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Original Research Article

Formulation and Evaluation of Liquid Loaded Tablets Containing Docetaxel-Self Nano Emulsifying Drug Delivery Systems

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Abstract

***Purpose:** To prepare and characterize tablets loaded with self-nanoemulsifying drug delivery system (SNEDDS) containing docetaxel (DTL).*
***Method:** SNEDDS of docetaxel were prepared using various oils, surfactants, co-surfactant and solvents to improve the dissolution rate and bioavailability of the poorly water-soluble chemotherapeutic agent. The SNEDDS components were preliminarily screened for the solubility of the drug in various vehicles, miscibility of excipients, rate of emulsification and ternary phase diagrams. The tablets were prepared by direct compression process with a porous carrier, magnesium alumino-metasilicate, and subsequently loaded with SNEDDS by a simple absorption method. The tablets were then characterized for physical parameters, including tablet hardness, weight variation, disintegration, drug content and in-vitro drug release.*
***Results:** Cremophor-EL, polysorbate-80 and dehydrated alcohol mixture in the ratio 85:10:5 yielded docetaxel SNEDDS with droplet size of 12.16 nm and polydispersity (PDI) of 0.039. Tablets with high porosity suitable for loading with SNEDDS and containg the super-disintegrants, crosscarmellose sodium and sodium starch glycolate, in a concentration of 3, 4 and 5 %, achieved complete dissolution of docetaxel from the tablets. In vitro release of docetaxel from SNEDDS and the tablets was similar ($p < 0.05$).*
***Conclusion:** SNEDDS of docetaxel is a promising approach to achieving a solid dosage form of the liquid-loaded drug delivery systems for enhancing the solubility and dissolution rate of the drug, and hence also its bioavailability.*

***Keywords:** Docetaxel, Drug carrier, SNEDDS, Self-nanoemulsifying, Solubility, Drug release, Anicancer, Surfactant, Co-surfactant*

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INTRODUCTION

High levels of insolubility in the formulation of anticancer injections pose serious problems and challenges to formulation scientists and physicians in terms of emulsifying and suspending injectable formulations. Currently, docetaxel injection is available as SNEDDS formulation with polysorbate-80, which accommodates effective therapeutic amount in smaller amount of surfactant mix. Hence, formulation development in these areas using SNEDDS is feasible to have pharmaceutical equivalent dosage form.

However, new technologies has been developed for sealing of soft and hard gelatin capsules [1,2]. Some formulators have focused on solid formulation of lipid systems and in particular formulation of liquids and semi-solid self-emulsifying drug delivery systems (SEDDS) [3]. Lipid-based formulation systems have become increasingly important in the formulation of lipophilic drug substances as they can facilitate the dispersion of a drug in the gastrointestinal tract resulting in enhanced oral bioavailability [4]. Self-nanoemulsifying mixture is an advanced form of nanoemulsion drug delivery systems, because water is not used and so the drug leaching from the nanosized oily droplets to the aqueous medium of the formulation during storage is minimized [6].

Generally, self-emulsifying mixtures are broadly classified according to their sizes such as: SMEDDS with droplets of emulsion size is more than 600 nm. SMEDDS with droplets of micron sizes, i.e., lies between 100 - 150 nm and SNEDDS with droplets of nanosized between 10-100 nm [5]. Transfer of liquid lipid systems into a solid oral dosage form has been attempted by several methods such as capsule filling and spray drying [6], adsorption onto solid carriers [7-9] and melt granulation as well as other techniques [10]. However, a large amount of carrier is required to solidify the liquid, which subsequently results in the production of a large dosage volume [11].

The objective of this study was to develop and evaluate self-nanoemulsifying formulations containing poorly water soluble anti-mitotic chemotherapy agent, docetaxel.

EXPERIMENTAL

Materials

Docetaxel (DTL) was obtained as a gift from Aptuit Laurus Laboratories, India. Polyethoxylated castor oil (CremophornEL), polysorbate-80, PEG (polyethylene glycol) 400, propylene glycol, polyethylene glycol-15-hydroxy stearate (Solutol®HS-15), propylene glycol monocaprylate (type II) NF (Capryol®90), glyceryl caprylate/caprate (Capmul®MCM), Capryol-90, Capmul-MCM, lauroglycol, capryl ocaproyl polyoxyl-8 glycerides NF (Labrasol®), propylene glycol dicaprylate/dicaprate NF (Labrafac®), highly purified diethylene glycol monoethyl ether EP/NF (Transcutol®P), dehydrated alcohol. Magnesium aluminum metatrisilicate and other chemicals used in the study were of analytical grade and procured locally.

Solubility studies

The solubility of docetaxel in various oils, surfactants, cosurfactants/solvents was determined. An excess amount of docetaxel was added into each vial containing 10 mL of selected vehicle. Then, the mixture was heated to 37 ^{o}C on water bath to facilitate the solubilization. Mixing of the systems was performed using a cyclo-mixer (CM 101, Remi, India) for 10 min in order to facilitate proper mixing of drug with the vehicle. The dispersions thus formed were shaken for 48 h in a mechanical shaker (Remi, India). After reaching equilibrium, the dispersions were centrifuged at 2500 rpm for 20 min to remove undissolved docetaxel, followed by filtration through a 0.45 μm millipore membrane filter paper. The concentration of docetaxel was quantified by high performance liquid chromatography (HPLC).

Construction of ternary phase diagrams

The ternary phase diagrams of oil, surfactant, co-surfactant/solvents and water were developed using surfactant titration method. The dispersions of oil and water at certain weight ratios were titrated with surfactant/co-surfactant mix in a drop wise manner. Until visual observation of phase clarity and flowability was obtained. After the identification of self-nanoemulsion region in the phase diagrams, the SNEDDS formulations were selected at the desired component ratios [13,14].

Preparation of DTL-SNEDDS

The DTL-SNEDDS were prepared by using surfactants, co-surfactant, oil/ solvent mix. The level of docetaxel was kept constant (i.e. 20 mg). The concentration of surfactant and other components were varied in different formulations until freely solubilized drug with stable SNEDDS were produced. The docetaxel (20 mg) was added into the mixture and mixed using magnetic stirrer at ambient temperature until complete dissolution of docetaxel. Prepared SNEDDS were stored at room temperature and evaluated for their droplet size and polydispersity, stability and spectral analysis.

Evaluation of SNEDDS

Droplet size and polydispersity (PDI)

Docetaxel SNEDDS was diluted with distilled water (a portion diluted 1 in 25 and if clear, the second portion was diluted 1 in 100). The two portions were gently mixed and sonicated for 30 s and allowed to settle. Clear solutions were used to measure droplet size/distribution and polydispersity was determined at 25 °C by photon correlation spectroscopy (PCS) using a Malvern Nanosizer/Zetasizer® (Malvern Instruments, USA). The analysis was performed to determine mean values/ Z-Average of particle size distribution. Turbid and opaque dispersions were evaluated visually. The droplet size and PDI for the optimized formulation was recorded.

Freeze-thaw cycle

Freeze thawing was employed to evaluate the stability of drug loaded SNEEDS. Formulations were subjected to 3 freeze-thaw cycles, which included freezing at −20 °C for 48 h followed by thawing to ambient room temperature (37 °C) for 48 h. Nanoemulsions were observed for physical stability conditions such as phase separation or drug precipitation.

Preparation of porous tablets

The porous tablets were prepared by direct compression process. Porous adsorbent magnesium aluminum metatrisilicate (MAMS) granules was mixed with super-disintegrants and lubricated. All the ingredients were mixed in a cylindrical blender and directly compressed into tablets using 16 station rotary compression tablet press (Mini Press manufactured by ELITE Scientific Pvt Ltd). Tablets average weight of 860 mg compressed using a round 12.5 mm flat-faced punches were produced. The compositions of various porous tablets are given in Table 1. The prepared tablets were subjected to evaluation of physical parameters such as thickness, hardness and disintegration test according to standard protocol.

Loading procedure

Tablets were placed in slightly excess of docetaxel-SNEDDS and allowed to absorb the liquid over a period of 24 h. Tablets surface exposed to SNEDD was rotated after 12 h. After the exposure, tablets surface was drained by using absorbent pad and the weight of tablets were recorded. The loaded tablets were dried at ambient conditions over a period of 3 days. Furthermore, the tablets were characterized for percentage loading by weight and for disintegration. To make maximum feasible time for loading, tablets were compressed as porous plugs with a thickness of 6.5 ± 0.3 mm.

In vitro dissolution studies

Dissolution rate studies of DTL-SNEDDS were performed using USP dissolution testing apparatus (type II) with rotating paddles at 100 rpm using 900 ml of distilled water as dissolution medium. The temperature was maintained at 37 ± 0.5 °C throughout the experiment. Aliquots (10 ml) were withdrawn at various time intervals and same volume of dissolution medium was replaced for maintaining the constant volume of dissolution medium. Samples were filtered through 0.45 µ filter and analyzed by HPLC [15,16].

Assay of DTL in SNEDDS

An HPLC system (Waters HPLC 2 2695 Series) consisting of pump, Auto sampler, UV-Vis detector, Thermostat column compartment connected with Waters (alliance) Empower software equipped with a 230 nm UV-detector and YMC ODS C18, 250 x 4.6 mm, 5 µ, was maintained at constant temperature of 30 °C. A sample volume of 20 µL DTL solution was injected. The gradient system consisted of 2 mobile phases with the compositions of mixed Phosphate buffer which consist of 1.6 g of potassium dihydrogen phosphate and 0.3 g of Dipotassium hydrogen phosphate in 1 L of water (pH 5.80): Acetonitrile in the ratio 30: 70. The flow rate was kept constant at 1.0 mL per min.

Table 1: Composition of porous tablets

	Content (mg)							
Ingredient	***A1***	***A2***	***A3***	***A4***	***A5***	***A6***	***B1***	***B2***
MAMS	830.25	821.75	813.25	830.25	821.75	813.25	791.60	791.60
Sodium starch glycolate	25.50	34.00	42.50	--	--	--	42.50	25.50
Crosscarmellose sodium	--	--	--	25.50	34.00	42.50	25.50	42.50
Magnesium stearate (0.5%)	4.25	4.25	4.25	4.25	4.25	4.25	4.25	4.25
Total weight (mg)	***860***	***860***	***860***	***860***	***860***	***860***	***860***	***860***

RESULTS

Solubility

Initially solubility studies were performed to identify suitable oily phase, surfactants, and cosurfactants for the development of SNEDDS of docetaxel. Because solubility of the drug is an important consideration when formulating a self-emulsifying formulations for avoiding precipitation of the drug on dilution in the *in vivo*. The concentration of docetaxel was quantified by HPLC. The results of solubility studies are reported in Figure 1.

Ternary phase diagrams

Based on the results of preliminary studies, ternary phase diagrams of the seven systems were constructed with the objective to study the relationship between the phase behavior and the composition also help to determine the concentration range of components for the formation of a nano emulsion. All the components were converted to weight/weight percent (w/w %) before constructing the phase diagrams. The bluish area enclosed in the triangle represents the region of self-emulsification (Fig 2). Within this area the SNEDDS form fine oil in water emulsion with only gentle agitation. Globule size (< 200 nm) and PDI (0.3 <) were the criteria for selection of the composition.

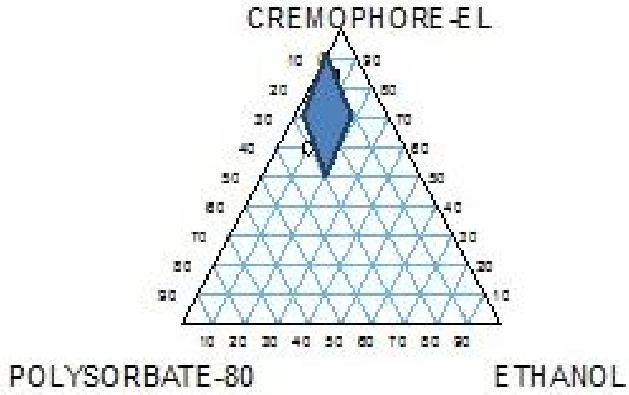

Fig 2: Representative ternary phase diagram indicating the efficient self-nanoemulsion region containing Cremophore-EL, Polysorbate-80 and Ethanol (85/10/05 %)

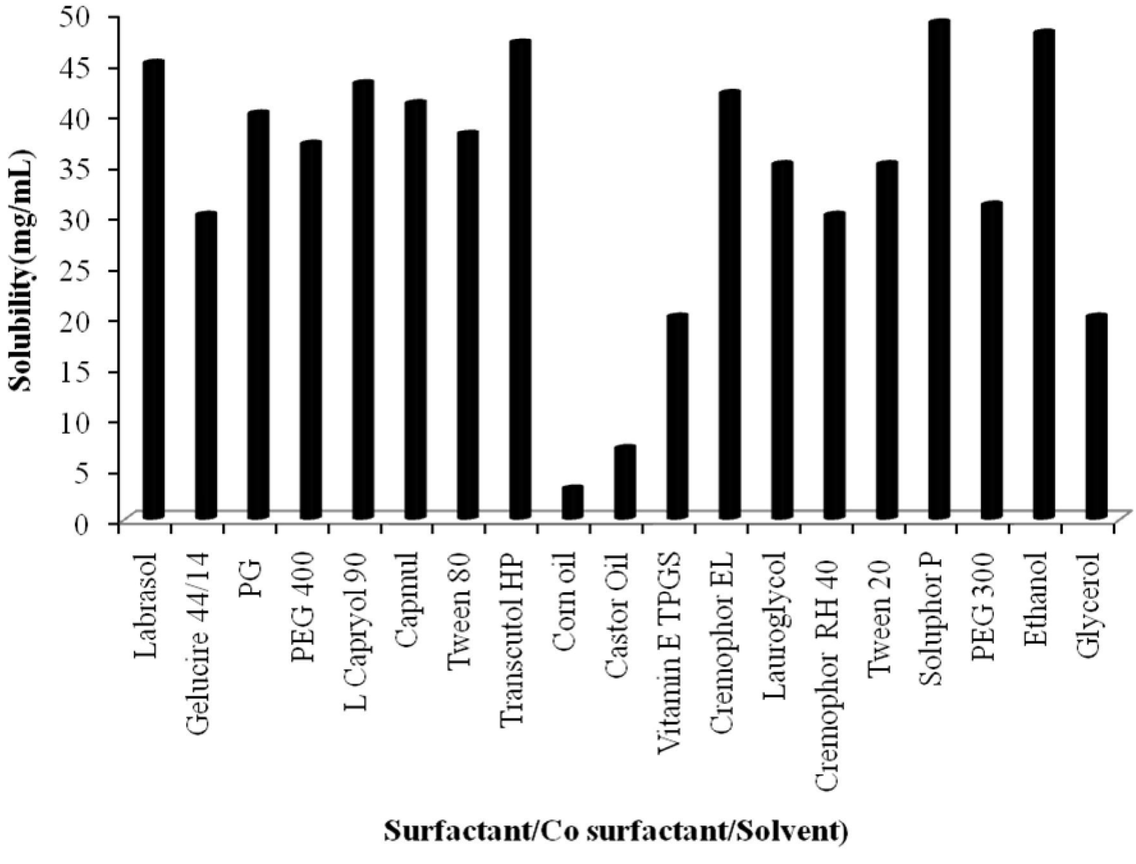

Figure 1: Solubility of docetaxel in various oils, surfactants, co-surfactants and solvents

Droplet size and polydispersity

Different surfactant systems were chosen for SNEDDS formulation. Presence of oil phase components Transcutol or Capmul in surfactant mix yielded droplet size range below 200 nm. Due to fluidity and collision over oil and co-surfactant phases upon dilution droplet growth was observed. Replacing oil phase with solvent phase made stabilization of the nano emulsion. Here the surfactant mix which provided the rigid micelle structure and the suitable solvent proportion decreased the friction between micellar layers and resulted in stable nano emulsion. The droplet size and polydispersity values of docetaxel SNEDDS formulations are given in Table 3.

Thermodynamic stability

The selected formulations were subjected to different thermodynamic stability by using heating and cooling cycle, centrifugation and freeze thaw cycle stress tests. Those formulations, which survived thermodynamic stress tests, were taken for dispersibility test to see the visual clarity after infinite dilution. There were no physical variations observed in set of SNEDDS developed with docetaxel, Cremophor, polysorbate-80 and ethanol.

Micrometrics

The granules were evaluated for their micromeritic properties. The results obtained were bulk density (0.615 g/cm^3), tapped density (0.510 g/cm^3) and angle of repose (18 °).

Physical characteristics of SNEDDDS-loaded tablets

Tablet weight was taken before loading and after loading as part of the characterization of loaded tablets. The tablet properties are given in Table 4.

***In vitro* dissolution of SNEDDS-loaded docetaxel tablets**

The dissolution profiles are shown in Figure 3. Formulations A1, A2, A3 contain sodium starch glycolate as superdisintegrant; formulations A4, A5 and A6 contain cross caremellose sodium as superdisintegrant, while formulations B1 and B2 contain the combination of both disintegrants.

Table 3: Droplet size and polydispersity (PDI) of docetaxel SNEDDS formulations

Composition	Dilution	Z-average (d.nm)	PDI
Polysorbate-80 +PEG-400+Transcutol-HP	1:25	85.43	0.209
	1:100	133.3	0.324
Polysorbate-80+Soluphor-P+Capmul-MCM	1:25	29.75	0.276
	1:100	39.30	0.243
Polysorbate-80+Glycerol+Capmul-MCM	1:25	96.89	0.434
	1:100	67.8	0.633
Cremophor-EL+Soluphor+Capmul-MCM	1:25	10.28	0.873
	1:100	40.06	0.137
Cremophor-EL+Glycerol+ Capmul-MCM	1:25	80.93	0.453
	1:100	78.4	0.784
Cremophor-EL+Glycerol+Capmul-MCM	1:25	98.64	0.305
	1:100	23.67	1.000
Cremophor-EL+Polysorbate-80+Ethanol	1:25	12.16	0.039
	1:50	12.36	0.029
	1:100	12.67	0.014

Table 4: Characteristics of SNEDDS-loaded tablets

Parameter	A1	A2	A3	A4	A5	A6	B1	B2
Mean weight	860 mg ± 0.4mg							
Diameter (mm)	12.5 ± 0.2							
Hardness (kg/cm^2)	2.2	1.8	2.0	2.4	2.2	2.2	2.0	2.2
Thickness (mm)	6.4±0.2	6.5±0.2	6.5±0.2	6.5±0.2	6.5±0.2	6.5±0.2	6.5±0.2	6.5±0.2
Disintegration time (min)	2-3	1-2	1-2	1-2	1-2	≤1	≤1	≤1

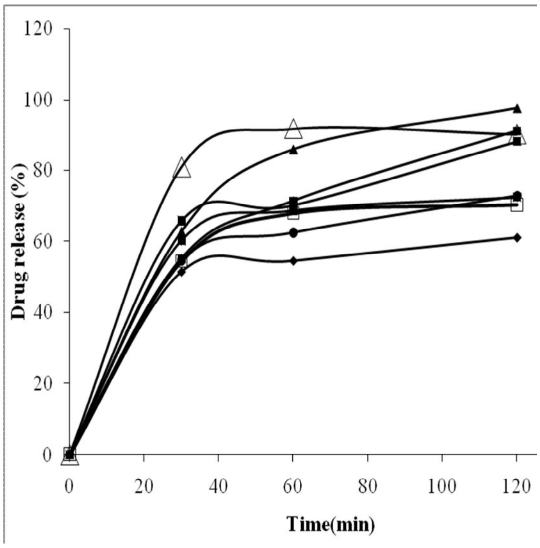

Fig 3: Dissolution profile of SNEDDS-loaded docetaxel tablets. **Note:** -♦- A1, -□-A2, -▲-A3, -■- A4, -●- A5, -●- A6, -■-B1, -∆- B2

DISCUSSION

Docetaxel SNEDDS used in preparing liquid-loaded tablets had a particle size of 12.16 nm. SNEDDS dramatically enhanced the solubility of docetaxel. The results obtained in the study suggest that SNEDDS is an efficient and potential carrier for delivery of docetaxel by oral route, From the results of tablet disintegration for LLT it was found to influence the release of the loaded DTL-SMEDDS *in vitro*. Surfactant and co-surfactant get preferentially adsorbed at interfaces, thus reducing the interfacial energy as well as providing a mechanical barrier to coalescence, and improving the thermodynamic stability of the nanoemulsion formulation [17].

Furthermore, co-surfactants increase interfacial fluidity by penetrating into the surfactant film creating void spaces between the surfactant molecules [18]. The optimum formulation of self-nanoemulsion containing docetaxel, cremophore-EL, polysorbate-80 and ethanol is represented by the ternary phase diagram in Figure 2. It was observed that at the dilution stage, a consistent droplet size was achieved when the polarity of docetaxel surfactant mix matches with that of water. Here, the association of oil phase with insoluble docetaxel created a high degree of non-polarity and micellar rearrangement, and thereby increased droplet size. The existence of emulsion after dilution is a promising SNEDD at micellar level as nanoemulsion with droplet size of 6-12 nm. Porous tablets were prepared by dry granulation and along with disintegrants the micromeritics were found to be in constant range and exhibited good flow properties.

SNEDDs loaded tablets were shown dissolution rate dependant to disintegrant, in which SSG was proved better than CCS for a release and dissolution of > 95% w/w of docetaxel. Based on the *in vitro* dissolution studies Liquid loaded tablets of formulation A3 and B2 were found as optimum formulations, which were exhibited high dissolution rate than compared to the others. For these two formulations dissolution rate was accelerated by content of disintegrant. From loaded magnesium aluminometasilicate MAMS powder (A3), almost 97.7 % was released. The idea has previously been investigated for tablets prepared from magnesium aluminometasilicate (MAMS) as carriers of chemical reagents and catalysts [12].

CONCLUSION

Docetaxel tablet formulations incorporating SNEDDS for enhancement of the solubility and dissolution rate of a poorly soluble drug is feasible using the approach presented in this study. Furthermore, appropriate inclusion of surfactant and co-surfactant improves the thermodynamic stability of the nanoemulsion formulation.

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