



KETOCONAZOLE LOADED SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM: FORMULATION AND IN-VITRO CHARACTERIZATION

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ABSTRACT

To enhance the solubility and bioavailability of poorly water soluble drug ketoconazole, self – emulsifying drug delivery system (SEDDS) composed of oil, surfactant and co-surfactant for oral administration of ketoconazole was formulated. The solubility of ketoconazole was determined in various oils and surfactants. The formulations were prepared using oil (IPM), surfactant (Tween-80) and co-surfactant (PEG-400). The formulation composed of 4% amount of oil and surfactant: co-surfactant ratio (4:1) was considered as optimized formulation as it shows the maximum microemulsion zone when observed in ternary phase diagram. The liquid SEDDS formulation was characterized by dilution test and percentage transmittance. The optimized liquid SEDDS formulation was converted into solid SEDDS by using lactose as an adsorbent. The solid SEDDS formulation was characterized by Percentage yield, drug content, drug entrapment efficiency, particle size analysis, zeta potential, in- vitro drug release and release kinetics, stability studies as per ICH guidelines and SEM study. Uniform particle size was observed and found to be 62.69 nm. Percentage release was found maximum compare to pure drug within 180 min. Optimized formulation shows maximum stability at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / 60 % RH \pm 5 % RH as compared to various storage conditions. From SEM study, spherical shape was confirmed. Thus, it could be concluded that this emulsifying drug delivery system may be an effective oral dosage form for improving oral bioavailability of lipophilic drug.

Keywords: Ketoconazole; Solubility; SEDDS, Adsorbent; Solid SEDDS.

INTRODUCTION

While developing solid oral formulation it is essential to avail drug in soluble form at site of action for its absorption. If drug has low aqueous solubility, dissolution rate may subject to rate limiting step in absorption process. In a pharmaceutical system, if aqueous solubility in 250 ml at pH 1-7.5 is less than its total dose considered as a lower solubility. Solubility of active pharmaceutical ingredients (API) has always been a concern for formulators, since inadequate aqueous solubility may lead to development of parenteral products and limit use of oral products. Solubility plays an important role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, is the product of permeability and solubility. Poor solubility has been

identified as the cause of numerous drug development failures. For drug that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs. Consequently, great efforts have been made to improve oral bioavailability of poorly water soluble drug by increasing their dissolution rate through various techniques^[1, 2].

Lipid-based formulations are well known approach to enhance water solubility and oral bioavailability particularly, the self-microemulsifying drug delivery system (SEDDS). SEDDS formulations are isotropic mixtures of an oil, a surfactant, a co-surfactant (or cosolvents), and a drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsion under gentle agitation following dilution by aqueous phases. This spontaneous formation of an emulsion in the GI tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption^[3, 4]. Further, the presence of oily phase in the formulation helps to improve bioavailability by influencing the drug absorption. SEDDS are generally encapsulated either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell^[5]. To overcome this problem SEDDS need to convert into Solid SEDDS. Numerous reports states that, the major techniques for converting SEDDS to S-SEDDS are spray cooling, spray drying, adsorption onto solid carriers, melt granulation, melt extrusion, super-critical fluid based methods and high pressure homogenization. But adsorption process is simple and involves simply addition of the liquid formulation to solid carriers by mixing in a blender^[5, 6].

Ketoconazole (KTZ) is chemically 1-[4-(4-{[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]ethan-1-one, a broad spectrum antifungal agent active against a wide variety of fungi and yeasts. It is readily but incompletely absorbed after oral dosing and is highly variable due to its poor water solubility leading to shorter half-life i.e. 2 h of the drug. Topically it is used in the treatment of candidal or tinea infections of the skin^[7].

The purpose of the present research work was to develop and evaluate on optimal solid SEDDS formulation of slightly water soluble drug, Ketoconazole to enhance the solubility.

MATERIALS AND METHODS

Materials

The following substances were used for the solid SEDDS preparations:

Ketoconazole was the drug of choice. Isopropyl Myristate (IPM) as an Oil phase, Tween 80 as surfactant and PEG 400 as a co-surfactant, Lactose as an adsorbent. All other chemicals were of AR grade.

Methods

Determination of saturation solubility of ketoconazole in different systems

The solubility of ketoconazole in various oil phases, surfactants, co-surfactants was determined by dissolving an excess amount of drug in 2 ml of each selected individual oils, surfactants and co-surfactants contained in stoppered vials (5 ml capacity) separately. The liquids were mixed using a vortex mixer and the vials were then shaken using orbital shaker at $37^{\circ}\text{C}\pm 1^{\circ}\text{C}$ for 72 h to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged (3000 rpm) for 15 min. The supernatants were taken out and filtered through a membrane. The concentration of ketoconazole in various phases was determined by UV spectroscopy (Shimadzu 1800) at their respective λ_{max} ^[4-8].

Construction of ternary phase diagram

Pseudo-ternary phase diagrams were prepared by CHEMIX software. In order to construct the phase diagram, ratios of surfactant and co-surfactant were selected. In present study, five different ratios of surfactant (Tween-80) to co-surfactant (PEG-400) were studied; i.e. 1:1, 2:1, 3:1, 4:1 and 5:1. These mixtures (S/Cos) were mixed with the oil phase to give the weight ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. This mixture was mixed thoroughly on a magnetic stirrer and was titrated drop wise against distilled water till the clarity of the system persists in order to determine the maximum water uptake. The tendency to emulsify spontaneously and also the progress of emulsion droplets were observed. The tendency to form an emulsion was judged as 'good' when droplets spread easily in water and formed a clear emulsion^[9-11].

Optimization of formulation

From pseudo ternary phase diagram study, the microemulsion existence area was identified with the relevant amount of oil and ratio of surfactant: co-surfactant (Smix). For optimization of formulation, a series of drug loaded microemulsion formulations were prepared. In first step, formulations were prepared by changing the concentration of oil with constant Smix to optimize the oil concentration. Once the oil concentration was optimized, concentration of Smix was changed in the second step with constant oil. Finally oil and Smix concentration was optimized. During optimization, parameters like % Transmittance and physical stability through dilution test were evaluated. This procedure was carried out for formulations with different Smix^[10].

Preparation of liquid SEDDS formulations

The formulations were prepared by dissolving the formulation amount of ketoconazole (0.1g) in the mixture of oil, surfactant, and co-surfactant at 37 °C. The mixture was homogenized with stirring. The blends were mixed titrated drop wise with water thoroughly using magnetic stirrer until a clear solution was obtained. The final drug content of the liquid SEDDS was 1% w/w ratio^[12].

Preparation of solid SEDDS Adsorption Method

The liquid SEDDS of ketoconazole was adsorbed onto lactose carrier at 1:1, 2:1, 1:2 ratio by physical mixing in a small mortar and pestle. The resulting solid SEDDS was uniformly homogenized to ensure that the mixture was uniformly distributed. The damp mass was passed through sieve No.120 and was dried at ambient temperature^[3, 13].

Characterization of liquid SEDDS

Dilution test

If the continuous phase is added in microemulsion, it will not crack or separate into phases. Maximum amount of water and oil were added to o/w and w/o formulations respectively and then inspected visually for clarity and phase separation. Here 50 and 100 times aqueous dilution of the formulation were visually checked for phase separation and clarity. Results were taken in triplicate and the average was taken in to consideration^[11].

Percentage transmittance measurement

Microemulsion formulation was diluted 50 and 100 times with distilled water. The percent transmittance of various formulations was measured at 630 nm using UV-VIS

spectrophotometer against distilled water as a blank. Results were taken in triplicate and the average was taken in to consideration^[11].

Characterization of Solid-SEDDS

Percentage yield

The prepared solid SEDDS was weighed to get the yield of the SEDDS formulated batch. Following equation was used to calculate the percentage yield:

$$\text{Percentage Yield} = \frac{W1}{W2+W3} \times 100$$

Where W1 is the weight of Solid SEDDS formulated (g),

W2 is the weight of drug added (g) and W3 is the weight of lactose (g)^[14].

Droplet size analysis

Solid SEDDS were diluted to 100 ml with distilled water. The droplet size distributions and polydispersibility index of the resultant microemulsions were determined using particle size analyzer (Malvern Zetasizer nanoZSP, Malvern Instrument Limited, USA)^[3, 15, 16].

Zeta potential

The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SEDDS formulation was measured using a Malvern Zetasizer nanoZSP, Malvern Instrument Limited, USA. The SEDDS were diluted with a ratio of 1:20 v/v with distilled water and mixed for 1 min using a magnetic stirrer^{[17][18]}.

Drug content of solid SEDDS

A 0.1g quantity of the solid SEDDS was placed in a 100 ml volumetric flask. The flask was made up to volume with distilled water and allowed to equilibrate for 24h at 40 °C with intermittent shaking in a thermostat water bath. The solution was thereafter cooled at room temperature, filtered through a filter paper and analyzed spectrophotometrically at the predetermined wavelength of 249 nm using UV/Vis double beam spectrophotometer (UV-1800, Shimadzu Corporation, Japan). This was repeated three times^[14].

Self-emulsification time

The self-emulsification time was determined by using USP dissolution apparatus I at 100 rpm, where 0.5 g of solid SEDDS formulations was added into two different basket containing 250 ml of 0.1N HCL and 250 ml of phosphate buffer 6.8 respectively. The

time for emulsification at room temperature is indicated as self-emulsification time for the formulation^[18].

Drug entrapment efficiency

The quantities of the drugs theoretically contained in the solid SEDDS were compared with the quantity actually obtained from the drug content studies i.e. the quantity loaded into the SEDDS formulated, to get the drug entrapment efficiency. Then it is calculated in terms of percentage.

$$EE (\%) = \frac{ADC}{TDC} \times 100$$

Where ADC is the actual drug content and TDC is the theoretical drug content^[14].

***In-vitro* drug release studies from solid SEDDS**

Drug release studies from solid SEDDS were performed using USP XXIV, dissolution apparatus I with 900 ml of phosphate buffer pH 6.8 as a dissolution medium at 37 ± 0.5 °C. The speed of the paddle was adjusted to 100 rpm. Ketoconazole loaded solid SEDDS (equivalent to 5 mg of drug was filled in hard gelatin capsule shell) and 5 mg of powder ketoconazole (pure drug) were placed separately in hard gelatin capsule and then in a dissolution test apparatus. At predetermined time intervals an aliquot (5 ml) of the sample collected, filtered and analyzed for the content of ketoconazole by USP dissolution medium. An equivalent volume (5 ml) of fresh dissolution medium was added to compensate for the loss due to sampling^[12].

Stability study

Solid SEDDS was tested for stability studies for three different storage conditions as per ICH guideline and was divided into 2 sample sets (in open and closed container) and stored at $25 \text{ }^{\circ}\text{C} \pm 2 \text{ }^{\circ}\text{C}/60\% \pm 5\% \text{ RH}$, $30 \text{ }^{\circ}\text{C} \pm 2 \text{ }^{\circ}\text{C}/65\% \pm 5\% \text{ RH}$ and $40 \text{ }^{\circ}\text{C} \pm 2 \text{ }^{\circ}\text{C}/75\% \pm 5\% \text{ RH}$ for 60 days. Solid SEDDS was evaluated for drug release study at each temperature at each 20 days of intervals of storage.

Scanning electron microscopy

The surface morphology of solid SEDDS of ketoconazole was determined using analytical electron microscope (JEOL-JSM-AS430, Japan). The sample was lightly sprinkled on double adhesive tape stuck on Aluminum stub. The stubs were then coated with platinum to a thickness of above 10°A under an Argon atmosphere using a Gold

sputter module under a high vacuum evaporator and the stub containing coated sample was placed in scanning electron microscope chamber^[12].

RESULTS AND DISCUSSION

Saturation solubility evaluation of ketoconazole

Oils can solubilize the lipophilic drug and is the most important excipients as it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Amongst the individual oil phases the saturation solubility of ketoconazole in oleic acid was far superior as compared to other oils and esters followed by IPM (figure 1).

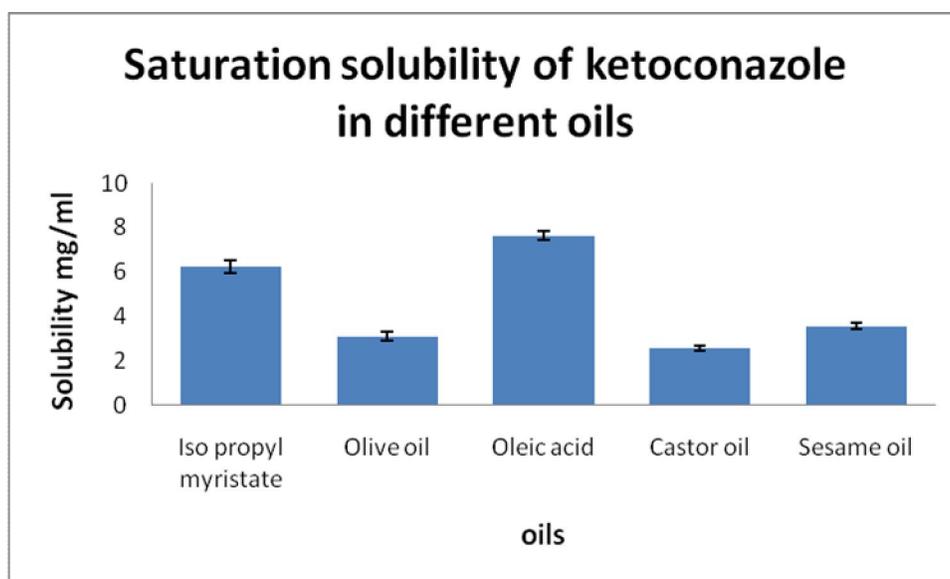


Figure 1: Saturation solubility profile of ketoconazole in different oils

Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. They form a layer around the emulsion droplets and reduce the interfacial energy as well as providing a mechanical barrier to coalescence. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules. Mostly, Non-ionic surfactants are used as they are known to be less toxic and less affected by pH and ionic strength compared to ionic surface-active agents. Amongst the surfactants the saturation solubility of ketoconazole in tween -80 was far superior then other surfactants (figure 2).

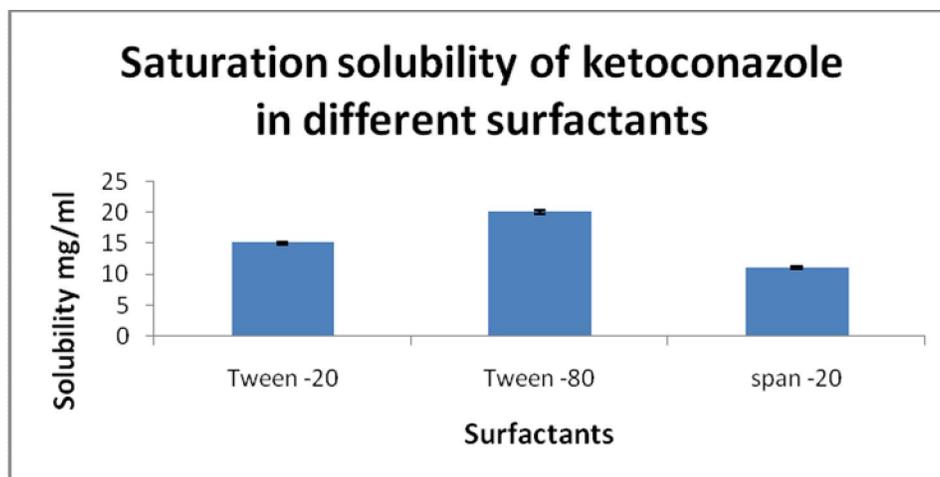


Figure 2: Saturation solubility profile of ketoconazole in different surfactants

The co-surfactant along with the surfactant, lower the interfacial tension to a very small, even transient negative value. They will be beneficial to form microemulsion at a proper concentration range. However, excessive amount of co-surfactant will cause the system to become less stable for its intrinsic high aqueous solubility and lead to increase in droplet size. Amongst the co-surfactants, the saturation solubility of ketoconazole in PEG 400 was far superior to other co-surfactants (figure 3).

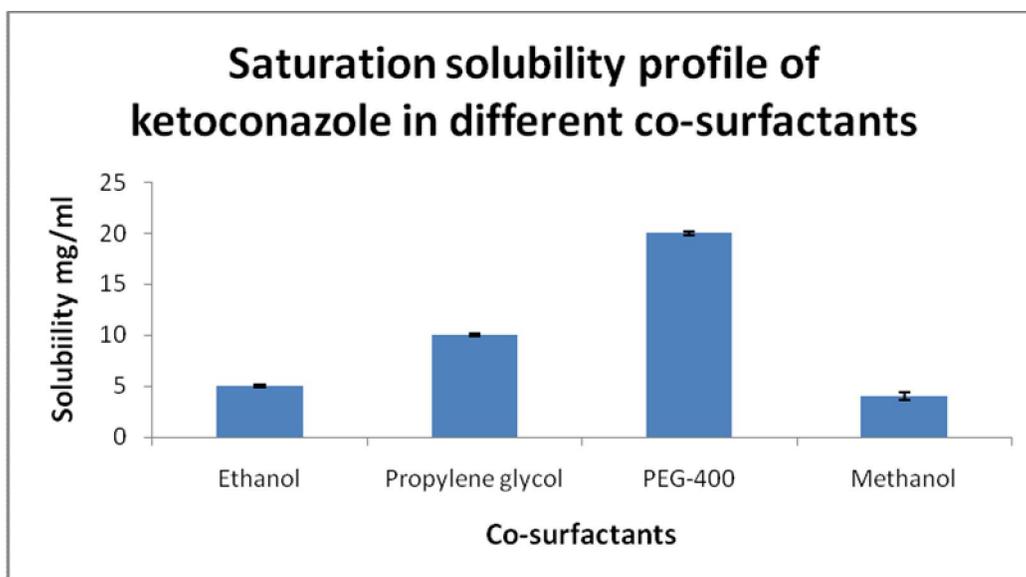


Figure 3: Saturation solubility of ketoconazole in different co-surfactants

From the above solubility study, it can be concluded that IPM (oil), tween -80(surfactant) and PEG 400 (co-surfactant) are suitable for the drug ketoconazole.

Pseudo ternary phase diagrams with varying proportion of Smix with oils

The SEDDS has an important characteristic of drug precipitation on dilution with water due to loss of solvent capacity. Selection of oil and surfactant and the mixing ratio of oil and other components plays an important role in the formulation of SEDDS. Therefore the phase behavior of each SEDDS needs to be carefully studied using the phase diagram constructed by using CHEMIX software as a guide (Figure 4). The microemulsion phase was identified as the area where clear and transparent formulations were obtained on dilutions based on visual inspection of samples. Phase diagram also helped to establish the study of micro emulsifying capacity and effect of drug on phase structure. It was found that the surfactant: co-surfactant ratio in 4:1 shows the maximum microemulsion zone. Hence, 4:1 surfactant: co-surfactant ratio was selected for the formulation. It was observed that increasing the concentration of the surfactant with respect to co-surfactant in SEDDS formulation decreased the spontaneity of the self-emulsification region. Therefore, much higher concentration of surfactant lowers the self-emulsifying region in phase diagrams (figure 4 - 8).

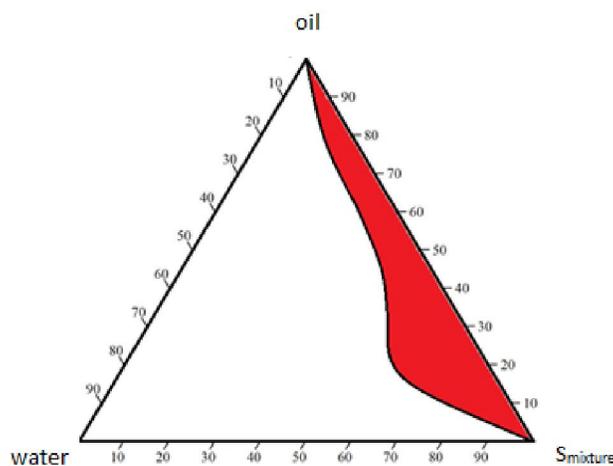


Figure 4: Ternary phase diagram of surfactant: Co-surfactant (1:1)

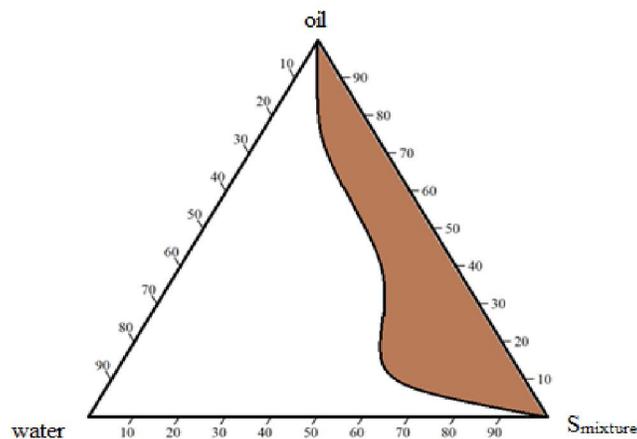


Figure 5: Ternary phase diagram of surfactant: Co-surfactant (2:1)

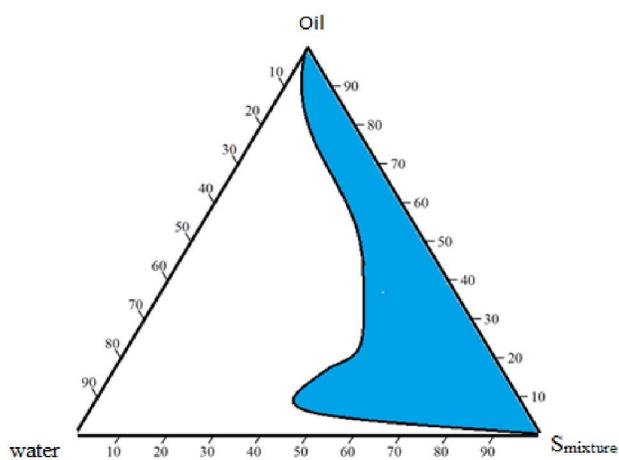


Figure 6: Ternary phase diagram of surfactant: Co-surfactant (3:1)

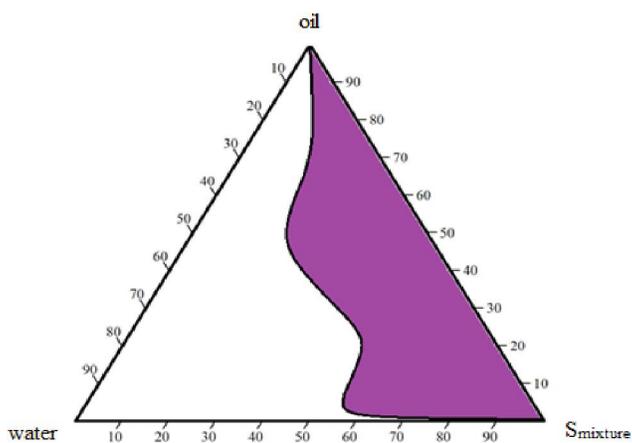


Figure 7: ternary phase diagram of surfactant: Co-surfactant (4:1)

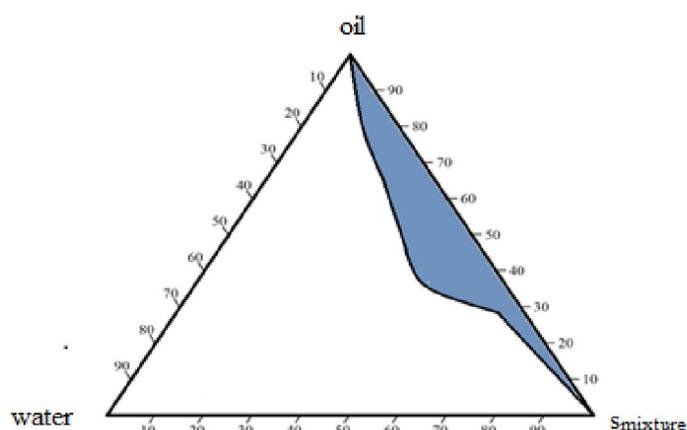


Figure 8: ternary phase diagram of surfactant: Co-surfactant (5: 1)

Optimization of formulation

For optimization of formulation, formulations were prepared by changing the concentration of oil with constant Smix to optimize the oil concentration. Here in present study, various concentrations of oils have been tried, i.e. 2, 4, 6 and 7 % v/v. Total 13 formulations were prepared and denoted as ME 1 to ME 13. Amongst all used concentrations, the percentage transmittance was in the range of 97.4 ± 0.2 to 99.7 ± 0.1 . The maximum transmittance was obtained for the batch ME 7 containing 4 % v/v oil concentration in the formulation indicates the maximum clarity of the formulation. When concentration was increased further from 4 %v/v, turbidity was obtained leads to zero transmittance. From the data, ME 7 was found as an optimized formulation for oil and Smix concentration (table 1).

Table 1: Drug loaded microemulsion formulation

Batch No.	Oil (%)	Smix (%)	Water (%)	%Transmittance
ME 1	2.0	20	78.0	$98.5 \pm 0.3\%$
ME 2	2.0	25	73.0	$97.4 \pm 0.2\%$
ME 3	2.0	30	68.0	$98.4 \pm 0.2\%$
ME 4	2.0	35	63.0	$99.0 \pm 0.1\%$
ME 5	2.0	40	58.0	**
ME 6	2.0	45	53.0	$98.8 \pm 0.2\%$
ME 7	4.0	40	56.0	$99.7 \pm 0.1\%$
ME 8	4.0	45	51.0	$99.2 \pm 0.2\%$
ME 9	6.0	20	74.0	**

ME 10	6.0	25	71.0	**
ME 11	7.0	30	66.0	**
ME 12	7.0	35	61.0	**
ME 13	7.0	40	56.0	**

Where, n = 3. ** = shows turbidity of formulation

Characterization of Liquid SEDDS

Batch ME 7 was when diluted to 50 to 100 times with aqueous phase produces no change in clarity and had not shown any phase separation. Hence it could be said that the developed formulation was o/w type of microemulsion and addition of continuous phase will not affect the physical stability.

Characterization of solid SEDDS

Solid SEDDS formulations were prepared by adding lactose as an adsorbent in the liquid SEDDS formulation. From the study, it was observed that, 250 mg of lactose was required to convert the 1 ml of liquid SEDDS to solid SEDDS.

Solid SEDDS was subjected to characterization studies like percentage yield, drug content, self-emulsification time, drug entrapment efficiency (table 2).

Table 2: Percentage yield, Drug content, Entrapment efficiency

Batch	% yield	Drug content (mg)	Self-emulsification time		%Entrapment efficiency
			In 0.1 N HCl	In Phosphate Buffer pH 6.8	
ME-7	99.9 ± 0.132	0.996 ± 0.012	10 - 15 seconds	10 - 15 seconds	99.60 ± 0.0243

* n = 3

Drug content of the optimized SEDDS formulation batch ME7 for ratio 4:1 was found to be maximum i.e. 99.60 %. So, it was considered as optimized batch for further evaluation.

Solid SEDDS was also subjected to characterization studies like particle size determination, polydispersibility index and zeta potential (table 3),

Table 3: Particle size and Zeta potential of optimized formulation

Batch	Parameters	Result
ME7	Particle size (nm)	62.69 nm
	Zeta potential (mV)	-35.9 mV
	PDI	0.368

The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles have a large negative or positive zeta potential they will repel each other and there is dispersion stability. Zeta potential of the system was found to be -35.9, which was closer to the range -20 mV indicating the stable microemulsion (Figure 7).

***In – vitro* drug release study:**

The optimized formulation was subjected to *in – vitro* release study, the percentage release was found 94.91 ± 0.1 at the end of 180 min which was much higher than the percentage release observed for the pure drug (figure 9).

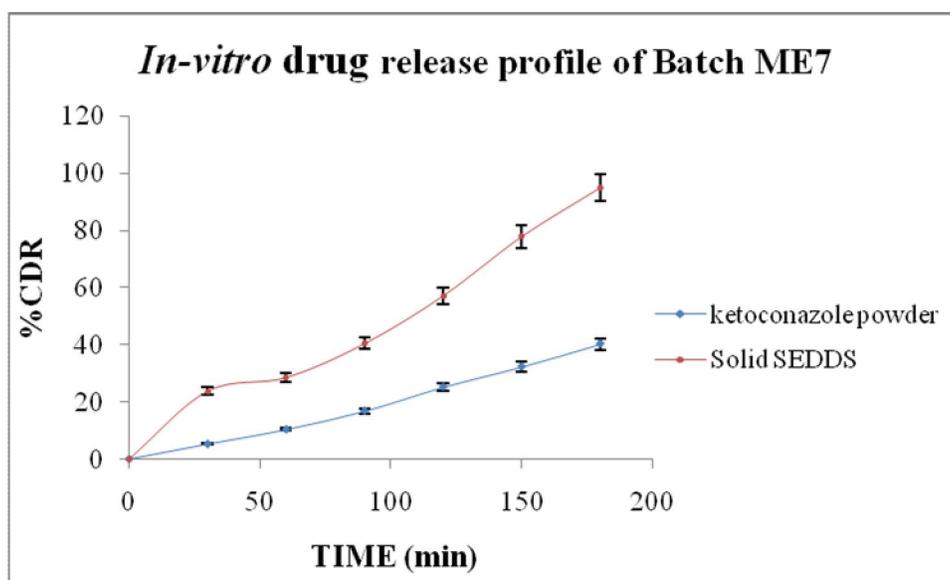


Figure 9: *In-vitro* drug release profile of ME7

The effective delivery of a drug from SEDDS is proposed to be governed primarily by small particle size and the polarity of the resulting oil droplets, which permits a faster rate of drug release into the aqueous phase. The solubilized drug may not precipitate in the lumen, and undergo rapid absorption which is independent of the lipid digestion process.

In – vitro studies were performed to compare the enhancement of solubility of ketoconazole with respect to pure drug. Thus, the optimized formulation ME7 indicated considerable enhancement of solubility of ketoconazole as compared to pure drug.

Stability study

The selected formulation was subjected to accelerated stability studies according to ICH guidelines by storing at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$, $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \pm 5\% \text{RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$ for 60 days. From the results, it was found that physical appearance, % drug content and in vitro release studies had shown that formulation was more stable at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ rather than $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \pm 5\% \text{RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$ storage conditions. So it can be said that product is most stable at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$.

Scanning electron microscopy

The SEM images of solid SEDDS showed well separated particles with no agglomeration (figure 10). Irregular shape and size of the solid SEDDS was observed.

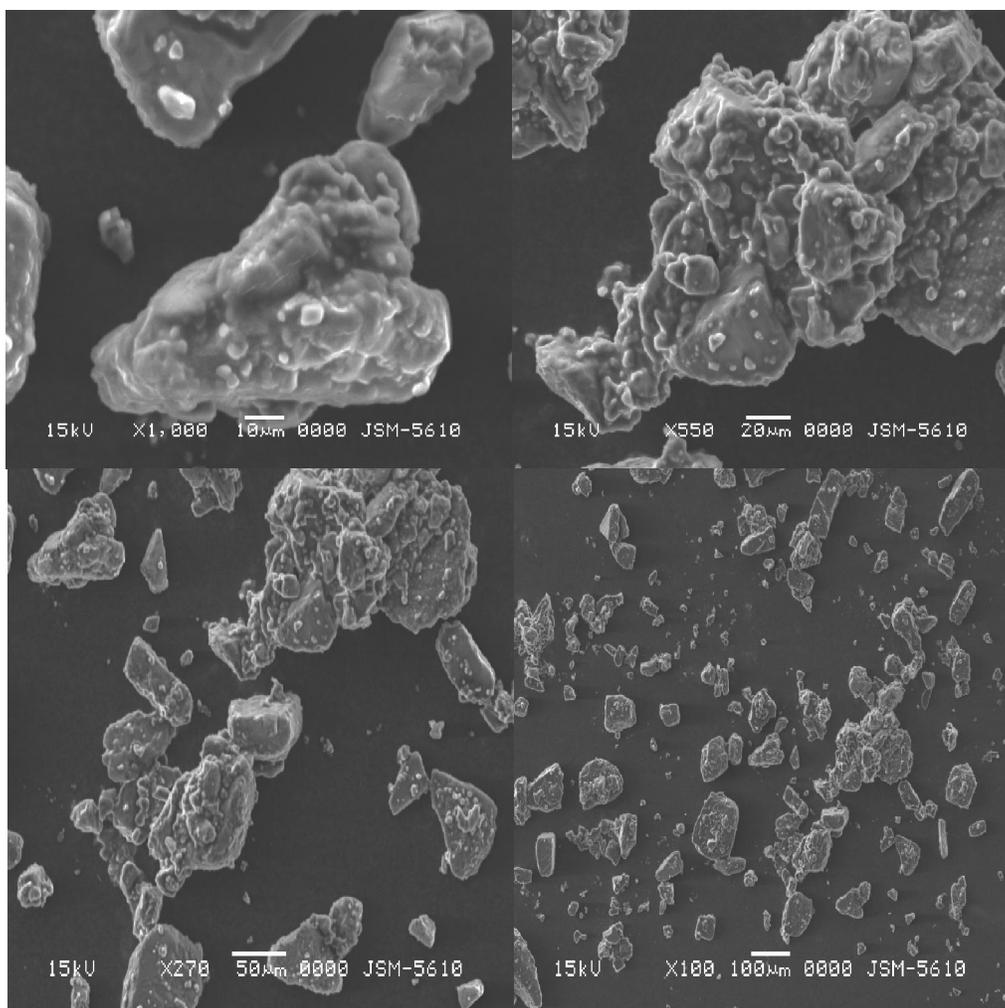


Figure 10: SEM images of solid SEDDS

CONCLUSION

Numerous studies have confirmed that Solid SEDDS improved solubility/dissolution, absorption and bioavailability of poorly water soluble drugs. In this study, the solid SEDDS of ketoconazole was prepared by adding lactose as an adsorbent in the liquid formulation.

The solid SEDDS consisted of well separated particles with smooth surface and preserved the self-emulsification performance of the liquid SEDDS. Both Particle size and zeta potential analysis suggested that ketoconazole in the solid SEDDS may be in the uniform size and shape. In Vitro release test showed that the solid SEDDS had a faster in vitro release rate than the powder. Thus, this solid self-emulsifying system may provide a useful oral solid dosage form for poorly water-soluble drug, ketoconazole.

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