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RESEARCH ARTICLE

# PREPARATION AND EVALUATION OF SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM FOR FEXOFENADINE HYDROCHLORIDE

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**ABSTRACT**

Developing a drug product with desirable bioavailability is a challenge for sparingly water soluble drugs such as Fexofinadine hydrochloride. **Objective:** In the present investigation self microemulsifying drug delivery system (SMEDDS) of Fexofenadine hydrochloride was developed for improving solubility and dissolution rate of drug. **Material Method:** Solubility of Fexofenadine hydrochloride was determined in various non-aqueous vehicles such as oils, surfactants, and co-surfactants. Psuedoternary phase diagrams were constructed to identify the self-micro emulsification region. Four formulations of SMEDDS were selected from the optimum concentration of oils, surfactant, and co-surfactants from psuedoternary diagrams. **Results and Discussion:** Selected formulations were evaluated for droplet size, in-vitro drug dissolution, drug content and solubility of drug. The optimum formulation was 20% oleic acid, 26.3% ACONON MC8 and 53.3% PEG 400. Self-micro emulsification with the combination of oleic acid and ACONON MC8 was found higher. **Conclusion:** The results obtained from in vitrodissolution indicated Fexofenadine hydrochloride in SMEDDS dissolved rapidly and completely in phosphate buffer pH 6.8 which was used as dissolution medium.

**Key-Words:** SMEDDS, ACONON MC8, Dissolution enhancement, Psuedoternary phase diagrams

## INTRODUCTION

SMEDDS is defined as isotropic mixture of lipid or oil, surfactant, co-surfactant and drug substance that rapidly form a fine oil-in-water microemulsionwhen exposed to aqueous media under condition of gentle agitation or digestive motility that would be encountered in the GIT.Self Emulsifying Drug Delivery Systems (SEDDS) andSMEDDS are the two types of self emulsifying systems[1].Both SEDDS and SMEDDS have distinct features associated with improvement of drug delivery properties. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm to 5 mm and its dispersion has a turbid appearance[2, 3]. SMEDDS, however, have a smaller lipid droplet size (<100 nm) and its dispersion has an optically clear to translucent appearance. Both systems are associated with the generation of large surface area upon dispersions resulting into increased absorption of poorly soluble drugs[4, 5, 6].

Fexofenadine hydrochloride is an antihistaminic drug used in the treatment of hayfever and allergy symptoms. It is a third-generation antihistaminic agent. It does not readily pass through the blood-brain barrier, and hence causes less drowsiness than first-generation histamine-receptor antagonists. Fexofenadine hydrochloride has 33% absorption and 60-70 % protein binding. Half life of drug is 14.4 hours. Log P and pKa values of drug are 5.6 and 13.2 respectively. Fexofenadine hydrochloride is poorly water soluble leading to lower absorption rate. Thus, there is a need to increase the solubility of drugto improve the absorption of drug via oral route.

Present investigation was aimed to increase oral bioavailability of Fexofenadine hydrochloride. Self microemulsifying drug delivery system was developed to enhance oral solubility and in-vitro dissolution of drug. SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drugs these systems may offer an improvement in the rate and extent of absorption and results in more reproducible plasma level concentrations.

## MATERIALS AND METHODS

### Materials

Fexofenadine hydrochloride was received as gift sample from Astron Research Centre, Ahmedabad, INDIA. ACONON MC8 was received as gift sample from ABITECH Corporation, INDIA. Aerosil200 was received as gift sample from Acron Pharmaceuticals, Ahmedabad, INDIA. Oleic acid, Polyethylene glycol 400 (PEG 400), Microcrystalline cellulose (MCC) was purchased from S. D. Fine Chemicals, Mumbai, INDIA. All other reagents used were of analytical grade.

### Experimental Methods

### Solubility studies

Excess amount of Fexofenadine hydrochloride was added to 2 ml of each excipients were placed in test tubes and the mixture was vortexed and heated in a water bath to facilitate drug solubilization. The mixture was finally kept at ambient room temperature (25°C) under continuous shaking for 24 hours to attain equilibrium. Aliquots of supernatant were diluted with phosphate buffer (pH-6.8) and the drug content was measured at 220 nm using a UV spectrophotometer.[7,8,9] Excipients used in solubility study were water, span 80, castor oil, oleic acid, polyethylene glycol 400, transcutol P, acconon MC8, isopropyl alcohol (IPA), LabrafilM1944 $C_s$, tween 80, and cremophore RH40.

### Construction of Psuedoternary Phase Diagrams

Self micro-emulsifying performance of Self Microemulsion (SME) mixture was assessed from their

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ternary phase diagrams. Only the specific combinations of oil, surfactant and a co surfactant in the specific composition range were observed to produce a fine microemulsion upon aqueous dilution[10, 11]. To check emulsification efficiency of SME mixtures, test for emulsification was performed on all combinations and the resultant dispersions were visually assessed. The dispersions either formed a clear microemulsion, a slightly turbid emulsion or a milky emulsion which immediately was phase separated[12, 13, 14]. Nine combinations were prepared with the ratios of oil:(surfactant/co-surfactant) as 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7,1:8 and 1:9. The surfactant/co-surfactant ratios ($K_m$) of 1:1, 1:2, 2:1 and 3:1 were evaluated. Surfactant and co-surfactant mixtures possessing various $K_m$ ratios were prepared by weighing appropriate quantities of surfactant and co-surfactant and were vortexed for 30 min to produce a homogenous mixture.

Mixtures with 12-50% of the oil, 25-66% of the surfactant and 12-44% of co-surfactant were evaluated for their self emulsifying properties. These mixtures were then mixed with the oil phase to form an isotropic SME mixture. Thus, each combination had a total of 9 samples with different proportions of oil, surfactants and co-surfactants.[15, 16]

**Preparation of SMEDDS**

Liquid SMEDDS formulation was prepared by dissolving 100 mg of Fexofenadine Hydrochloride in the optimized SMEDDS mixture consisting of oleic acid, Aconon MC8 and PEG 400.Drug containing mixture was vortexed until a clear solution was obtained. These mixtures were observed for any signs of turbidity or phase separation for a period of 48 hours. Composition of Liquid SMEDDS for Fexofenadine Hydrochloride is shown in Table 1.

**Table 1: Composition of Fexofenadine SMEDDS**

| Batch | $K_m$ ratio | Drug (mg) | Oil (%) | Surfactant (%) | Co-Surfactant (%) |
|---|---|---|---|---|---|
| F1 | 1:1 | 100 | 25 | 37.5 | 37.5 |
| F2 | 1:2 | 100 | 20 | 26.3 | 53.3 |
| F3 | 2:1 | 100 | 16.6 | 55.5 | 27.7 |
| F4 | 3:1 | 100 | 50 | 37.5 | 12.5 |

*Drug: Fexofenadine hydrochloride*
*Oil: Oleic acid*
*Surfactant: Acconon MC 8*
*co-surfactant: Polyethylene Glycol 400*
*$K_m$ ratio: Surfactant : co- surfactant ratio*

**Preparation of Solid SMEDDS (S-SMEDDS)**

The optimized liquid SMEDDS formulation was converted into free flowing powder by adsorption of liquid SMEDDS onto solid carriers. The solid carriers used for adsorption comprised of materials that provided a high surface area with good disintegration characteristics[17, 18]. The solid carriers used include microcrystalline cellulose (MCC) and colloidal silicon dioxide (Aerosil 200). High levels of adsorption up to 95% (w/w) can be observed with the carriers chosen. The conversion process involved addition of liquid formulation on to carriers under continuous mixing in a blender. The optimized ratio for MCCand Aerosil 200 was 1:1 which was used for preparingS-SMEDDS of all batches. The S-SMEDDS powder was used for further evaluation of parameters. The powder was dried and filled directly into capsules.

**Characterization of SMEDDS**

**Test for Self Emulsification**

0.5 mL of sample mixture placed in 400 mL of water and contents were agitated with magnetic stirrer. The spontaneity of emulsification, clarity of dispersion, and apparent stability evaluated. The optimized formulation emulsified into a clear, transparent microemulsion and showed no signs of instability for 24 hours.

**Particle size of SMEDDS**

The Particle size of the resultant liquid SMEDDS was measured using Dynamic Light Scattering (Malvern Zeta analyzer Particle Sizing Systems). The liquid SMEDDS samples were taken in disposable glass tubes (VWR Scientific products) and particle size was determined.

**Drug Content**

10 mL petroleum ether was added to 1 mL of liquid SMEDDS containing Fexofenadine hydrochloride and mixed by shaking. The mixture was vortexed and centrifuged at 1000 rpm for 3minutes.Finally, the upper liquid phase was collected and assayed spectrophotometrically for the drug content at the wavelength 220nm with proper dilution of petroleum ether as blank.

**In-vitro drug release studies of SMEDDS**

In-vitro drug release studies from liquid SMEDDS were performed using USP Type I dissolution apparatus (basket apparatus) at 100 rpm. Liquid SMEDDS preparation equivalent to 100mg Fexofenadine Hydrochloride was filled into soft gelatin capsule. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 maintained at 37 ±0.5°C. At predetermined time intervals 5ml of aliquot was withdrawn, and an equivalent volume of fresh dissolution medium was immediately added. The amount of drug released was estimated by measuring absorbance at 220 nm using a spectrophotometer.

**Angle of repose**

A funnel was kept vertically in stand at a specified height above a paper placed on horizontal surface. The bottom

 

was closed and 10 gm of sample powder was filled in funnel. The funnel was opened to release the powder on paper to form a smooth conical heap. The height of heap was measured using the scale. A border of heap was marked circularly and its diameter was measured at four points. The average diameter was calculated and radius was found out from it. The angle of repose was calculated using following formula:

$$\tan \theta = h/r \text{ ---------- (2)}$$

Where; h = height of the heap, r = radius of the heap

**In-vitro Drug Release Studies From S-SMEDDS**

In vitro drug release studies from S-SMEDDS were performed using USP Type I dissolution apparatus (dissolution tester) with number of basket rotations set to 50 rpm. The dissolution medium consisted of 900 mL of phosphate buffer pH 6.8 maintained at 37 ±0.5°C. S-SMEDDS containing 100 mg of Fexofenadine Hydrochloride was introduced into a gelatin capsule shell and was put into the dissolution medium. At predetermined time intervals 5 mL of aliquot was withdrawn and an equivalent volume of fresh dissolution medium was immediately added. The amount of drug released was estimated by measuring absorbance at 220 nm using a Double beam spectrophotometer (Shimanzdu UV 1800 spectrophotometer). Dissolution of liquid SMEDDS and marketed preparation was also determined in identical manner. The calibration curve of drug was made in phosphate buffer pH 6.8 and at 220 nm.

## RESULTS AND DISCUSSION

**Solubility studies**

Solubility study of drug in different oils, surfactant, co-surfactant was shown in Table 2. According to that Fexofenadine hydrochloride showed higher solubility in oleic acid, acconon MC8 and PEG 400. Solubility of drug in oleic acid was found 6.38 ± 005 mg/mL. Solubility of drug in Acconon MC8 was found 22.48 ± 0.38 mg/mL.

**Table 2: Solubility of Fexofenadine Hydrochloride in various Solvents**

| Solvents | Solubility (mg/mL ) ± SD |
|---|---|
| Water | 1.62 ± 0.05 |
| Span 80 | 11.56 ± 0.04 |
| Castor Oil | 0.38 ± 0.02 |
| Oleic Acid | 6.38 ± 0.05 |
| PEG 400 | 17.12 ± 0.4 |
| Transcutol P | 15.13 ± 0.5 |
| Acconon MC8 | 22.46 ± 0.38 |
| IPA | 20.57 ± 0.26 |
| Labrafil M1944 $C_s$ | 0.24 ± 0.05 |
| Tween 80 | 13.27 ± 0.14 |
| Cremophore RH40 | 9.67 ± 0.27 |

**Ternary Phase diagrams**

Solubility of drug in mixture of oleic acid, Acconon MC8 and PEG 400 were selected for construction of pseudoternary phase diagrams. Total nine combinations were prepared. Phase diagrams for various ratios of surfactant and co-surfactant (1:1, 1:2, 2:1, 3:1) were constructed.[19] The phase diagrams for surfactant- co-surfactant ratio 1:1, 1:2, 2:1, 3:1 were shown in Figure 1, 2, 3 and 4 respectively. Phase diagrams for $K_m$ ratio 1:1 and 1:2 was quite similar while phase diagrams for $K_m$ Ratio 2:1 and 3:1 were similar.

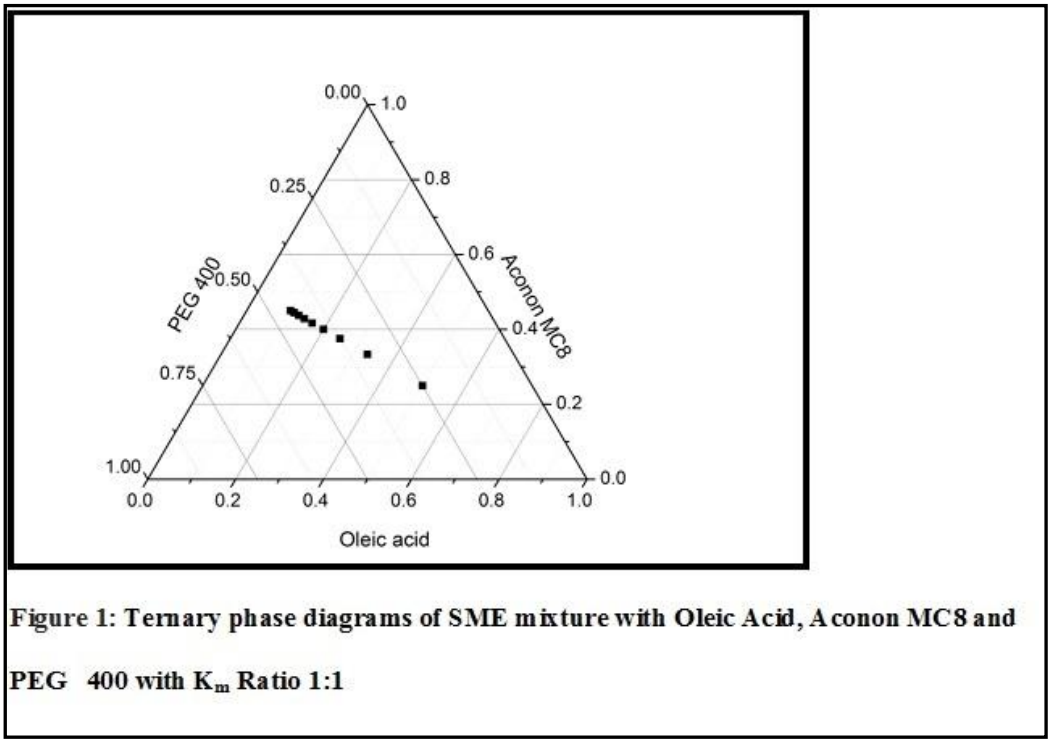


**Figure 1: Ternary phase diagrams of SME mixture with Oleic Acid, Aconon MC8 and PEG 400 with $K_m$ Ratio 1:1**

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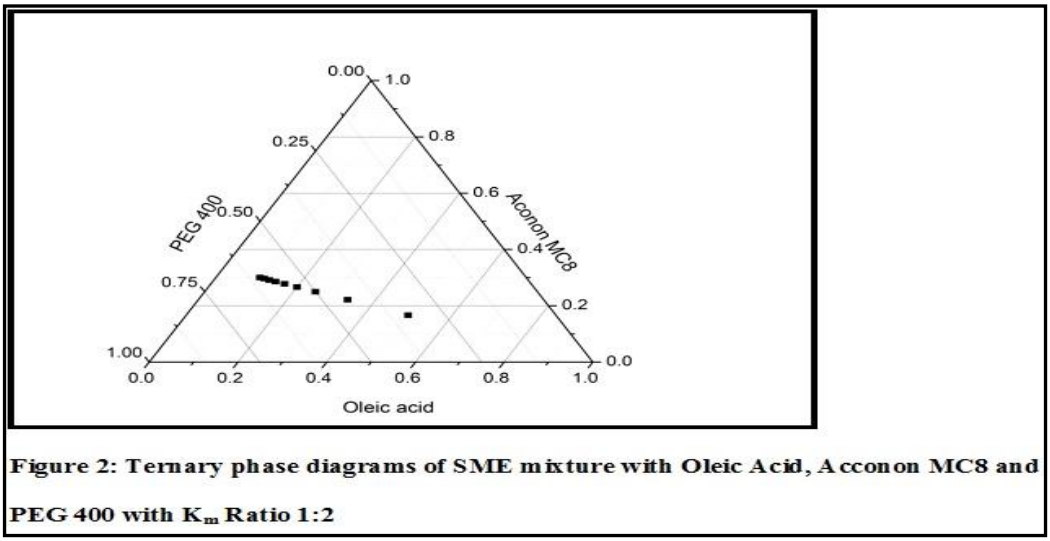


**Figure 2: Ternary phase diagrams of SME mixture with Oleic Acid, Acconon MC8 and PEG 400 with $K_m$ Ratio 1:2**

From the results of self emulsification time, droplet size and visual inspection of all the combination of $K_m$ ratio 1:1, 1:2, 2:1 and 3:1, four batches were selected as best formulation for preparation of liquid SMEDDS. Ratio of oleic Acid, Acconon MC8 and PEG 400 for $K_m$ ratio 1:1, 1:2, 2:1 and 3:1 were presented in Table 3. All four combinations were also evaluated for particle size, self emulsification time and visual Inspection.

Self microemulsifying performance of SME mixture was assessed from their ternary phase diagrams and time taken to produce a fine microemulsion. To check emulsification efficiency of SME mixtures, test for emulsification was performed on all combinations and the resultant dispersions were visually assessed. Resulting dispersions either formed a clear microemulsion, a slightly turbid emulsion or a milky emulsion which immediately phase separate.[20, 21, 22, 23]

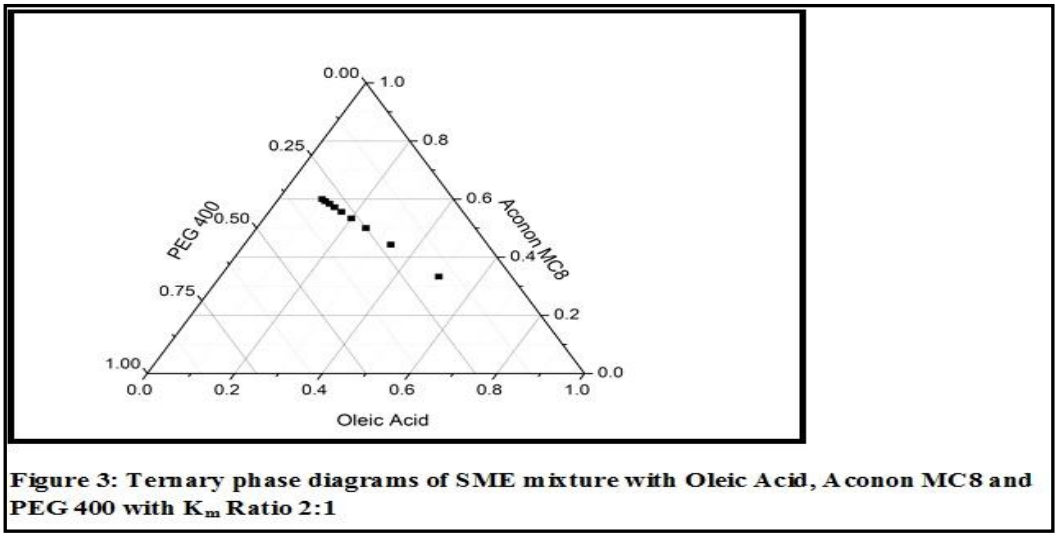


**Figure 3: Ternary phase diagrams of SME mixture with Oleic Acid, Aconon MC8 and PEG 400 with $K_m$ Ratio 2:1**

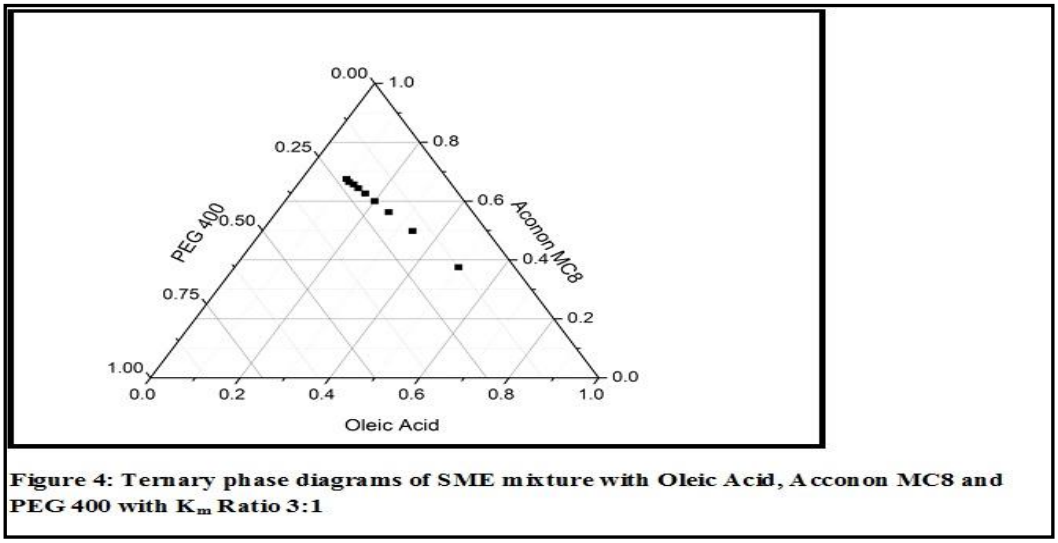


**Figure 4: Ternary phase diagrams of SME mixture with Oleic Acid, Acconon MC8 and PEG 400 with $K_m$ Ratio 3:1**

 

**Table 3: Composition of Liquid SMEDDS**

| Batch | $K_m$ ratio | Drug(mg) | Oil (%) | Surfactant(%) | Co-Surfactant (%) |
|---|---|---|---|---|---|
| F1 | 1:1 | 100 | 25 | 37.5 | 37.5 |
| F2 | 1:2 | 100 | 20 | 26.3 | 53.3 |
| F3 | 2:1 | 100 | 16.6 | 55.5 | 27.7 |
| F4 | 3:1 | 100 | 50 | 37.5 | 12.5 |

**Characterization of Liquid SMEDDS**

**Test for Self Emulsification**

The SMEDDS formed either a visually clear microemulsion, or a slightly turbid emulsion, or a milky emulsion that immediately phase separated. The optimized formulation emulsified into a clear, transparent microemulsion and showed no signs of instability for 24 hours. Results of self-emulsification time were shown in Table 4.

**Table 4: Self Emulsification Time of Batches F1-F4**

| Batch | $K_m$ ratio | Self Emulsification Time (Second) | Visual Observation |
|---|---|---|---|
| F1 | 1:1 | 45 | Good |
| F2 | 1:2 | 42 | Good |
| F3 | 2:1 | 62 | Good |
| F4 | 3:1 | 56 | Good |

**Particle size analysis**

The Particle size of the liquid SMEDDS is important since it determines the rate and extent of drug release and absorption. The drug can diffuse faster from smaller droplets into the aqueous phase, thereby increasing the drug dissolution. Smaller droplet size presents large surface area for drug absorption.[24] Increase in surfactant concentration decreases the droplet size up to a certain level but thereafter anyfurther increase results in an increase in droplet size. The reduction in droplet size can be attributed to the stabilization of oil droplets due to localization of surfactant monolayers at the oil-water interface.[25] Increase in surfactant concentration causes enhanced water penetration into oil droplets leading to breakdown of oil droplets and resultant bigger droplets. The droplet size of the nanoemulsion was measured using dynamic light scattering. The loaded SMEDDS displayed a Gaussian distribution of droplet sizes.[26, 27, 28]Theparticle size of the resultant Liquid SMEDDS was measured using Dynamic Light Scattering (Malvern Zeta Analyser Particle Sizing Analyser). Results of particle size analysis as presented in Table 5. Particle size of batch F1 and F4 were found to be 117.3 nm and 166 nm respectively. Batch F2 and F3 showed lower particle size 57.30 nm and 61.21 nm.

**Table 5: Average particle size of liquid SMEDDS**

| Batch | $K_m$ ratio | Size(nm) | % Intensity | Width(nm) |
|---|---|---|---|---|
| F1 | 1:1 | 117.3 | 100 | 20.56 |
| F2 | 1:2 | 57.30 | 97.4 | 7.14 |
| F3 | 2:1 | 61.21 | 88.5 | 10.47 |
| F4 | 3:1 | 166 | 100 | 26.14 |
| *$K_m$ ratio: Surfactant- co-surfactant ratio* | | | | |

**Drug Content**

All the batches F1-F4 were assayed spectrophotometrically for the drug content at the wavelength 220 nm with proper dilution of formulations taking phosphate buffer (PH-6.8) as blank[29, 30]. Results of content uniformity were shown in Table 6. It showed all the batches have a minimum of 98% content uniformity. Among all the batches F2 had highest content uniformity 99.12%.

**Table 6: % Drug Content**

| Batch | % Drug Content±SD |
|---|---|
| **F1** | 98.45 ± 0.04 |
| **F2** | 99.12 ± 0.24 |
| **F3** | 97.38 ± 0.08 |
| **F4** | 98.52 ± 0.17 |

**Drug release studies of SMEDDS**

The *in vitro* dissolution of the Liquid SMEDDS Formulation F1-F4 was performed in phosphate buffer of pH 6.8 using a USP Type I dissolution apparatus with a basket speed of 100 RPM. Liquid SMEDDS dissolution medium and were sampled at regular intervals until complete drug release was observed. The amount of drug released was calculated from the calibration curve of Fexofenadine Hydrochloride. In vitro dissolution curve of batches F1 to F4 were shown in Figure 5. According to results batch F3 and F4 were found to have complete drug release in 140 min and 180 min respectively. Both F1 and F2 showed complete drug release in 70 and 80 min. Higher dissolution rate of batch F1 and F2 was observed due to lower globule size of liquid SMEDDS. From the of in-vitro drug release data, content uniformity and particle size

 

batch F2 was selected as optimized batch for pre-formulation of solid SMEDDS.

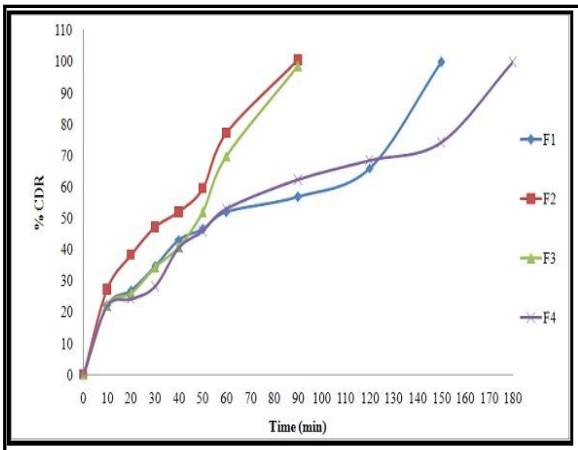


Figure 5: In-vitro Drug Release of Liquid SMEDDS Batch F1-F4

### Angle of Repose

Angle of Repose of all four Batch F1-F4 was found with having good flow properties. Batch F1, F2, F3 and F4 having angle of repose 24.17 ± 0.017, 26.32 ± 0.24, 28.56 ± 0.053, 24.83 ± 0.64 respectively.

### In vitro drug release studies From Solid SMEDDS

The *in-vitro* dissolution of the Solid SMEDDS Formulation F1 to F4 was performed in phosphate buffer of pH 6.8 using a USP Type I dissolution apparatus with a basket speed of 100 RPM. Solid SMEDDS dissolution medium and were sampled at regular time intervals until complete drug release was observed. The amount of drug released was calculated from the calibration curve of Fexofenadine Hydrochloride. Figure 6 showed in-vitro dissolution curve of solid SMEDDS. According to that almost complete drug release was observed within 90 min which was compared with marketed product and liquid SMEDDS.

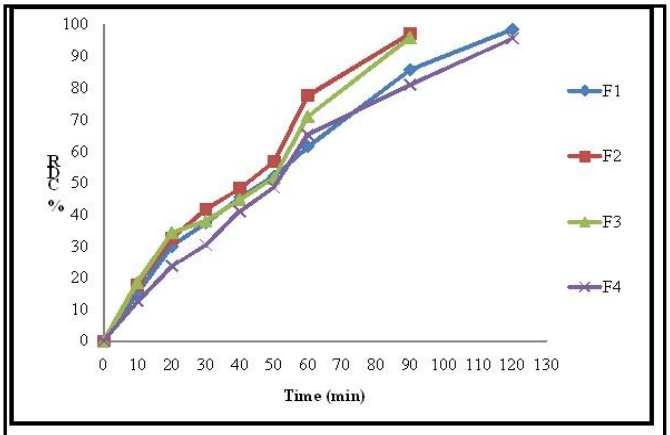


Figure 6: In-vitro Drug Release of Batch Solid SMEDDS

## CONCLUSION

A particular SME mixture comprising of oleic acid, Aconon MC8 and PEG 400 was selected and optimized for the purpose for delivering Fexofenadine hydrochloride. Four different formulations of different $K_m$ ratio were prepared. Among this four prepared formulations of Liquid SMEDDS, formulation F2 containing 20% oil, 26.3% surfactant and 53.3% co-surfactant was selected as optimized formulation. Optimized formulation had 57.30µm particle size and complete drug release in 90 minutes.In conclusion, Self emulsifying drug delivery systems were a promising approach for the formulation of Fexofenadine Hydrochloride. The oral delivery of hydrophobic drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability.

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**CONFLICT OF INTEREST:** The author(s) do not have any conflict of interest.

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