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DESIGN AND CHARACTERIZATION OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM FOR DOCETAXEL

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ABSTRACT

The main objective of this study was to develop self-nano emulsifying drug delivery system (SNEDDS) to enhance the oral absorption of the poorly water-soluble drug Docetaxel. The influence of the oil, surfactant and co-surfactant on the drug solubility and their ratios on forming stable SNEDDS were investigated in detail. The SNEDDS were characterized by morphological observation, droplet size, zeta potential measurement, freeze thawing and in vitro release study. The optimum formulation consisted of 40% Capryol 90, 20.66% Cremophor EL and 10.33% Polyethylene glycol 400. In vitro release test showed a complete release of Docetaxel from SNEDDS in an approximately 4 h. The absorption of Docetaxel from SNEDDS showed increase in absorption compared with that of the marketed formulation Taxotere. Our studies demonstrated the promising use of SNEDDS for the delivery of Docetaxel by the oral route.

Keywords: Docetaxel, Self nanoemulsifying drug drlivery system, Pseudoternary phase diagram

INTRODUCTION

Docetaxel, is sold under the brand name Taxotere among others, is a chemotherapy medication used to treat a number of types of cancer. This includes breast cancer, head and neck cancer, stomach cancer, prostate

cancer and non-small-cell lung cancer. It may be used by itself or along with other chemotherapy medication. It is given by slow injection into a vein.[1]

The oral route is the most physiologically beneficial and easily accepted by patients. Therefore, it is necessary to develop alternative oral routes of administration to enhance the bioavailability of poorly water-soluble drugs, and furthermore obtain more successful therapeutic effects. The use of self-nano emulsifying drug delivery system (SNEDDS) is one of the most interesting approaches to improving the solubility, dissolution and oral absorption for poorly water-soluble drugs **[1, 2, 3]**. Now, much more attention has been focused on SNEDDS due to its excellent efficiency in delivering poor water soluble drugs and achieving an increase in bioavailability. Over the past decades, SNEDDS have been extensively investigated to deliver various kinds of drugs **[4- 6]**. Only a few studies have been reported on the effective composition of traditional Chinese medicines.

SNEDDS are isotropic mixtures of oil, surfactant, co- surfactant, and drug substance. Nano emulsion can be generated rapidly upon gentle mixing with water or aqueous media. It is thought that the Nano emulsion is spontaneously formed by the combined action of the specific pharmaceutical excipients with low free energy **[7]**. The Nano emulsion droplets dispersed in the gastrointestinal tract provide large surface area and promote a rapid release of dissolved form of the drug substance and mixed micelles containing drug substance, and they may be also responsible for transporting the drug through the unstirred water layer to the gastrointestinal membrane for absorption. In addition to the enhanced dissolution of drugs by SNEDDS, another factor contributing to the increasing bioavailability is that lymphatic transport is responsible for a portion of the entire drug uptake as well. The lipid composition of SNEDDS may be related to facilitate the extent of lymphatic drug transport by stimulating lipoprotein formation and intestinal lymphatic liquid flux **[8, 9]**.

MATERIALS AND METHODS

Chemicals and Reagents

Docetaxel was kindly supplied by Cipla Ltd, Pune with a purity of 99.9%. Capryol 90 and Vitamin-E was supplied by Abitec Corporation, castor oil, (Cremophor EL) was donated by Piramal Health care Mahad, Raigadh. Polyethylene glycol-400 given by Dr.SKCP College Sangli and Neusilin were given by Bioven ingridents Uttarpradesh all other chemicals used were of analytical grade.

Solubility Studies

The solubility of Docetaxel in various oils, surfactants and co surfactants was measured,

respectively. An excess amount of Docetaxel was added into each selected vehicle, and the mixture was continuously stirred for 72 h at 30^0C. After equilibrium was achieved, the mixture was centrifuged at 2000 rpm for 5 min, and the supernatant was filtered through a membrane filter. The concentration of Docetaxel was determined by UV spectroscopy at 231 nm.

Pseudo-ternary Phase Diagram Construction

A pseudo-ternary phase diagram was constructed by titration of four component mixtures of oil; surfactant and co-surfactant with double distill water at room temperature. After equilibrium, the mixture was visually observed. The generated sample which was clear or slightly bluish in appearance was determined as nano emulsion. A series of pseudo-ternary phase diagrams was constructed to identify nano emulsion region among the diagrams was compared by direct observation. Pseudo ternary phase diagram of oil (Capryol 90), surfactant (Cremophor EL), and co-surfactant (Polyethylene glycol 400) were developed using the water titration method. First of all the ratio of surfactant to co-surfactant were prepared, that is 1:1,2:1,3:1 and 4:1 then mixture of Capryol 90 with (s/cos) cremophor EL, polyethylene glycol 400 in different ratio such as (in percentage w/w) 9:1, 8:2, 7:3, 6:4, 5:5, 4:6,3:7, 2: 8 and 1:9 were prepared in different vials. For each phase diagram at specific ratio of S/Cos (surfactant/co- surfactant at) i.e.1:2,2:1,3:1 and 4:1 were added to oil phase and vortexed for 5 min.to get a transparent homogenous mixture. Then each mixture was titrated with water. After each addition, the mixtures in the vial were vortexed for 2-3 min and allowed to equilibrate at 25°C for 30 min. After equilibrium the mixture were visually examined for phase separation, transparency and flow ability. The concentration of water at which turbidity to transparency and transparency to turbidity transition occurred was derived from the measurements. These values were then used to determine the boundaries of the nano-emulsion domain corresponding to the chosen value of oils as well as S/CoS mixing ratio. Phase diagram were then constructed using chemix software.

Preparation of SNEDDS

The formulations were prepared by dissolving the formulation amount of Docetaxel in the mixture of Polyethylene glycol 400, Cremophor EL and Capryol 90 at 50^0C in an isothermal water bath. This mixture was mixed by Neusilin carrier to form semisolid SNEDDS as shown in **Table 1**.

Table 1: Preparations of SNEDDS Formulations

Formulation code	Docetaxel (mg)	Capryol 90 (gm)	Cremophore EP (gm)	Polyehylene glycol 400 (gm)	Neucilin (gm)	S/Cos
A1	50	3	0.33	0.16	4.20	2:1
A2	50	2.75	0.66	0.33	3.95	2:1
A3	50	2.5	1.00	0.50	3.70	2:1
A4	50	2.25	1.33	0.66	3.45	2:1

SNEDDS Characterization

- **Determination of Droplet Size and Zeta Potential:** The droplet size/distribution and zeta potential were determined with NicompTM 380 ZLS Zeta Potential/Particle sizer (PSS Nicop, Santa Barbara, CA, USA). The detection range was from 2 to 5000 nm. Each sample was analyzed in triplicate.
- **In-vitro Release:** In vitro release of Docetaxel SNEDDS was tested by the method of with some modifications **[10]**. A dialysis method was used based on Chinese Pharmacopoeia (2005 version) release test method. After Docetaxel SNEDDS was instilled into the dialysis bag (MWCO 10000, Spectrum Medical Industries Inc., USA), the dialysis bag was firmly sealed with dialysis clamp and was placed in 900 ml, Phosphate buffer of pH 6.8 as the dissolution medium at 37^0 C. The revolution speed of the paddle was maintained at a rate of 50 rpm. 5 ml. samples were drawn out at the 30 min. intervals, and the same volume of fresh dissolution medium was replenished. The release of Docetaxel from SNEDDS formulation was compared with the tablet of Docetaxel containing the same quantity of drug.

RESULTS AND DISCUSSION

Screening of Oils and Surfactants

The consideration for screening formulation of SNEDDS usually involves the formulation composition should be simple, safe, and compatible; it should possess good solubility; a large efficient self-nano emulsification region which should be found in the pseudo-ternary phase diagram, and have efficient droplet size after forming nano emulsion **[10-12]**. Appropriate vehicles should have good solubilizing capacity of the drug substance, which is essential for composing a SNEDDS. The results of solubility of Docetaxel Cremophor EL followed by Capryol 90 as shown in **Table 2**. Their phase behaviour was compared by constructing pseudo-ternary phase diagram. The maximum region of self-nano emulsion was obtained when the mixture of Cremophor EL and Polyethylene glycol 400 in the ratio of 2:1 was used as Surfactant co-surfactant ratio. Hence, the mixture of Cremophor EL and Polyethylene glycol 400 in the ratio of 2:1

was selected as oil phase.

Non-ionic surfactants were used in most of the investigation about SNEDDS because they are less toxic and less affected by pH and ionic strength. The self-nano emulsion region Cremophor EL was larger than that of Tween 80 and also Cremopher EL required a longer time to disperse. This was of concern in terms of affording efficient and rapid drug release. Therefore, the desirable surfactant should be Cremopher EL. As to the selection of co- surfactant, Ethanol, 2-propanol and PEG-200 have relatively higher hydrophilic ability, increasing the risk of destroying the nano emulsion compared with PEG 400. In addition, PEG 400 provided the highest drug solubility among all vehicles tested in our studies except ethanol. Therefore, it is reasonable to select PEG 400 as the co-surfactant. The phase diagrams of the systems containing Capryol 90 and Cremopher EL: PEG 400 (2:1, w/w) were shown in **Figure 2**. Although it is considered that the large content of oil in the formulation will be beneficial to the SNEDDS, a proper droplet size distribution is also an important factor for selecting a suitable self-nano emulsifying vehicle. The effect of the oil concentration on the droplet size was investigated as well. The droplet size decreased from 205 to 170 nm when the oil concentration decreased from 60 to 45%. The ratio of surfactant to co-surfactant was very effective to a stable and efficient SNEDDS formation. The phase diagrams were constructed at the ratio of surfactant/co-surfactant 1:1, 2:1, 3:1 and 4:1 (w/w) as shown as **Figure 1, 2, 3 and 4** respectively. The maximum self-nano emulsifying region was found to be at the ratio of 2:1. Pseudo-ternary phase diagrams composed of Capryol 90 oil, Cremophor EL and PEG 400 dispersed with distilled water at 37 ^{0}C. The shadow area represents self nano emulsion region. The influence of the different ratios of surfactant (Cremophor EL) to co-surfactant (PEG 400) on the droplet size was also investigated. There were minor differences in mean droplet size when the ratio of surfactant increased from 10 to 30%. Co-surfactant will be beneficial to form nano emulsion at a proper concentration range. However, excessive amount of co-surfactant will cause the system to become less stability for its intrinsic high aqueous solubility and lead to the droplet size increasing as a result of the expanding interfacial film **[13, 14]**. Hence, the optimal ratio of surfactant to co-surfactant was selected to be 2:1.

Table 2: Solubility of Docetaxel in Different Vehicles

S. No.	Vehicle	Solubility
1	Capryol 90	67.85 ± 1.20
2	Capmul MCM	70.23 ± 2.00
3	Vitamin-E	32.44 ± 0.92
4	Soya bean Oil	45.64 ± 1.00
5	Almond oil	35.85 ± 1.10
6	Tween-80	84.60 ± 2.34
7	Cremophore EL	110.45 ± 2.50
8	Polyethylene glycol	170.68 ± 2.90

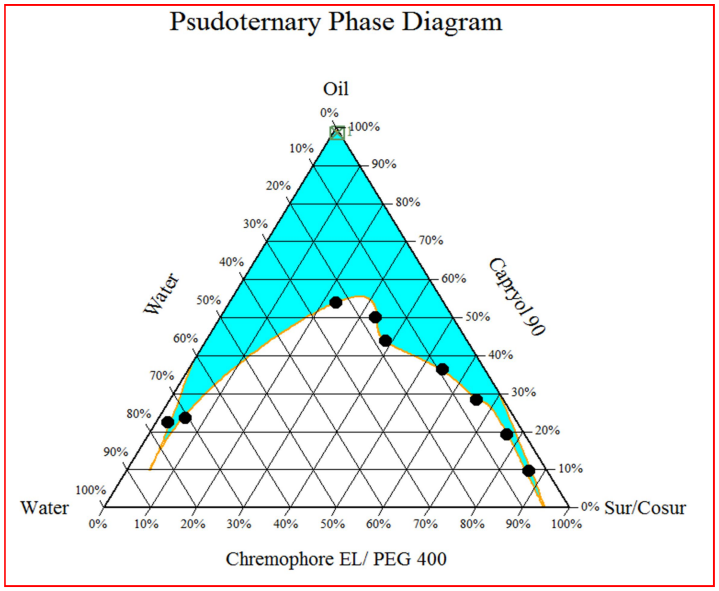

Figure 1: Phase diagram of Capryol 90, Cremophor EL+ PEG 400 (1:1) and Water

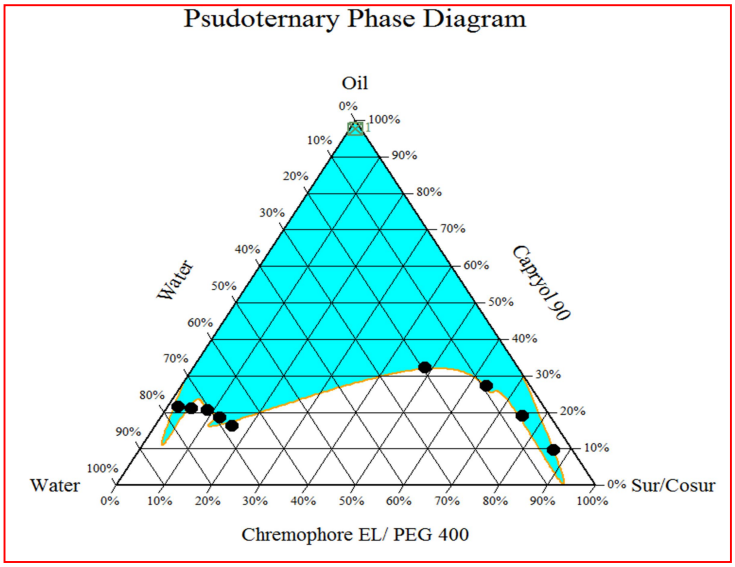

Figure 2: Phase diagram of Capryol 90, Cremophor EL+ PEG 400 (2:1) and Water

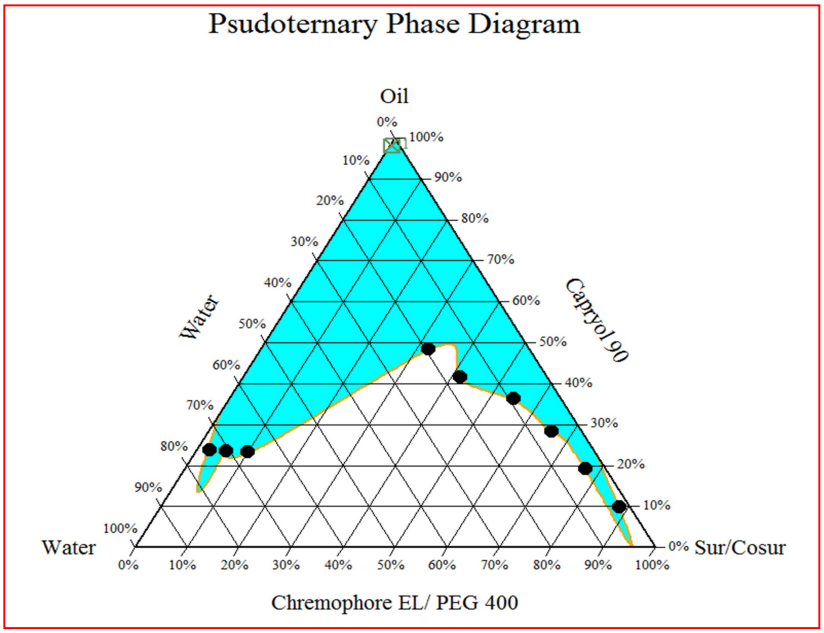

Figure 3: Phase diagram of Capryol 90, Cremophor EL+ PEG 400 (3:1) and Water

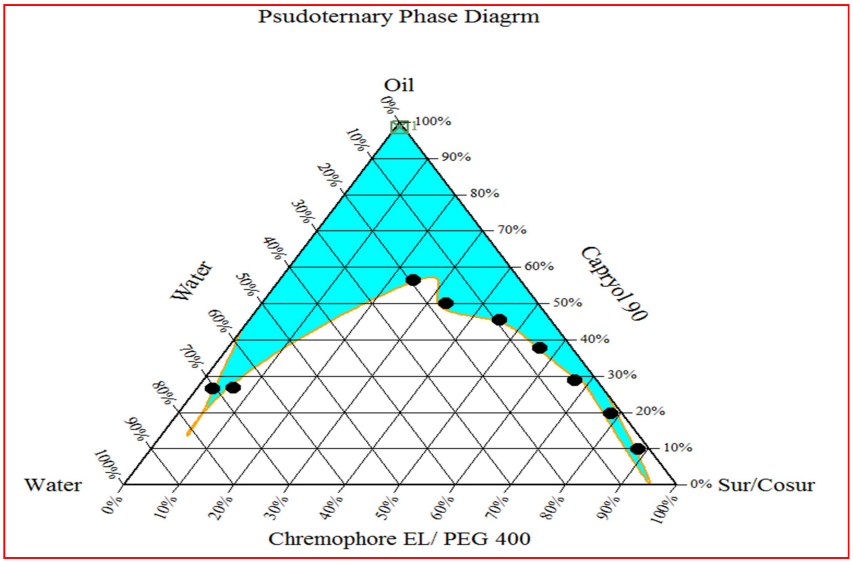

Figure 4: Phase diagram of Capryol 90, Cremophor EL+ PEG 400 (4:1) and Water

SNEDDS Characterization

Morphological Characterization: The Docetaxel SNEDDS turned into nano emulsion when diluted with distilled water. Scanning electron nanoscopy (SEM) was used to determine the particle morphology of pure drug and optimized SNEDDS. Result revealed that the Neusilin form coat around the surface of oil droplet and changed the morphology of particle, to become moreporous.

- **Droplet Size Analysis:** Droplet size distribution following self-nano emulsification is a critical factor to evaluate a self-Nanoemulsion system. Droplet size isthought to have an effect

on drug absorption as has been illustrated in several papers. The smaller the droplet size, the larger the interfacial surface area will be provided for drug absorption **[15]**. In our study, we investigated several variables on droplet size including dilution volume, different media, drug concentration (drug loading), and dispersing method. The average droplet size of Nanoemulsion dispersed from the Docetaxel SNEDDS was within 230 nm and showed Gaussian distribution. The effect of dilution on droplet size in distilled water was measured. When the dilution time was 1000-fold, the droplet size seemed to be unchanged, which revealed that the Nanoemulsion formed upon dilution was as large as 1000 times capable of keeping Docetaxel solubilized. As the drug loading increased from 0.2 to 2.5%, the droplet size remained almost unchanged, which indicated that the drug loading had no obvious effect on droplet size in water. The effect of medium on droplet size was also investigated in our study. When the SNEDDS dispersed in distilled water, 0.9% NaCl, 0.1N HCl and pH 6.8 phosphate buffers, the resulted droplet size was 170.1±3.6 nm, 170.6±1.7 nm, 170.9±1.8 nm and 170.7±3.3 nm, respectively. There is no significant difference among the four different media, which demonstrated that the formulation was not affected by pH and the ionic strength. The effect of the various mixturing ways on the droplet size was measured. Different mixturing ways including oscillate, whisk (25 rpm, 50 rpm, and 100 rpm) and swirl seem to have no obvious effect on droplet size. This result predicts stable274 P. Zhang et al. / International Journal of Pharmaceutics 355 (2008) 269–276 **(Table 3)**.

- **Zeta Potential Analysis:** Generally, an increase of electrostatic repulsive forces between nano emulsion droplets prevents the coalescence of nano emulsion droplets. On the contrary, a decrease of electrostatic repulsive forces will cause phase separation. Docetaxel SNEDDS was diluted with distilled water the resulted zeta potential was --18.14±0.33mV, -20.30±0.41mV, -22.11±0.29mV, and -24.40±0.47mV as shown in **Table 4**. There is no marked difference in the zeta potential value among the four formulations. Out of these formulations F4 has maximum stability.
- **Freeze Thawing:** Freeze thawing was carried out to evaluate the stability of formulation. For the development of SNEDDS formulation, right blend of emulsifier is necessary to form stable

nano emulsion. It was observed that in formulation F1 shows separation of two layers, and this formulation were excluded for further studies. It was also observed that the solubility of drug was more in s/Cos phase. When compared with oil phase. Hence higher the concentration of oil, more unstable was the emulsion. Thus formulations A2, A3, and A4 which were stable to freeze thawing and used to for further evaluation.

- **In-vitro Release:** To understand the characteristics of drug release from SNEDDS, an in vitro release study was carried out. When SNEDDS encountered aqueous media, the drug existed in the system in different forms including a free molecular form, or mixed in the micelles or in the nano emulsion droplets. Under this circumstance, it is necessary to separate the isolated drug molecules from those trapped by micelles or Nanoemulsions for a real in vitro release test. Therefore, it is not rational to use the routine release approach in this case. Recently, dialysis method was applied for SNEDDS in vitro release study **[17, 18]**. The profile of drug release was illustrated in **Figure 5**. Vitro- release profile of Docetaxel from SNEDDS and marketed formulation in PH 6.8 phosphate buffer. Release of drug from SNEDDS was markedly boosted compared with that of Tablet in the following 4 h. In the case of SNEDDS, more than 85% of Docetaxel was released during the first 2 h and total amount of drug release in 4 h was, 98.30% indicating a complete release.

Table 3: Particle Size Data of the Reconstituted SNEDDS

S. No.	Formulation Code	Droplet Size (nm)	Poly-disperse Index (PDI)
1	A1	206	0.190
2	A2	186	0.039
3	A3	178	0.233
4	A4	170	0.136

Table 4: Zeta Potential of Reconstituted SNEDDS Formulation

S. No.	Formulation Code	Zeta Potential (mv)
1	A1	-18.14
2	A2	-20.30
3	A3	-22.11
4	A4	-24.40

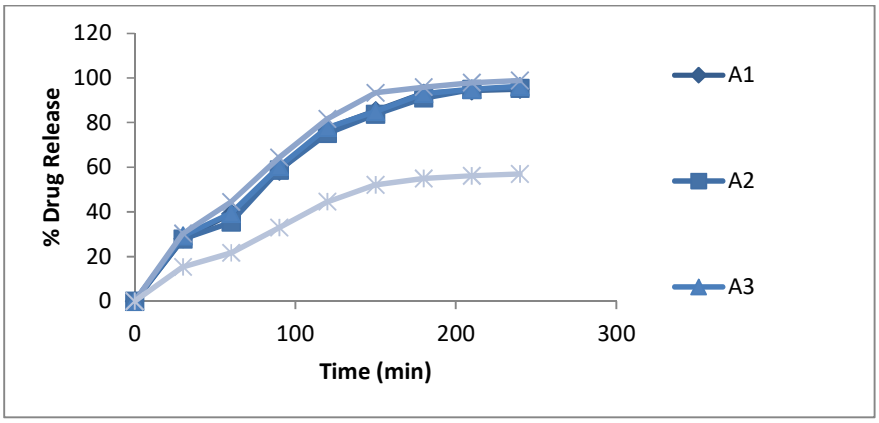

Figure 5: Vitro- release profile of Docetaxel from SNEDDS and marketed formulation

CONCLUSION

A SNEDDS containing poorly water-soluble drug, Docetaxel, was formulated for oral application. The components and their ratio ranges for the formulation of SNEDDS were obtained by solubility study, pseudo-ternary phase diagram construction, and droplet size analysis. The optimum formulation of the SNEDDS consisted of 40% Capryol 90, 20.66% Cremophor EL, and 10.33% PEG-400, which had sufficient drug loading, rapid self-nano emulsification in aqueous media, and forming droplet size in the range of nano emulsion. The formulation showed greater extent of absorption than the marked formulation. Thus the study confirmed that SNEDDS formulation can be used as possible alternative to conventional oral formulation of Docetaxel to improve its solubility and oral absorption.

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