**Enhancement of Solubility and Dissolution of Piroxicam by Self Emulsifying Drug Delivery Technique**

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**ABSTRACT**

Self-emulsifying drug delivery systems (SEDDS) help to deliver lipophilic drugs with improved bioavailability. The objective of this study was to develop SEDDS to improve solubility and enhance the oral absorption of the poorly water soluble drug, piroxicam. The influence of the oil, surfactant and co-surfactant types on the drug solubility and their ratios on forming efficient and stable SEDDS were investigated by construction of Pseudo ternary phase diagrams. Formulations were characterized for thermodynamic stability studies, Self-emulsification, Viscosity, Droplet size, Zeta potential, Differential Scanning Calorimetry, *in vitro* drug release, Diffusion and Stability studies. The drug diffusion from the optimised formulation C1 was 98.18±0.84% while from the marketed piroxicam capsule was 95.13±2.98%. The developed piroxicam SEDDS formulation showed greater dissolution, and diffusion than the pure drug and marketed capsule. Release kinetics showed that the mechanism of drug release is super class-II, as it follows zero order release and fits with korsmeyer-peppas model.

Key words: SEDDS, Bioavailability, Lipophilic, Piroxicam, Diffusion, Thermodynamic stability, Release kinetics.

**INTRODUCTION**

Oral delivery route is the most convenient route for drug administration to achieve desired therapeutic effects and the greatest degree of patient compliance, especially for chronic condition diseases [1]. Despite some clinical oral formulations have been developed, their low oral bioavailability is still a major hurdle, leading to challenges for manufacturers to design delivery systems that can provide improved pharmacokinetic profiles and therapeutic responses. Currently, many efforts have been made to overcome the challenges of low oral bioavailability resulting from low drug solubility, poor permeation and enzymatic degradation, which limiting drug effective delivery.

**Self-Emulsifying Drug Delivery System**

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SEDDS requires the use of a co‐surfactant to generate a micro emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200nm–5mm and the dispersion has a turbid appearance. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing cosolvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic. Upon oral administration, these systems form fine emulsions in GIT with mild agitation provided by gastric mobility. In comparison with ready-to-use emulsions, SEDDS possess improved physical and/or chemical stability profile upon long-term storage, and also easy manufacture property. Thus, for the lipophilic drugs that exhibit poor water solubility and rate−limited dissolution, SEDDS may offer an improvement in the rate and extent of absorption and result in more reproducible blood−time profiles.

SEDDS include both self-micro emulsifying drug delivery systems (SMEDDS) and self-nano emulsifying drug delivery systems (SNEDDS). SMEDDS indicate the formulations producing transparent micro emulsions with droplets size range between 100-250 nm while SNEDDS form emulsions with the globule size range lower than 100 nm. The micro emulsion is a thermodynamically stable colloidal dispersion consisting of small spheroid particles dispersed within an aqueous medium and thus in equilibrium. In contrast, the Nano emulsion is non equilibrium colloidal dispersion system that over time spontaneously will exhibit coalescence of the dispersed droplets. [2]

**Objective of the study:**

To carry out pre-formulation studies. To study effect of various excipients on the self emulsification region by pseudoternary phase diagrams. To design and develop effective dosage form of SEDDS to avoid patient compliance, decrease frequency of dosing, for better utilization of drug.To carry out *in-vitro* release studies and apply release rate kinetics. To carry out stability studies on the optimised formulation as per ICH.

**MATERIALS AND METHODS**

**Materials:** Piroxicam was a generous gift from EMCO Laboratories Ltd.(Hyderabad, India). Sesame oil, Sunflower oil, Safflower oil, Olive oil, Peanut oil from ACALMAR Oils and fats Ltd. Hyderabad. Polyethylene glycol-400, Propylene Glycol, Glycerine, Ethyl alcohol, Castor oil, Span-20, Span-80, Tween 80 and all other chemicals and solvents used were of analytical grade.

**DRUG-EXCIPIENTCOMPATIBILITY STUDIES:**

**Fourier Transform Infra Red Studies3 (Ftir):** FT-IR spectroscopy was employed to ascertain the compatibility between drug and the selected excipients. The pure drug and drug with excipient were scanned separately. Liquid cell method was used for analysis. FT-IR spectrum of drug was compared with FT-IR spectra of SEDDS.

**Differential Scanning Calorimetry4: (DSC)** The thermal characteristics of formulation was investigated using a differential scanning calorimeter (DSC Q200 v24.2 build 107, Central Analytical Facility Lab, Osmania Unversity, Hyderabad). Samples were placed in sealed aluminum pans before heating under a nitrogen flow at a heating rate of 10 C/min from 50C to 200C.

**CHARACTERIZATION METHODS:**

**Optical Microscopy5:** A drop of micro emulsion was placed on a glass slide and diluted. A cover slip was placed over it and examined under an ordinary microscope for vesicle size and shape, using a pre calibrated ocular eye piece micro meter under 45 X 10 and 100 X 10.

**Solubility Studies6:** Adequate amount of all the selected vehicles were taken in different screw-capped glass vials, to these vials, excess of the drug was added and mixed Dry for 48hrs at 37°C and analysed for drug absorbance using UV visible Spectrophotometer.

**Construction of the ternary phase diagram:** Peanut oil, Tween 80 and PEG 400 are mixed in nine different Smix ratios of 1:1, 1:2, 1:3, 1:4 1:5, 1:6, 1:7, 1:8, 1:9, and then titrated with water to get Nano emulsion regions. Nano emulsion regions were observed visually and graded as transparent with good flow: oil/water Nano emulsions as clear (C), Slightly clear (SC),Turbid(T) Slightly turbid(ST).

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| Formulation codes | **A1**  | **A2**  | **A3**  | **A4**  | **A5**  | **B1**  | **B2**  | **B3**  | **B4**  | **B5**  | **C1** | **C2** | **C3** | **C4** | **C5** |
| **Piroxicam** | 10  | 10  | 10  | 10  | 10  | 10  | 10  | 10  | 10  | 10  | 10 | 10 | 10 | 10 | 10 |
| **Smix ratio**  |  |  | **1:2**  |  |  |  |  | **1:3** |  |  |  |  | **1:4** |  |  |
| **Oil: Smix**  | 1:1  | 1:2  | 1:3  | 1:4  | 1:5  | 1:1  | 1:2  | 1:3  | 1:4  | 1:5  | 1:1 | 1:2 | 1:3 | 1:4 | 1:5 |
| **Peanut oil**  | 245 | 163.3  | 122.5  | 98 | 81  | 245 | 163.33 | 122.5 | 98  | 81.66 | 245 | 163.33 | 122.5 | 98 | 81.66 |
| **Tween 80**  | 81.67  | 108.9  | 122.5 | 130.66  | 136.33  |  61.25 | 81.66 | 91.87 | 98 | 102.85 | 49 | 65.33 | 73.5 | 78.4 | 81.66 |
| **PEG 400**  | 163.3 | 217.8  |  245 | 261.33  | 272.22  |  183.75 | 245.01 | 275.63 | 294.0 | 306.25 | 196 | 26.134 | 294 | 313.6 | 326.68 |

**Preparation of piroxicam self-emulsifying drug delivery system7 :** Based on the area of nano emulsification from the phase diagrams, Smix ratio were selected for the formulation development studies. SEDDS formulations were prepared using Tween 80 as surfactant and PEG 400 as a co-surfactant with 6 different Smix ratio. Level of piroxicam in all the formulation was kept constant. Piroxicam was accurately weighed and placed in a glass vial with the respective required quantity of peanut oil. The components were mixed by gentle stirring and vortex mixing. Respective quantity of surfactant and cosurfactant were added to the vial and mixed by vortex mixing.

Table no.1: SEDDS formulations with their compositions

**CHARATERIZATION OF SOLID SEDDS:**

**THERMODYNAMIC STABILITY STUDIES8:** The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well.

**Heating cooling cycle:** Six cycles between refrigerator temperature (40ºC) and 45ºC with storage at each temperature of not less than 48hrs is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

**Centrifugation:** Passed formulations are centrifuged thaw cycles between 21 ºC and +25 ºC with storage at temperature for not less than 48hrs is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test. **Freeze thaw cycle:** Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

**SELF EMULSIFICATION ASSESSMENT9 :** The self-emulsifying properties of SEDDS formulations were evaluated by visual assessment based on clarity and apparent stability of the resultant emulsion. SEDDS were added into distilled water and stirred magnetically. The solution was then assessed visually for drug precipitation.

### **DRUG PRECIPITATION ASSESSMENT10 :** After 24hrs of visual inspection of the resultant emulsion were performed for assessment of drug precipitation. The formulations were categorized as clear (transparent), non-clear (turbid), stable (no precipitation at the end of 24 h), or unstable (precipitation within 24 h).

**VISCOSITY DETERMINATION11:** SEDDS was diluted 10 times with distilled water in a beaker with constant stirring on magnetic stirrer. Viscosity of the resultant micro emulsion and initial SEDDS was measured using Brookfield viscometer.

**DETERMINATION OF DROPLET SIZE AND ZETA POTENTIAL12:** Droplet size and the zeta potential of the formed emulsion were determined by photon correlation spectroscopy (PCS) that analyzes the fluctuations in light scattering due to Brownian motion of the particles, using a Zetasizer ZS 90 Light scattering was monitored at 25°C at a 90° angle.

**DRUG CONTENT13:** SEDDS formulation equivalent to 25mg of Piroxicam was taken and diluted in methanol and absorbance measured at 332 nm using UV-Visible Spectrophotometer.

**DRUG RELEASE PROFILES OF SELECTED SEDDS14:** All the Selected formulations of the ratios 1:2, 1:3 and 1:4 are prepared and filled in capsules, and using dissolution medium as 0.1NHCL, and Dissolution apparatus type - II, at 100rpm. The amount of drug release was analysed using UV visible spectroscopy.

### **EVALUATION OF ISOTROPIC NATURE15:** Emulsion was placed on a glass slide and viewed under a microscope with cross polarized light.

***In vitro* DIFFUSION STUDIES USING FRANZ DIFFUSION CELL16:** *In vitro* diffusion study of the piroxicam SEDDS was compared with a conventional marketed suspension using a dialysis technique, through Franz diffusion cell. The dialyzing medium was 0.1M HCl. One end of dialysis was clamped and then the experimental formulation sample, was placed in it. The other end of the tubing was also secured with dialysis closure clips and was placed in 900 mL of dialyzing medium and stirred at 100 rpm over a magnetic stirrer at 37°C. Samples were withdrawn and each time replaced with the fresh dialyzing medium. These samples were analyzed for Piroxicam present in the dialyzing medium at corresponding time by UV-visible spectrophotometer at 332nm.

***In vitro* DISSOLUTION STUDIES17 :** SEDDS of piroxicam was filled in size “00” capsules. *In vitro* release profiles of SEDDS of piroxicam, pure piroxicam powder, and marketed piroxicam formulation were studied using USP apparatus II at 37±0.5°C with a rotating speed of 100 rpm in 0.1N HCL, as the dissolution media. Samples were withdrawn from the dissolution medium and replaced with fresh media. Absorbance was measured using UV visible Spectrophotometer and the amount of Piroxicam released was calculated.

## **STABILITY STUDIES18 :** The optimized SEDDS formulations was subjected to stability studies at accelerated conditions of 40 °C/75% RH as per ICH guidelines. Samples were charged in stability chambers with humidity and temperature control. They were withdrawn at specified intervals for analysis over a period of 3 months for accelerated conditions. The charged samples were evaluated for self-emulsification capacity, drug precipitation assessment and emulsion globule size analysis and drug release.

**RESULTS AND DISCUSSION**

**DRUG-EXCIPIENT COMPATABILITY STUDIES:**

**Fourier Transform Infrared studies (FTIR): (Pure Piroxicam)**



 **Fig.01. FTIR Spectra of Piroxicam SEDDS**

FTIR analysis shows that the drug Piroxicam is compatible with the polymers used.

**Differential Scanning Calorimeter: (DSC)**

**Fig 02: DSC Curve of pure Piroxicam Fig 03: DSC Curve of Piroxicam SEEDS**

**PSEUDOTERNARY PHASE DIAGRAMS:**

**Construction of Pseudo ternary phase diagrams:** 

**Fig 04: Pseudo ternary phase diagrams of 1:2, 1:3 and 1:4 surfactant: co surfactant ratios**

Pseudo-ternary phase diagrams of the formulations composed of oil, surfactants and co-surfactant dispersed with distilled water at 37 °C. Surfactant=Tween 80, Cosurfactant =PEG-400. The shadow area represents micro emulsion region.

Among the nine surfactant: Surfactant co-surfactant ratios of 1:2, 1:3,1:4 has larger micro emulsion region. Larger the size of micro emulsion region in ternary phase diagram, greater is the self-emulsification efficiency. In contrast Surf ratios of 1:1, 1:5, 1:6, 1:7, 1:8, 1:9 showed a small micro emulsification region. So, depending on the results, ratios of 1:2, 1:3, and 1:4 were selected for further studies.

**THERMODYNAMIC STABILITY STUDIES:**

Thermodynamic stability tests are performed to eliminate the metastable systems Formulations A1 to A5 (Smix ratio 1:2), B1 to B5 (Smix ratio1:3) and C1 to C5 did not show any signs of phase separation. But formulations A5, B3 and B4, C2, C3, C4 separates out into two phases

**Heating cooling cycle:** All the formulations were stable under heating cooling cycle. And hence further subjected to centrifugation test.

**Centrifugation:** Formulations A5, B3 and B4, C3, C4 separates out into two phases.

**Freeze thaw cycle:** Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking. Formulations A5, B3 and B4, C2, C3, C4 separates out into two phases.

**SELF EMULSIFICATION AND PRECIPITATION:**

Self-emulsification ability of surfactants and co-surfactants was assessed to select the best ratio of Smix. A1, A2, formed clear dispersion and did not show any drug precipitation and thus were considered as stable. Formulation A3, B1, B2, C1, C2 showed drug precipitation Since formulation B3, B4, C2, C3, C4 were not stable during thermodynamic studies and also exhibited drug precipitation, these formulations were excluded from further study. Formulations **A1, A2, A3,** and **B1** were subjected to further evaluation.

#### **ROBUSTNES TO DILUTION:**

Formulation A1-A3, B1–B3, showed no signs of drug precipitation or phase separation on dilution of 10,100 times. This implies that all the developed formulations were robust to dilution in the aqueous medium.

#### **VISCOSITY DETERMINATION:**

The viscosity of the formulation A1 was found to be 17.2cps, for A2-169cps, A3-16.5cps, A4-16.0cps, B1-17.0cps, B2-16.8cp, B3-16.3cps, and for C3-15.8cps. This suggests possibility of rapid absorption of SEDDS as viscosity of SEDDS will decrease on being diluted with body fluids inside.

**DETERMINATION OF DROPLET SIZE AND ZETA POTENTIAL:**

The globule size of the formulation B1 was found to be 204.0nm, and formulation B2 was found to be 205.3nm, whereas for formulation C1 was 191.5nm and formulation C2 as 203.0nm. The formulation C1 which has lesser globule size was selected to be fit for further studies.

Piroxicam SEDDS was diluted with distilled water, and the resulted zeta potential was found to be -28.7mV for formulation B1, -26.0mV for formulation B2, for C1 and C2 -33.0mV, -35.8mV,respectively.

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| **Fig 05 Particle size and Zeta potential of formulation (B1)** | **Fig 06 Particle size and Zeta potential of formulation (B2)** |
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| **Fig 07 Particle size and Zeta potential of formulation (C1)** | **Fig 08 Particle size and Zeta potential of formulation (C2)** |

#### **EVALUATION OF ISOTROPIC NATURE18:**

Formulation A1 to A3, B1 to B3 and C1 exhibited dark field under cross polarized light. This suggests that all the tested formulations are isotropic in nature.

**EFFECT OF pH OF DILUTION MEDIA:**

No sign of drug precipitation or phase separation was observed on storage in various dilution media which suggests that the various *in vivo* media are suitable for the release of the drug from SEDDS.

**DRUG RELEASE PROFILES OF SELECTED SEDDS:**

The in vitro drug release of 1:2, 1:3 and 1:4 optimized SEDDS formulations is shown in the figures 9-11. Formulation C1 has showed higher drug release.

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| **Fig 09 Drug release profiles of Formulation (1:2)** | **Fig 10 Drug release profiles of Formulation (1:3)** |

**Fig 11 Drug release profiles of Formulation (1:4)**

#### **In vitro DISSOLUTION STUDIES IN COMPARISION WITH PURE DRUG AND MARKETED TABLET:**

Optimized Piroxicam SEDDS showed an immediate burst in drug release followed by steady release and thus showed an improvement in the *in vitro* dissolution as compared to the marketed piroxicam tablet and pure Piroxicam powder in the dissolution media.

**Fig 12 In-vitro dissolution profiles of Piroxicam SEDDS, pure drug and marketed drug**.

***In vitro* DIFFUSION STUDY USING FRANZ DIFFUSION CELL:**

Almost all the drug 98.18 ± 0.81% diffused from the SEDDS formulation compared to 95.13±2.98% drug released from the marketed capsule. The drug release from the piroxicam SEDDS was found to be significantly higher as compared to that of the marketed capsule.

**Fig 13 *In-vitro* Diffusion studies of Piroxicam SEDDS and Marketed drug.**

**STABILITY STUDIES**

All the SEDDS were found to form clear dispersion and none of the formulation of C1 showed any drug precipitation, capsule leak. The formulations showed a drug release of 98.37±0.31 by the end of 3rd month. These results confirm that the developed SEDDS was stable.

**DRUG RELEASE KINETICS**

The mechanism and kinetics of drug release of piroxicam is determined by the application of Zero order, First order, Higuchi, and Korsmeyerr-peppas kinetics. Based on the correlation coefficient values for the various kinetic models the zero order kinetics has an r2 value of 0.448. The Higuchi model also shows r2 value of 0.739 hence the mechanism of drug release is Non- Fickian transport. Koresmeyer- Peppas model yields an r2 value of 0.836 and the ‘n’ value is 1.133 (n>1.0); hence the drug release follows case II transport.

The aim of the present study was to develop and characterize self

emulsifying drug delivery system of Ibuprofen using edible and

natural castor oil and nonionic surfactant Tween 80 and Span 20

in varying concentrations. Span 20 was used as co surfactant in the

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self emulsifying capsules.

**CONCLUSION**

The present research was aimed to develop and characterize self-emulsifying drug delivery system of Piroxicam. The components and their ratio ranges for the formulation of SEDDS were selected by solubility study, pseudo-ternary phase diagram construction, and droplet size analysis. The optimum formulation of the SEDDS consisted of 9.56 % of Peanut oil, 58.52% of Tween-80 as surfactant and 29.27% of PEG-400 as co-surfactant, which had sufficient drug loading, rapid self-emulsification in aqueous media, and formed droplet size in the range of microemulsion. In- vitro dissolution test showed that the release rate of the self-emulsifying capsules of Piroxicam was higher than conventional tablet. As the globule size decreased, the release rate increased. This suggests that the SEDDS formulation results in spontaneous formation of a micro emulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase and greater permeability. From the results formulation(**C1**), was found to be optimized with 97.9±0.23% drug release. The developed piroxicam SEDDS formulation showed greater dissolution, and diffusion than the pure drug and marketed capsule. The stability testing depicts the formulation was stable for a period of 3M. Release kinetics showed that the mechanism of drug release is super class-II, as it follows zero order release and fits with korsmeyer-peppas model. Thus an efficient SEDDS of piroxicam was developed with enhanced drug loading capacity and release, thus showing possible increase in bioavailability.

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