**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:** An adequate number of each selected vehicle was placed in different screw-capped glass vials, to these vials, excess of the drug was added and mixed 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 were combined in nine different Smix ratios of 1:1, 1:2, 1:3, 1:4 1:5, 1:6, 1:7, 1:8, 1:9, titrated using water to obtain nano emulsion regions. Visual observations of the nano emulsion regions led to a classification of transparent with good flow: oil/ water

 Nano emulsions as clear (C), Slightly clear (SC), Turbid(T) Slightly turbid(ST).

**Preparation of piroxicam self-emulsifying drug delivery system7 :** For the formulation development, the Smix ratio was chosen based on the area of nano emulsification from the phase diagrams. With six different Smix ratios, SEDDS formulations were made with Tween 80 as the surfactant and PEG 400 as the co-surfactant. To Piroxicam, the appropriate amount of peanut oil was added to a glass vial, the appropriate amount of cosurfactant and surfactant was then added to the vial, the mixture was vortexed.

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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 |

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 equal to 25 mg of Piroxicam was taken, diluted in methanol, and the UV-visible spectrophotometer was used to measure the absorbance at 332 nm.

**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. UV visible spectroscopy was used to analyze the release quantity.

### **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:** Using a Franz diffusion cell and a dialysis approach, the in vitro diffusion study of the piroxicam SEDDS was compared with a conventionally suspension. 0.1M HCl was used as dialyzing medium. The samples were examined using a UV-visible spectrophotometer set to 332 nm.

**STABILITY STUDIES18 :** In accordance with ICH, stability tests were conducted on the optimized SEDDS formulation at 40 °C/75% RH. They were taken out at regularly for analysis of drug release, emulsion globule size, drug precipitation assessment, and self-emulsification capacity.

**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 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:** 

**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, Co surfactant =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. As micro emulsion region in ternary phase diagram increases, self-emulsification efficiency increases. In contrast ratios 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:**

Formulations A1 - A5, B1 - B5 and C1 to C5 showed no 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:** Except formulations A5, B3 and B4, C2, C3, C4 all the remaining showed good stability with no phase separation, creaming, or cracking.

**SELF EMULSIFICATION AND PRECIPITATION:**

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, B3, B4, C2, C3, C4 were unstable.

#### **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.

**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 Globule size- Zeta potential of formulation (B1)** | **Fig 06 Globule size- Zeta potential of formulation (B2)** |
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| **Fig 07 Globule size- Zeta potential of formulation (C1)** | **Fig 08 Globule size- 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, suggests all these are of isotropic nature.

**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 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* DIFFUSION STUDY USING FRANZ DIFFUSION CELL:**

C1 showed 98.18 ± 0.81% of drug diffusion, while marketed commercial capsule showed a release of 95.13±2.98%. The drug release from the piroxicam SEDDS was found to be significantly higher as compared to that of the marketed capsule.

**Fig 12 *In-vitro* Diffusion studies of Piroxicam SEDDS and Marketed drug.**

**STABILITY STUDIES**

The C1 SEDDS was to be found to form clear dispersion and there was no sign of drug precipitation or capsule leak during the stability studies. The formulation showed a drug release of 98.37±0.31 by the end of 3rd month.

**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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**CONCLUSION**

The present research was aimed to develop and characterize self-emulsifying drug delivery system of Piroxicam. The components 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 increased as the globule size decreased. This suggests that the prepared SEDDS formulation resulted 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 diffusion than the marketed capsule. The stability testing depicts that C1 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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