

Enhancement of Oral Bioavailability of Poorly Water-Soluble Drugs Using Self-Emulsifying Drug Delivery Systems

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ABSTRACT

By enhancing NVP's solubility, dissolution rate, and diffusion profile, the current work aimed to develop and optimize Posaconazole (PN) self-emulsifying drug delivery systems (SED DS) to improve oral absorption. When added to the aqueous phase with little agitation, SED DS— isotropic mixes of oil, surfactant, co-surfactant, and medication— form an oil-in-water microemulsion

Keywords: Monophasic, Dissolution, Solubility, Morbidity, Immunocompromised

1. INTRODUCTION

In hospitalized patients, fungal infections continue to be a significant source of morbidity and mortality (MCNeil et al. 2001). Although critically ill patients in the intensive care unit are also susceptible, immunocompromised patients are more at risk for fungal infections (Kauffman et al. 2006). individuals in the intensive care unit now experience *Candida* species infections more frequently than immunocompromised individuals. Infections brought on by non-albicans *Candida* species have become more common in recent years. Patients with weakened immune systems are also more susceptible to mold infections. Although there has been a noticeable rise in mold infections brought on by *Scedosporium*, *Fusarium*, and zygomycetes, *Aspergillus* species are the most common cause of mold infections. Posaconazole inhibits the fungal enzyme lanosterol 14- α -demethylase, just like the other triazole antifungals (Noxafil, 2006). Fungal ergosterol synthesis, which is essential for the development of fungal cell walls, decreases when this enzyme is reduced. Either cell death or slowed cell development are the outcomes of the defects in the cell wall (Torres et al. 2005).

Approximately, 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system. The rate limiting step for the absorption of these drugs is often their solubilization in the gastrointestinal (GI) tract. These drugs are classified as class II drug by BCS, drugs with poor aqueous solubility and high permeability. Lipid-based drug delivery Systems have been demonstrated to be useful in enhancing the bioavailability of highly lipophilic compounds because they can keep the drug in the dissolved state until it is absorbed, thus overcoming the barrier of slow dissolution rates. In practice, lipid formulations range from pure oils to formulations containing some proportions of surfactants, co-surfactants or co-solvents. Recently, a number of studies related to lipid formulations focused attention on microemulsion formulations with particular emphasis on self-emulsifying or self-emulsifying drug delivery systems (SED DS) to improve oral bioavailability of poorly water soluble drugs.[Pallavi et al. 2012, Bajaj et al. 2008]

Self-emulsifying drug delivery systems are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/surfactants. On mild agitation followed by dilution in aqueous media such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsion.(Khoo et al. 1998) It is thought that the microemulsion is spontaneously formed by the combined action of the specific pharmaceutical excipients with low free energy (Iwanaga et al. 2006) The microemulsion droplets dispersed in the GI tract provide large surface area and promote a rapid release of dissolved form of the drug substance and/or mixed micelles containing drug substance, and they may be also responsible for transporting the drug through the unstirred water layer to the GI membrane for absorption. In addition to the enhanced dissolution of drugs by SED DS, another factor contributing to the increasing bioavailability is that the lymphatic transport is responsible for a portion of the entire drug uptake as well. The lipid composition of SED DS may be related to facilitate the extent of lymphatic drug transport by stimulating lipoprotein formation and intestinal lymphatic liquid flux (Wu et al. 2005, Lachman et al. 1999).

2. MATERIAL AND METHOD

Construction Of Pseudoternary Phase Diagram

The aqueous titration method was used to generate a pseudoternary phase diagram to determine the concentration range of components for the SEDDS. First, the surfactant–cosurfactants mixture (*S* mix) was prepared by mixing surfactant (Kolliphor EL) into glycerol solution (1:1, w/w) and cosurfactant (Kollisolv MCT 70) according to a certain mass ratio ($K_m = 3:1, 2:1, 1:1, 1:2, 4:1$). Pseudoternary phase diagram was prepared by titrating a homogeneous combination of oil, *S* mix, and water. The oil (eucalyptus oil) and *S* mix were mixed at various ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 in numerous vials. The oil and *S* mix were titrated with distilled water. Each time water was added, the mixture was vortexed to homogenize it before the sample was examined for differences in optical clarity. At equilibrium, the mixtures were examined for a key change in transparency. Pseudoternary phase diagrams were created for each *S* mix to find a suitable *S* mix ratio (Subrahmanyam et al. 2001).

Formulation of SEDDS

Following the identification of the monophasic region, different formulation batches were prepared. For the preparation of SEDDS, *S* mix (3:1) was selected. In an isothermal water bath at 50 °C, 100 mg of PN was accurately weighed and dissolved in 1.2 g of Kollisolv MCT 70 with 1.08 g of eucalyptus oil in beaker-A. The drug dissolves in a mixture of cosurfactant and oil, in beaker-A, within 1–2 min. After that, 1.8 g of glycerol and 1.8 g of Kolliphor EL were mixed for 2 min at room temperature in a different beaker-B. The mixture (beaker B) was then gradually put dropwise into the beaker-A mixture. Then, this combined mixture was vortexed until a clear preparation was obtained. *S* mix (3:1) was diluted in oil at several concentrations (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) before being titrated with water (aulton et al. 2002, Wu et al. 2014). A vortex was used to uniformize the mixture, and the turbidity was visually assessed (Table 1).

Table 1: Formulation batches developed for 3:1 with different concentration for optimization

Ingredients	F1(1:9)	F2(2:8)	F3(3:7)	F4(4:6)	F5(5:5)	F6(9:1)	F7(8:2)	F8(7:3)	F9(9:1)
Posaconazole	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Eucalyptus oil	0.12 g	0.24 g	0.36 g	0.48 g	0.6 g	1.08 g	0.96 g	0.84 g	0.72 g
Glycerol	16.2 g	14.4 g	12.6 g	10.8g	9 g	1.8 g	2.6 g	5.4 g	7.2 g
Kolliphor EL	16.2 g	14.4	12.6 g	10.8 g	9 g	1.8 g	3.6 g	5.4 g	7.2 g
Kollisolv MCT 70	10.8 g	9.6 g	8.4 g	7.2 g	6 g	1.2 g	2.4 g	3.6 g	4.8 g

In Vitro Drug Release

The dissolution test apparatus USP type II was utilized to perform the in vitro dissolution evaluation of the SEDDS formulation using the dialysis bag technique. The liquid and solid PN-SEDDS formulation F6 was inserted into the dialysis bag, locked with a clamp, and placed in 900 mL of phosphate buffer pH 6.8 dissolution media at 37 °C. The paddle's rotational speed was kept at 50 rpm. At predetermined time intervals of 5, 15, 30, 45, and 60 min, 5 mL aliquots were taken out, and the same volume of fresh dissolution medium was replenished to maintain the sink conditions. The aliquots were subjected to UV spectroscopy at 260 nm for analysis. The release of the drug from liquid and solid SEDDS formulations was compared with those of the pure drug suspension and marketed diffused tablets (Prashanti et al. 2012, Prashr et al. 2014).

Stability Studies

The SMEDDS formulations were put into empty hard gelatin capsules (size 0) and subjected to stability studies at 40°C/75% RH. They were withdrawn at specified intervals for analysis over a period of 3 months. Drug content of the capsules was analyzed using UV spectrometric method. The SMEDDS formulations were evaluated for particle size, clarity of microemulsion, polydispersive index, and zeta potential. The sampling was done on a 0, 30th, 60th and 90th day (Reddy et al. 2014, Ganju et al. 2017).

3. RESULT AND DISCUSSION

The drug content of formulations was determined by UV spectrophotometrically at 260 nm. The drug content of PN-SEDDS was determined and the results were presented in table. The results indicate that formulation code F6 showed maxim drug content of 99.27 % show in figure 1.

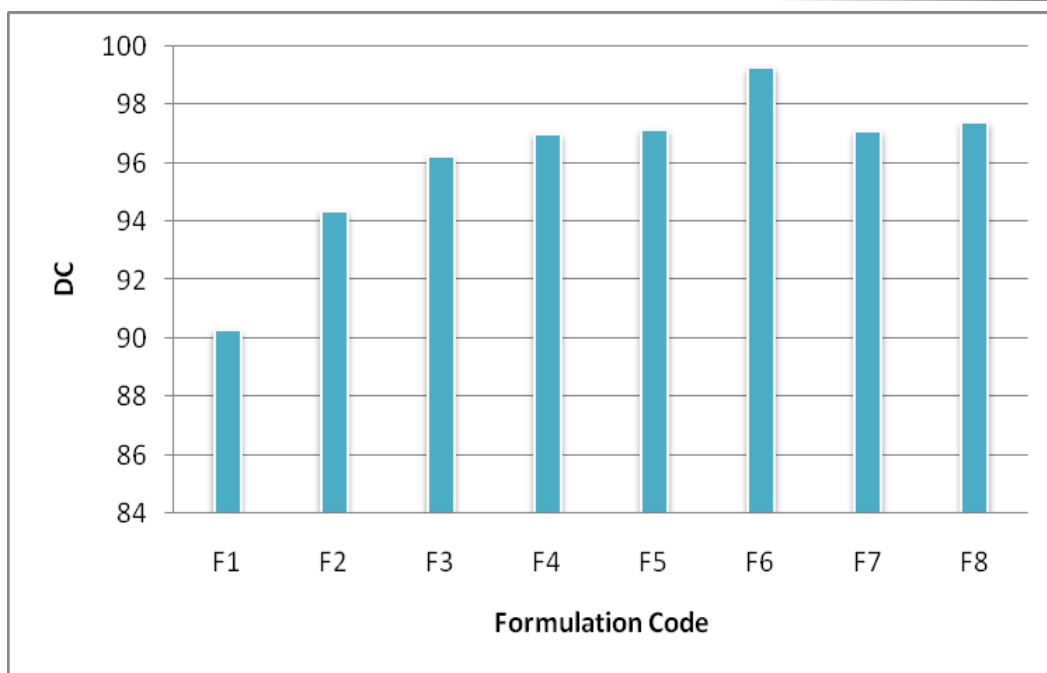


Figure 1:- Drug content of formulation

Figure 2 depicts the drug release profile of the optimized PN-SEDDS F6 formulation (solid-S, liquid-L) in comparison to pure PN and marketed PN-diffused tablets. The formulation liquid PN-SEDDS (F6)-L was thought to have the fastest and complete drug release. The drug release from F6 reached more than 50% within 30 min and then attained a value of around 80% at 45 min and reached more than 90% by a time of 60 min. However, the drug release from liquid SEDDS (LSEDDS) is slightly higher than the solid SEDDS (S-SEDDS) formulation. The S-SEDDS have slightly delayed release compared to L-SEDDS because S-SEDDS needed more steps such as desorption of adsorbed SEDDS from the Neusilin US2 during the dissolution process. Formulation F6 SEDDS has the fastest release due to its small globule size and low PDI. PN's solubility was significantly improved by the selected oil, surfactant, and cosurfactant. Hence, SEDDS F6 is expected to quickly dissolve PN in the GI fluid after taking it, making it easier to absorb via oral delivery.

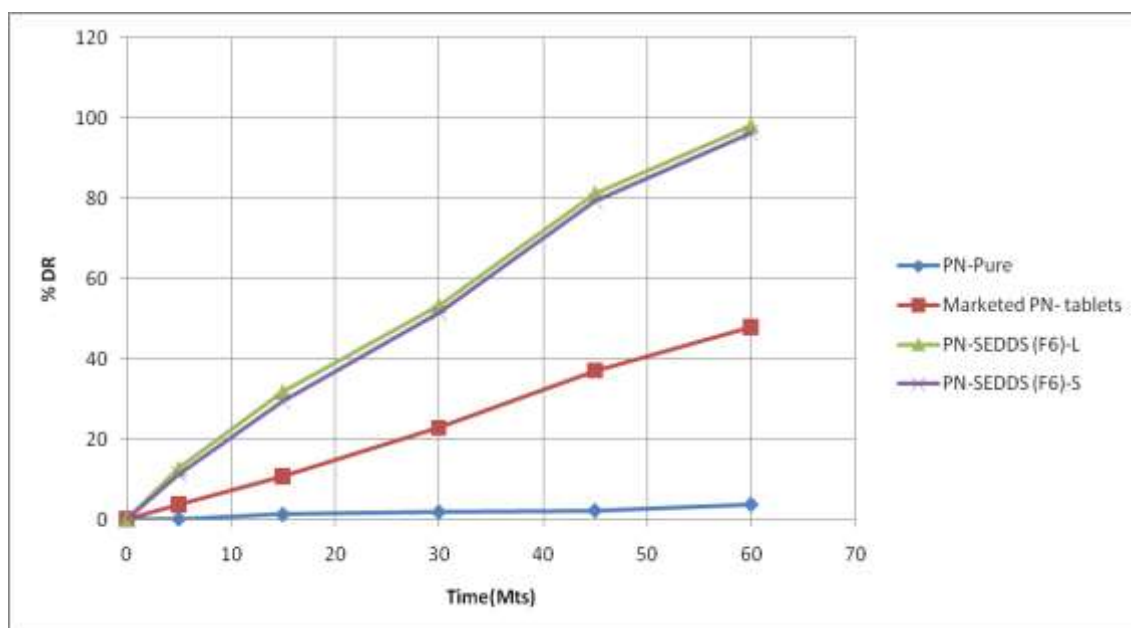


Figure 2:- Drug release profile of the optimized formulation PN-SEDDS (F6)-L and PN-SEDDS (F6)-S in comparison to the drug PN and marketed PN-diffused tablets

Generally, SMEDDS formulations are put into hard gelatin capsules as the final dosage form. However, liquid-filled hard

gelatin capsules are susceptible to leakage, and the entire system has a very limited shelf life owing to its liquid characteristics and the possibility of precipitation of the drug from the system. Thus, the developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. Table gives the results of the evaluation test conducted on stability samples. The formulation was found to be stable for 3 months. There was no significant change in the drug content, or particle size of the resultant emulsion. It was also seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. Furthermore, the formulation was found to show no phase separation, drug precipitation, or capsule leaks. Thus, these studies confirmed the stability of the developed formulation and its compatibility with hard gelatin capsules (Table 2).

Table 2:- Stability studies of PN-SMEDS formulation (F6)

Parameters	Storage (Temperature 40°C & RH 75%)			
	0 Day	30 Days	60 Days	90 Days
Particle size (nm)	98.82	97.23	97.11	97.06
PDI (mV)	0.20	0.17	0.16	0.16
Drug Content (%)	99.27	99.08	98.87	98.26
Dispersion Time (m)	<1	<1	<1	<1
% Drug Release	98.26	97.76	97.10	97.04

4. CONCLUSION:-

SEDDS, one of the novel emulsion formulations, is a viable method for creating PN. With further advancements in this technology, SEDDS have been demonstrated to significantly increase oral bioavailability, enabling the oral delivery of water-insoluble medications such as PN. When compared to all other SEDDS formulations and the pure form of the drug, these current results showed that SEDDS were successfully developed with an increased solubility and increased dissolution rate of a poorly water-soluble drug, PN. The stability of the new formulation is confirmed by the results of the thermodynamic stability investigations. With better solubility and drug release, the study thus validates that SEDDS of PN might be utilized as a potential substitute drug delivery method for conventional oral formulations of PN.

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