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ORIGINAL ARTICLE

Formulation and Characterization of a Self Nano-Emulsifying Drug Delivery System with Paclitaxel for Improved Oral Absorption

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ABSTRACT
Paclitaxel has an extremely low bioavailability due to its limited water solubility and permeability. The primary goal of the experiment was to design Paclitaxel-loaded self nano emulsifying drug delivery systems (P-SNEDDS) and assess their ability to impart Paclitaxel with better absorption and therapeutic efficacy by oral administration. The SNEDDS were described using morphological observations, droplet size, zeta potential measurements, freeze thawing, and an in vitro release investigation. This composition calls for 35 percent Capryol 90 (Propylene Glycol Monocaprylate Type II), 18.20 percent Cremophor EL, and 11.40 percent Transcutol. After 3.5 hours of in vitro drug release studies, paclitaxel was entirely released from SNEDDS. Paclitaxel absorption from SNEDDS was shown to be superior to that of commercially available Taxol. As a result of this research, paclitaxel for SNEDDS was produced.
KEYWORDS: *Paclitaxel phase diagram, self-nano emulsification drug delivery system.*

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INTRODUCTION

Paclitaxel (PTX), often known as Taxol, a widely recommended chemotherapeutic agent used to treat a variety of malignancies. [3] Ovarian cancer is not the only case; esophageal and pancreatic cancers are also examples. [3] For delivery, it is administered intravenously.[3] The most physiologically advantageous and patient-friendly method of administration is via mouth. New oral delivery strategies must be developed in order to modify the biopharmaceutical characteristics of poorly water soluble chemical moieties and impart desired therapeutic applications . The development of self-nano emulsifying drug delivery systems (SNEDDS) is most promising techniques to improve the biopharmaceutical parameters of drugs with low aqueous solubility[1,2,3]. SNEDDS has recently received a lot of interest due to its suitability in developing formulation with poorly water-soluble medications and enhancing bioavailability. For several decades, researchers have been studying SNEDDS' ability to administer a wide range of medications. Only a few scientific studies have been conducted on traditional Chinese remedies. Owing to isotropic characteristics SNEDDS comprise of oil, a suitable surfactant, along with co-surfactant, sometimes a suitable solvent and a medicinal component. A nano emulsion can be easily formed by mixing a little volume of water or aqueous solution. A nano emulsion should form naturally due to the low free energy of certain therapeutic excipients. Nanoemulsion droplets dispersed throughout the digestive system can carry medications to the intestinal wall for absorption via an undisturbed water layer due to their large surface area and capacity to quickly release drug-containing dissolved and mixed micelles. Medication dissolution aided by SNEDDS is only one component of overall drug absorption; lymphatic transport also contributes to higher bioavailability. The higher fatty acid composition in the form of lipids or oils SNEDDS may be benefitted with improved lymphatic medication delivery by increasing lipoprotein production and intestinal lymphatic liquid flux [8, 9]. Taxol's oral

administration has been challenged due to its poor water solubility rendering it for poor absorption, P-glycoprotein (P-gp) driven drug efflux, gut membrane-bound cytochrome enzyme pre-absorptive metabolic process, hepatic first-pass metabolic process, and decreased intestinal membrane permeability [5-7].

MATERIAL AND METHODS

Reagents and Chemicals

Paclitaxel was procured from Shaivya Pharmachem Gujrat India. Capryol 90, Transcutol HP, and TRANSCUTOL were gratefully donated by Gattefosse in India. The tocopherol polyethylene glycol succinate used in this experiment was supplied by Sigma in India (Vit E TPGS). Taxol was donated by Sanofi-Aventis. HPLC and LC-MS/MS grade ethyl acetate and methyl-tertiary-butyl ether, Methanol, and acetonitrile given by Sigma, India, for use in these investigations. The majority of the chemicals were of analytical grade. The polyethylene glycol-400 was supplied by Dr.SKCP College Sangli, and the neusilin was supplied by Bioven Ingridents Uttarpradesh. According to the analytical criteria, all of the other compounds used were of the greatest purity conceivable.

Solubility Studies

Paclitaxel solubility was studied in a variety of oils, surfactants, and co-surfactants. Paclitaxel was loaded into each vehicle, and the mixture was swirled at 300°C at a rate of one revolution per minute for 72 hours. After centrifuging for 5 minutes at 2000 RPM, the clear solution was subjected filtration through membrane filter assembly. Amount of paclitaxel at 230 nm was measured using a UV spectrometer.

Designing of a Pseudo-Ternary Phase Diagram

A possible equilibrium phase diagram was generated after titrating four different combinations of oil as Capryol 90, surfactant as Cremophor EL , and co-surfactant as Transcutol at room temperature in double distil water. When the mixture was allowed reached equilibrium, it was possible to see it. The end result was identified as a nano emulsion, as it was with formation of clear or slightly blue tinch color. To determine the nano emulsion area, a series of pseudo-ternary phase diagrams were compared using direct observation. To begin, we mixed Capryol 90 with (s/cos) cremophor EL and Transcutol in various ratios such as (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9) with keeping constant concentration of cosurfactant as 1 part and surfactant concentration range from 1 part to 4 parts. The mixture was vortexed for five minutes after a particular amount of S/Cos was introduced to the oil phase for each phase diagram to ensure a transparent, uniform blend. The mixes were titrated with water. After vortexing for 2-3 minutes after each addition, it took 30 minutes to equilibrate the vial mixtures at 25°C. The combination was visually inspected for physically separation stability, transparency, and viscous nature after reaching steadiness. The measurements were used to calculate the water concentrations at which the system stability in terms of turbidity and clear transparency repetitive cycle mode. Finally, the oil value and S/CoS mixing ratio were used to calculate how far they could go into the nano-emulsion domain. The chemix software was then used to produce the phase diagram.

PREPARATION OF SNEDDS

Paclitaxel was dissolved in an isothermal water bath at 500 degrees Celsius in a mixture of Transcutol, Cremophor EL, and Capryol 90. This mixture was combined with a Neusilin carrier to generate semisolid SNEDDS, as per table 1.

Table 1: Preparations of SNEDDS Formulation batches

Formulation code	Paclitaxel (mg)	Capryol 90 (gm)	Cremophore EP (gm)	Transcutol (gm)	Neucilin (gm)	S/Cos
P1	10	3	0.33	0.16	4.20	2:1
P2	10	2.75	0.66	0.33	3.95	2:1
P3	10	2.5	1.00	0.50	3.70	2:1
P4	10	2.25	1.33	0.66	3.45	2:1

SNEDDS CHARACTERIZATION

Assessment of Zeta Potential and Droplet Size : Droplet size and distribution, as well as zeta potential, were estimated in triplicate using the ZLS Zeta Potential and Particle Sizer (PSS Nicop, Santa Barbara, CA, USA). The detecting wavelength spanned from 2 nm to 5000 nm.

***In-vitro* kinetics study:** A modified technique was adopted to investigate the *in vitro* dissolution of paclitaxel SNEDDS [10]. The release test method provided in the Chinese Pharmacopoeia was used in the dialysis operation (2005 version). The dialysis bag was tightly secured and placed in a temperature-controlled solution (PH 6.8 buffer, Spectrum Medical Industries Inc., USA) that was heated to 370 C before

dissolving the Paclitaxel SNEDDS that had been injected into it. The paddle rotated at a constant speed of 50 revolutions per minute. Every 30 minutes, 5 mL samples were extracted with fresh dissolving solution. The Paclitaxel release of the SNEDDS formulation was compared to that of a Paclitaxel tablet carrying the same amount of drug.

RESULTS AND DISCUSSION

Oils and Surfactants Phase study

A simple, safe, and appropriate SNEDDS screening formulation is a common requirement. A successful nano emulsion should have significantly better solubility, a well controlled large self-nano emulsification zone, and an efficient droplet size in the pseudo-ternary phase diagram [10, 11, 12]. To formulate a SNEDDS, the medicinal ingredient must be solubilized in an appropriate vehicle. Table 2 shows the solubility values for Paclitaxel Cremophor EL and Capryol 90. To compare their respective phase behaviors, a pseudo-ternary phase diagram was required. The most self-nano emulsion was created by a surfactant co-surfactant ratio of a 2:1 blend of Cremophor EL and Transcutol. In the lipid phase, a 2 parts and 1 part mixture of Cremophor EL and Transcutol respectively was utilised.

Because of their lower toxicity and less susceptibility to pH and ionic strength, non-ionic surfactants were used in the majority of SNEDDS tests. Cremophor EL was thus more difficult to disseminate than Tween 80. The efficacy and timing of medicine distribution were both a source of worry. As a result, Cremopher EL is the preferred surfactant. If ethanol, 2-propanol, and PEG-200 are utilised as co-surfactants instead of Transcutol, the nano emulsion is more likely to fracture. Only ethanol exhibited a higher transcutol solubility than any other vehicle we examined. Transcutol is an appropriate choice because it is a co-surfactant. The phase diagrams of two solutions containing Capryol 90 and Cremopher EL: Transcutol (2:1, w/w) are shown in Figure 2. Even if the formulation's high oil content is meant to enhance the SNEDDS, a good self-nano emulsifying vehicle must also have a correct droplet size distribution. The relationship between oil content and droplet size was also investigated. The oil content reduced from 60% to 45%, and droplet size decreased from 205 to 170 nm. By titrating the ratio of surfactant to co-surfactant, stable and efficient SNEDDS can be created. The phase diagrams in Figures 1, 2, 3, and 4 were generated using surfactant with constant co-surfactant concentration of 1 part and varying concentration of surfactant from 1 part to 4 parts. A 2:1 ratio was discovered to be the optimal self-nano emulsifying zone. Data from the ternary combinatory phase study of Capryol 90 dispersed in aqueous base at 37°C, as well as Cremophor EL and Transcutol. The self-nano emulsion zone is hidden in the shadows. We also investigated the impact of varying surfactant/co-surfactant ratios (Cremophor EL/Transcutol) on droplet size. When the surfactant ratio was raised from 10% to 30% there were inconsiderable fluctuations in mean particle size. Co-surfactant, when employed at the correct concentration, can aid in the creation of nano emulsions. When too much co-surfactant is added, the system loses stability due to its high aqueous solubility and droplet size increases due to the rising interfacial film [13, 14]. As a result, a 2:1 surfactant as to co-surfactant ratio was optimal.

Table 2: Solubility of Paclitaxel in Different Vehicles

Sr.No.	Vehicle	Solubility
1	Propylene glycol monocaprylate (Capryol 90)	67.95 ± 1.20
2	Capmul MCM	68.23 ± 2.00
3	Acconon MCM	62.23± 1.30
4	Vitamin-E	31.44 ± 1.92
5	Soya bean Oil	42.54 ± 1.40
6	Almond oil	33.85 ± 1.10
7	Tween-80	81.60 ± 2.34
8	Tween -20	63.45± 1.40
9	Cremophore EL	112.45 ± 2.80
10	Tranascutol	135.25± 1.42
11	Polyethylene glycol-400	150.68 ± 2.90

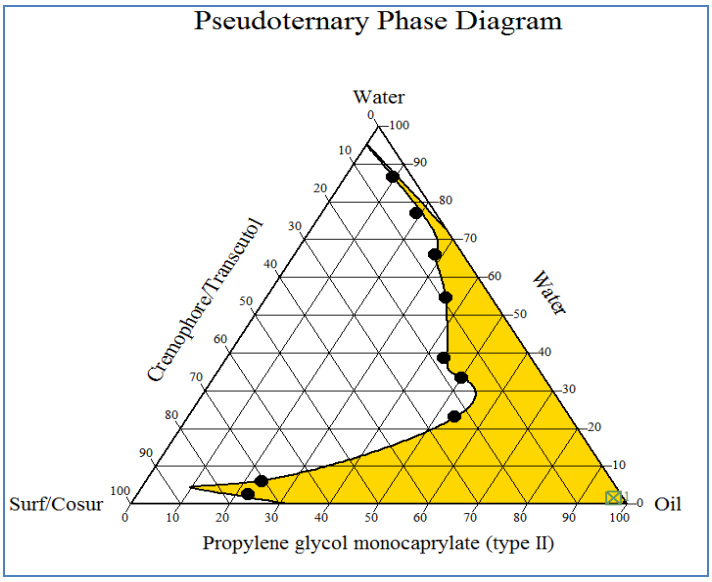

Fig 1 Phase diagram of Propylene glycol monocaprylate, water and Cremophor EL+ Transcutol (1:1)

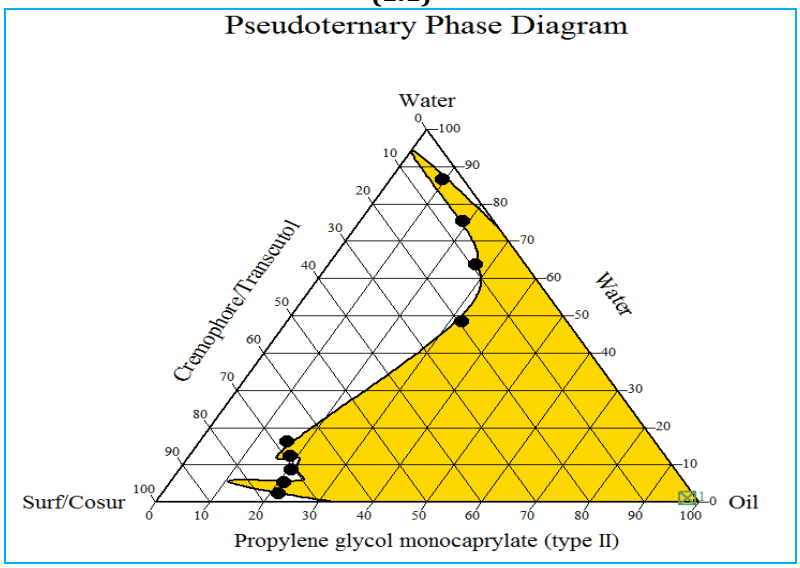

Fig 2 Phase diagram of Propylene glycol monocaprylate, water and Cremophor EL+ Transcutol (2:1)

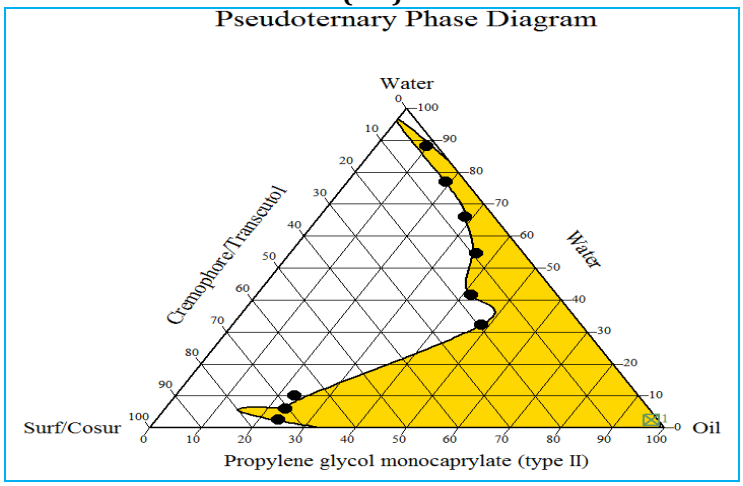

Fig 3 Phase diagram of Propylene glycol monocaprylate, water and Cremophor EL+ Transcutol (3:1)

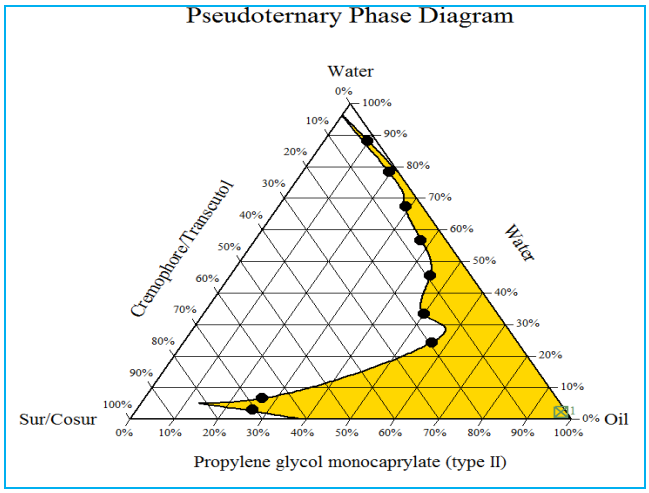

Fig 4 Phase diagram of Propylene glycol monocaprylate, water and Cremophor EL+ Transcutol (4:1)

SNEDDS Characterization

Droplet Size Analysis: When analysing a self-Nanoemulsion, it is critical to look at the distribution of droplet sizes following self-nano emulsification. The size of droplets has been studied in context of effect on drug absorption. The accessible interfacial surface area for molecule absorption is always inversely proportional to droplet size i.e. large interfacial surface area, smaller will the droplet size [15]. Droplet size was assessed with consideration of various media, volume used for dilution, drug loading capacity and dispersion technique. The Nanoemulsion dispersed from Paclitaxel SNEDDS had an average droplet size of 220 nm, assuming a Gaussian distribution. Scientists have also tried to find out whether there is any dilution impact on particle size of droplet in distilled water. When the duration of dilution was doubled by 1000, the droplet size remained constant, indicating that the Nanoemulsion formed during dilution could retain Paclitaxel even after it had been solubilized 1000 times., Droplet size remain unaffected Even when the drug loading in water was raised from 0.3 to 2.5 percent. In addition, in our research, we have also tried to study the impact of medium on droplet size. Droplet diameters for SNEDS dispersion in water, NaCl, 0.1N HCl, and buffers of pH 6.8 were 172.23.6 and 172.81.7 nanometers, respectively. The four testing media did not exhibit any significant changes in their results, proving that pH and ionic potential had no effect on the formulation. An inquiry was conducted into the impact of various mixing procedures on droplet size. Oscillation, whisking (at 25, 50, or 100 rpm), or swirling do not appear to impact droplet size. This finding points to the existence of Stable274. 355 (2008) 269–276 International Pharmaceutics Journal P. Zhang led a group of researchers.

Table 3: Particle Size Data of the Reconstituted SNEDDS

Sr.no.	Formulation Code	Droplet Size (nm)	Poly-disperse Index (PDI)
1	P1	210	0.180
2	P2	190	0.038
3	P3	181	0.229
4	P4	172	0.137

Zeta Potential Analysis: Typically substantial increase in electrostatic repulsive forces forms a stable SNEDDS due to presence of nano droplets inhibiting coalescence. When repulsive forces from electrostatic origin decreases often concludes with physical insatbility. In the presence of the paclitaxel-SNEDDS, distilled water-dilution generated zeta potentials of 19200.333, 21110.411, 23250.29, and 23.910.47, as shown in table 4. The four formulations are indistinguishable in terms of zeta potential values. The formula with the highest degree of sturdiness is F4.

Table 4: Zeta Potential of Reconstituted SNEDDS Formulation

Sr.no.	Formulation Code	Zeta Potential (mv)
1	P1	-19.20
2	P2	-21.11
3	P3	-23.25
4	P4	-23.91

Freeze Thawing: The formulation's stability was tested using freeze-thawing. To create a stable nano emulsion, the SNEDDS formulation requires a specific blend of emulsifiers. Due to the detection of a layer separation, Formulation F1 was ruled out of further testing. The drug was also proven to be more soluble during the s/Cos phase. This is, in comparison, a dry period. When a result, as the oil content grows, the emulsion becomes more unstable. Because of their great resistance to freezing and thawing, compositions P2, P3, and P4 were chosen for further testing.

Release kinetics : In-vitro release study was planned to analyse release kinetics from SNEDDS. When SNEDDS came into contact with water, it took the shapes of free molecules, micelles, and nano-emulsion droplets. Detachment of drug molecules from those associated with micelles or nanoemulsions is required for a optimum *in vitro* release assay. As a result, adopting the standard release approach would be unproductive. Dialysis has recently been employed to analyse SNEDDS release *in vitro*. (17, 18) Figure 5 displays the Paclitaxel release pattern from P-SNEDDS as well as in buffer media . In the following 3.5 hours, drug release kinetics from SNEDDS was significantly superior than that of Tablet. In the case of SNEDDS, the first two hours of Paclitaxel release generated more than 85% of the total amount of medication released in 3.5 hours, indicating that the drug was completely absorbed.

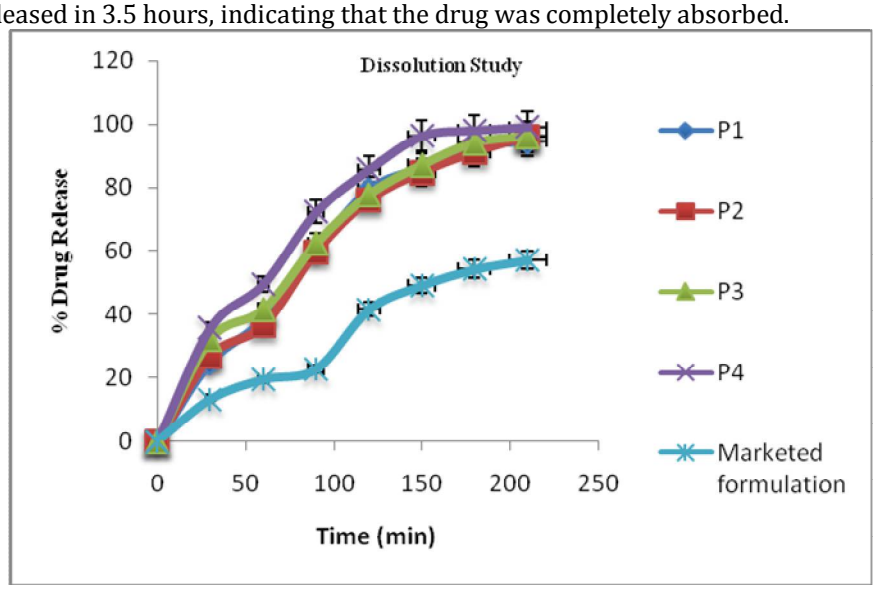

Figure 5. *In Vitro*- release kinetics of Paclitaxel from P-SNEDDS and marketed formulation

CONCLUSION

Paclitaxel, a medication that is only weakly water soluble, was used to create a SNEDDS for oral delivery. To determine the system suitability of different components and their inter impacting ratios for the formulation of SNEDDS, solubility studies, phase stability diagram, and droplet size analyses were undertaken. The optimum batch contains 35 percent Capryol 90 (Propylene glycol monocaprylate type II), 18.20 percent Cremophor EL, and 11.40 percent Transcutol, as well as optimum drug loading, characteristic fast self-nano-emulsification in water base media, and desired droplet size in the nano-emulsion range. The formulation outperformed the competitors in terms of absorption. The SNEDDS formulation, an alternative to the standard oral formulation of Paclitaxel, has been identified and can be utilised to enhance solubility and oral absorption.

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