flow: Emulsion; milky gel with medium flow: Emulgel. The area of the microemulsion region obtained with different ratios of surfactant: co-surfactants (Smix ratios) was compared.[9]

Preparation of SMEDDS formulation

A series of SMEDDS formulations were carried out using Tween 80, PEG 400 as S/CoS, and oleic acid as oil. In all formulations, the level of cefixime trihydrate was kept constant (i.e. 50 mg/mL), and varying the ratio of oil, surfactant, and co-surfactant were added then the components were mixed by a magnetic stirrer until cefixime trihydrate was completely dissolved.[10]

Thermodynamic stability studies

Freeze-thaw cycle

This test was performed for accelerated stability testing of microemulsion formulations. The formulations were exposed at two different temperatures, that is, −21°C and 21°C, for each temperature cycles not more than 24 h. For the better estimation of accelerated stability studies, six such cycles were run for each batch of formulation. The formulations which showed the maximum stability were selected for further study.[11]

Centrifugation

To estimate metastable systems, the optimized SMEDDS formulations are diluted with purified distilled water. Then, the microemulsion is centrifuged at 1000 rpm for 15 min at 25°C and is observed for any change in homogeneity of microemulsions.

Self-emulsification time

The emulsification time of SMEDDS was determined according to the Chinese Pharmacopoeia (2005 version), dissolution apparatus 3. One gram of each formulation was added into 100 mL of distilled water pH6.8 phosphate buffer saline and 0.1N HCL at 37°C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 100 rpm. A three-milliliter sample was collected at 30 s, 1, 1.5, 2, 2.5, and 3 min, and the turbidity was measured at 550 nm. The time of self-emulsification was recorded by turbidity that became unchanged when self-emulsification reached equilibrium.[12]

In vitro dissolution studies

The quantitative *in vitro* release test is performed in 0.1N HCL dissolution medium, which is based on the USP 24 method. SMEDDS are placed in gelatin capsule during the release period to compare the release profile with the conventional dosage form. Sample solutions are withdrawn at predetermined time intervals dilute suitably, and analyzed spectrophotometrically. An equal amount of fresh dissolution medium is replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals is calculated using the Beer-Lambert equation.[13]

Droplet size analysis

It is a precise method for evaluation of stability. Size of droplet is measured Dalsa nano sizer. All measurements are carried out at scattering angle of 90°C and 25°C temperatures. Before measurement, the microemulsion is diluted in two steps with pure water, then it is filtered through a 0.22 µm filter just before it is added to a cuvette. In the first step, it is diluted with an equal amount of water. In the second step, the mixture is further diluted to an appropriate concentration for the measurement. That depends on droplet size (Usually diluted 100–200 times).[14]

Zeta potential measurement

Zeta potential for micro emulsion is determined using Zetasizer. Samples are placed in clear disposable zeta cells, and results are recorded. Before putting the fresh sample, cuvettes were washed with methanol and rinsed using the sample to be measured before each experiment.[15]

RESULTS

Solubility study

The solubility screening demonstrated that PEG 400 had the highest solubilization capacity for cefixime trihydrate among the investigated excipients is shown in Figure 1. On the basis of these findings, PEG 400 was selected as the solubilizing agent, Tween 80 as the surfactant, and oleic acid as the oil phase for subsequent formulation development.

Pseudoternary phase diagram

Pseudoternary phase diagrams were constructed using S_{mix} ratios of 1:1, 2:1, and 3:1 (Figure 2) to identify the self-emulsifying region. On dilution with water, formulations prepared at S_{mix} ratios of 1:1 and 3:1 showed precipitation. In contrast, the 2:1 S_{mix} ratio produced a clear, transparent dispersion over extensive dilution. Therefore, the 2:1 ratio was selected for further optimization.

Thermodynamic stability

All ten formulations (F1–F10) passed the reported freeze–thaw, heating–cooling, and centrifugation tests. As Shown in Table 2 and Figure 3 noted no visible changes were recorded in any formulation during these assessments.

Table 1: Developed formulations with their compositions

S. No.	S_{Mix} ratio	O/S ratio	Batch code
1.	1:1	1:4	F1
2.		1:5	F2
3.		1:6	F3
4.		1:7	F4
5.	2:1	1:4	F5
6.		1:5	F6
7.		1:6	F7
8.	3:1	1:4	F8
9.		1:5	F9
10.		1:6	F10

Table 2: Screening of formulations on the basis of thermodynamic stability studies

S.No.	Batch code	Observation based on thermodynamic stability studies			Inferences
		Freeze throw cycle	Heating/Cooling cycle	Centrifugation	
1.	F1	N	N	N	Passed
2.	F2	N	N	N	Passed
3.	F3	N	N	N	Passed
4.	F4	N	N	N	Passed
5.	F5	N	N	N	Passed
6.	F6	N	N	N	Passed
7.	F7	N	N	N	Passed
8.	F8	N	N	N	Passed
9.	F9	N	N	N	Passed
10.	F10	N	N	N	Passed

N: No change occurs in SMEDDS formulation

Table 3: Results of self-emulsification studies

Formulation	Self -emulsification time (min)	Observation
F1	1.21±0.0040	Clear dispersion; no precipitation
F2	1.32±0.0189	Clear dispersion; no precipitation
F3	1.43±0.0561	Clear dispersion; no precipitation
F4	1.48±0.0012	Slightly clear; precipitation reported
F5	1.41±0.0413	Clear dispersion; no precipitation
F6	1.32±0.0215	Clear dispersion; no precipitation
F7	2.10±0.0012	Slightly clear; precipitation reported
F8	2.14±0.0145	Slightly clear; precipitation reported
F9	2.11±0.0328	Clear dispersion; no precipitation
F10	2.24±0.0124	Slightly clear; precipitation reported

Table 4: Microemulsion F2 particle size cumulants results

S.No.	Cumulants Results	Observation
1.	Diameter (d)	125.0 nm
2.	Polydispersive index (PDI)	0.128
3.	Diffusion const. (D)	4.732e-008 (cm^2/s)
	Measurement condition	
1.	Temperature	25.0 (°c)
2.	Diluent name	Water
3.	Refractive index	1.3328
4.	Viscosity	0.8878 (cP)

Thermodynamic stability studies

Table 2 and Figure 3.

Self-emulsification assessment

The results of self-emulsification studies are given in Table 3. It was observed that an increase in the proportion of S mix in the formulation resulted in decreasing self-emulsification time. F1, F2, F3, F5, F6, and F9 were found to be clear dispersion and did not show any drug precipitation and thus were considered as stable. While F4, F7, F8, and F10 formed a slightly clear dispersion, they showed drug precipitation and thus were not stable. This may be due to the presence of a high percentage of co-surfactant in the formulation, which, being water-soluble, is anticipated to enter the water phase and redistribute mainly between the water phase and the emulsion-water interface, resulting in a loss of solvent capacity of the vehicle.

F1, F2, F3, F5, F6, and F9 formed clear dispersions without visible drug precipitation. F4, F7, F8, and F10 were reported to produce slightly clear dispersions with precipitation. F2 was identified as the optimized formulation in the study.

In vitro dissolution study

Figure 4 shows the dissolution curves of marketed tablet formulation and SMEDDS formulation in 0.1N HCL. It was observed that the SMEDDS improved the dissolution rate of cefixime trihydrate significantly compared with the marketed formulation (ZAKTER200DT). The marketed drug showed a poor dissolution rate as compared with its SMEDDS formulation. The F2 SMEDDS formulation shows enhancement in dissolution profile.

Table 5: Appearance study of cefixime trihydrate-Tween 80, cefixime trihyrate-PEG400 and cefixime trihydrate-oleic acid

Storage time (days)	Cefixime+Tween 80	Cefixime+PEG 400	Cefixime+oleic acid
0	Slightly yellowish liquid	Clear, colorless liquid	Clear, colorless liquid
7	Slightly yellowish liquid	Clear, colorless liquid	Clear, colorless liquid
15	Slightly yellowish liquid	Clear, colorless liquid	Clear, colorless liquid
30	Slightly yellowish liquid	Clear, colorless liquid	Clear, colorless liquid
60	Slightly yellowish liquid	Clear, colorless liquid	Clear, colorless liquid
90	Slightly yellowish liquid	Clear, colorless liquid	Clear, colorless liquid

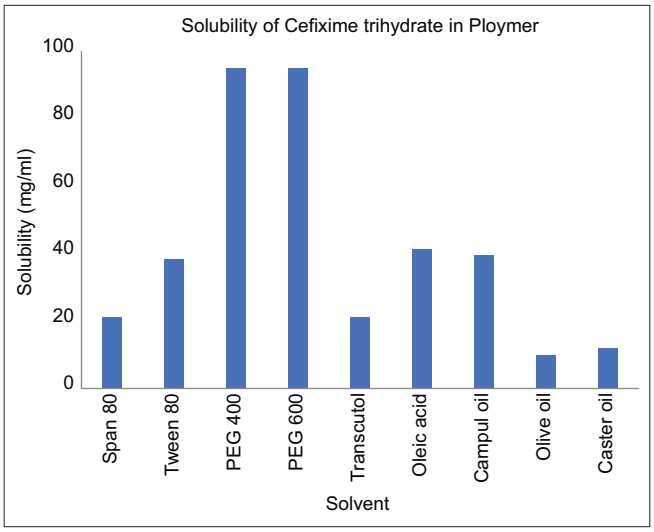


Figure 1: Solubility of cefixime trihydrate in surfactants

Droplet size and polydispersity

There is a relationship between the droplet size and the concentration of the surfactant being used (Figure 5). In some cases, increasing the surfactant concentration could lead to droplets with a smaller mean droplet size. Measurements were reported at 25°C using water as the diluent (refractive index 1.3328; viscosity 0.8878 cP) as shown in Table 4.

Zeta potential

The optimized F2 formulation exhibited a zeta potential of −8.78 mV (Figure 6). Tween 80 and PEG 400 were identified in the source report as nonionic excipients. The measured value provides a description of the dispersion's surface-charge characteristics; zeta potential alone does not establish physical stability.

Drug-excipient compatibility by appearance

The recorded appearance of each drug-excipient mixture remained unchanged over the 90-day observation period.

DISCUSSION

Excipients and drug solubilization

The solubility study identified PEG 400 as the excipient with the greatest solubilization capacity for cefixime trihydrate among those screened. Selecting an excipient with adequate drug-solubilizing capacity is important in SMEDDS because dilution after administration can alter the solvent environment and may cause drug precipitation. The use of PEG 400 together with Tween 80 and oleic acid provided the basis for the subsequent formulation and phase-behavior studies. The supplied data do not include the numerical solubility values, so the magnitude of the difference between excipients cannot be quantified here.

Interpretation of the pseudoternary phase diagram

The observed differences between Smix ratios indicate that the surfactant-to-co-surfactant proportion affected the formulation's behavior on aqueous dilution. Precipitation at 1:1 and 3:1, contrasted with the clear dispersion obtained at 2:1, supported selection of the 2:1 ratio for further development. This finding highlights the value of phase-diagram screening as a formulation-selection tool. The reported outcome is based on visual appearance and dilution behavior; the exact area of each self-emulsifying region was not supplied in the text.

Thermodynamic stability

All ten formulations showed no recorded visible change during the freeze–thaw, heating–cooling, and centrifugation assessments (Table 2). These results indicate that the formulations tolerated the specific stress conditions applied during screening. Such tests are useful early indicators of physical robustness, but they do not replace long-term or accelerated stability studies under defined storage conditions (Figure 3).

Self-emulsification and selection of F2

Self-emulsification times ranged from 1.21 to 2.24 min. F1 had the shortest reported time, while F2 emulsified in

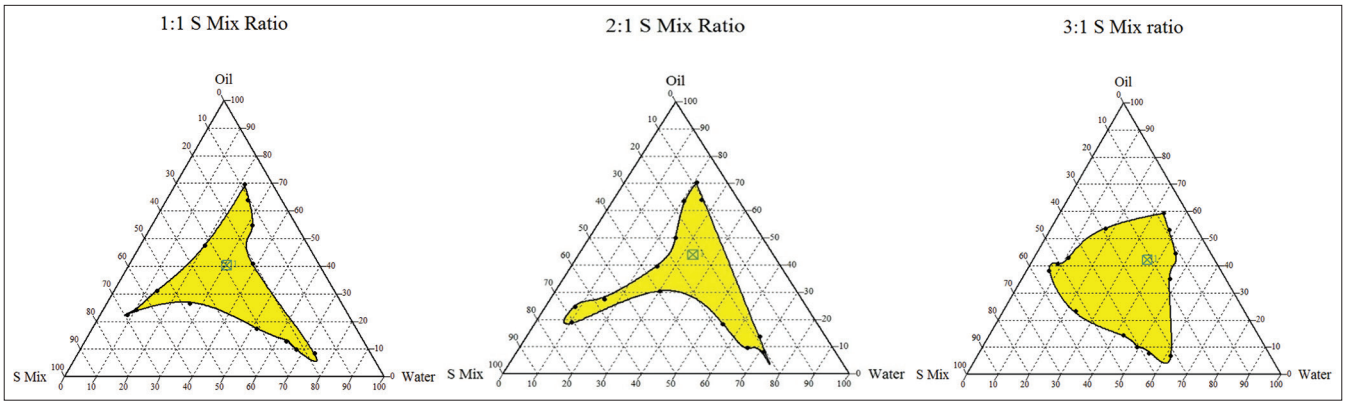


Figure 2: Ternary Phase diagram of 1:1 ratio, 2:1 and 3:1 ratio



Figure 3: Screening of F1-F10 formulations on the basis of thermodynamic stability studies

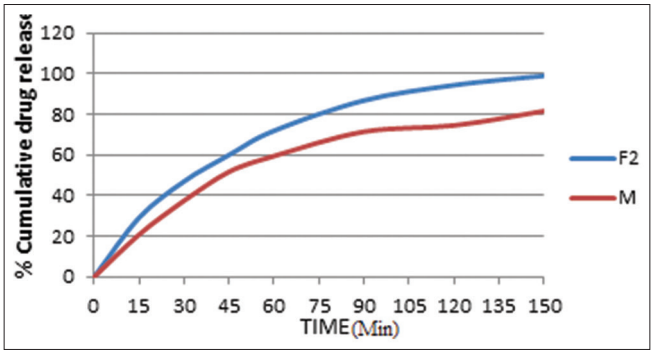


Figure 4: *In vitro* dissolution study of F2 self-microemulsifying drug delivery systems and marketed tablet formulations (M: Marketed formulation, F2: Optimized formulation)

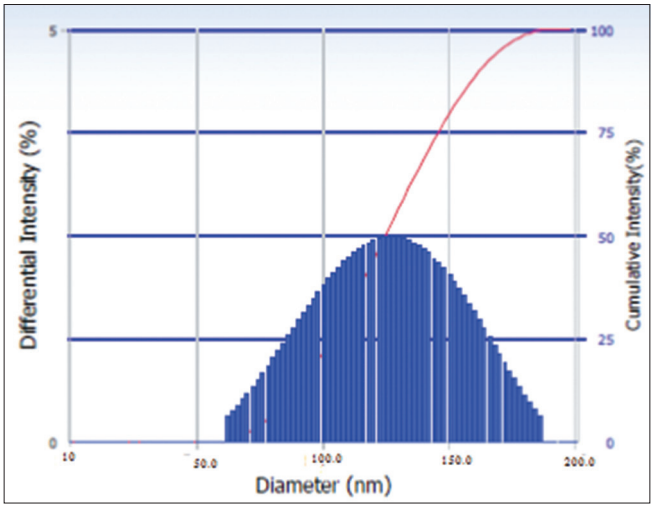


Figure 5: Microemulsion droplet size of F2 formulation

1.32 ± 0.0189 min and produced a clear dispersion without reported precipitation. F2 was selected as the optimized formulation in the study. The results also show that short emulsification time alone was not sufficient to distinguish formulations: Clarity and absence of precipitation were additional practical criteria. The source text suggests that increasing S_{mix} proportion reduced emulsification time, but the tabulated values do not show a uniform trend across all batches; this statement should therefore be interpreted cautiously.

Comparative *in vitro* dissolution

The dissolution comparison in 0.1 N HCL showed a higher dissolution profile for F2 SMEDDS than for ZAKTER 200 DT as indicated in Figure 4. This result is consistent with the intended role of SMEDDS: formation of a fine dispersion and improved drug presentation in the dissolution medium. Nevertheless, because the supplied report does not provide the underlying percentage-release values, sampling

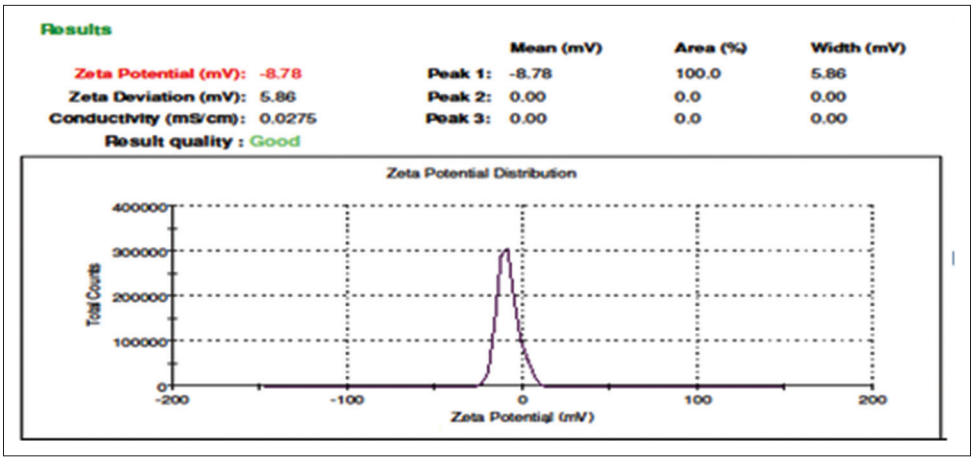


Figure 6: Graph of F2 zeta potential

times, replicate variability, or statistical analysis, the size and statistical significance of the improvement cannot be independently assessed from the text alone. The finding supports improved *in vitro* dissolution under the tested conditions, but does not by itself demonstrate increased *in vivo* bioavailability.

Droplet size and PDI

As shown in Figure 5 F2 produced a mean droplet diameter of 125.0 nm and a PDI of 0.128. These measurements indicate that the diluted formulation formed nanosized droplets with a relatively narrow size distribution. The small droplet size is consistent with the formation of a fine dispersion, while the PDI provides an indication of the distribution's uniformity. The relationship between surfactant concentration and droplet size can be formulation-dependent: surfactant may stabilize the oil–water interface, but changes in interfacial behavior can also affect droplet formation. The present dataset characterizes F2; it does not provide a comparative droplet-size dataset across all formulations.

Zeta potential

The zeta potential of F2 was −8.78 mV (Figure 6). Since Tween 80 and PEG 400 are nonionic, the measured negative value should be reported as an observed surface-charge characteristic rather than interpreted as proof of electrostatic stabilization. In nonionic systems, physical stability may also depend on steric effects and the overall formulation composition. Stability conclusions should therefore be based on the combined evidence from the stability tests and other characterization results, rather than zeta potential alone.

Drug-excipient compatibility

The appearance observations showed no visible change in the cefixime–PEG 400 and cefixime–oleic acid mixtures over 90 days; both remained clear and colorless. The cefixime-Tween 80 mixture remained slightly yellowish throughout the same period. The consistency of appearance provides preliminary evidence of visual compatibility under the conditions observed. However, appearance testing cannot establish chemical compatibility or exclude degradation; instrumental studies such as Fourier-transform infrared spectroscopy, differential scanning calorimetry, or stability-indicating chromatographic analysis would be needed for stronger conclusions.

Overall interpretation

Taken together, the findings support the selection of PEG 400, Tween 80, and oleic acid as the formulation components and a 2:1 S_{mix} ratio for further optimization. F2 was reported as the optimized formulation and showed clear self-emulsification, nanosized droplets, a relatively low PDI, and improved *in vitro* dissolution compared with ZAKTER 200 DT under the tested conditions. The conclusions should remain limited to the reported *in vitro* and visual assessments. Claims of enhanced bioavailability, increased drug-loading efficiency, or long-term stability would require additional supporting experiments.

CONCLUSION

An optimized SMEDDS containing oleic acid, Tween 80, PEG 400, and cefixime trihydrate was successfully developed and evaluated for improving the *in vitro* dissolution performance of cefixime trihydrate, a poorly water-soluble drug. PEG 400 demonstrated the highest solubilization capacity among the investigated excipients, while Tween 80 and oleic acid were selected as the surfactant and oil phase, respectively. Pseudoternary phase-diagram studies identified a 2:1 surfactant-to-co-surfactant ratio as the most suitable composition for obtaining a clear and stable dispersion on dilution.

Among the developed formulations, F2 was selected as the optimized formulation based on its satisfactory

self-emulsification characteristics and absence of visible precipitation. The optimized formulation exhibited a mean droplet size of 125.0 nm, a polydispersity index of 0.128, and a zeta potential of −8.78 mV. The formulation also demonstrated satisfactory thermodynamic stability under freeze–thaw, heating–cooling, and centrifugation stress conditions.

Importantly, the optimized F2 SMEDDS showed improved *in vitro* dissolution of cefixime trihydrate compared with the marketed formulation, ZAKTER 200 DT, in 0.1 N HCL. The enhanced dissolution may be attributed to spontaneous self-emulsification and the formation of fine droplets, which can provide a greater interfacial area for drug dissolution. The drug-excipient appearance study further showed no apparent visual changes in the investigated cefixime trihydrate–excipient mixtures during the 90-day observation period.

Overall, the findings demonstrate that SMEDDS is a promising formulation approach for enhancing the *in vitro* dissolution performance of cefixime trihydrate. The optimized F2 formulation exhibited satisfactory solubilization, self-emulsification, thermodynamic stability, nanoscale droplet formation, and improved dissolution compared with the marketed formulation. However, increased *in vivo* bioavailability and enhanced drug-loading efficiency were not directly established in the present study. Therefore, further pharmacokinetic and *in vivo* studies are warranted to confirm whether the improved dissolution characteristics translate into enhanced oral bioavailability.

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