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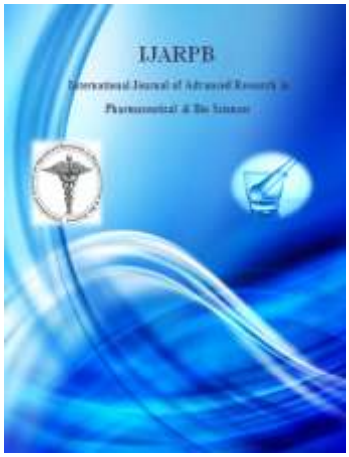
Micellar Solubilization of Poorly Water Soluble Drug Using Non Ionic Surfactant

Chauhan C S, Udawat H S *, Naruka P S, Chouhan N S, Meena M S.
Department of Pharmaceutics, Bhupal Noble's College of Pharmacy, Udaipur, 313001



Corresponding Author:

Harshvardhan Singh Udawat,
Department of Pharmaceutics, Bhupal Noble's College of Pharmacy, Udaipur, 313001
Mobile: 09413174956
Email:harshvardhansinghudawat@gmail.com

ABSTRACT

An important property of micelles with particular significance in pharmacy is their ability to increase the solubility of poorly soluble drug in water, this increase their bioavailability. The micellar soulibilization is a powerful alternative for dissolving hydrophobic drugs in aqueous environments. In this work, the soulibilization of ketoconazole was studied in micellar solutions of two surfactant, namely Tween 80 and Brij 35. The solubility of ketoconazole increased linearly with increasing surfactant concentration, as a consequence of the association between the drug and the micelles. Critical micelle concentration of the non ionic surfactant (Tween 80 and Brij 35) in aqueous solution was determined by iodine probe method.

KEY WORDS – ketoconazole, Critical micelle concentration, Tween 80, Brij 35.

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INTRODUCTION

Surfactants are known to play a vital role in many processes of interest in both fundamental and applied science. One important property of surfactants is the formation of colloidal-sized clusters in solutions, known as micelles, which have particular significance in pharmacy because of their ability to increase the solubility of sparingly soluble substances in water. Micelles are known to have an anisotropic water distribution within their structure. Consequently, the spatial position of a solubilized drug in a micelle will depend on its polarity: nonpolar molecules will be solubilized in the micellar core, and substances with inter-mediate polarity will be distributed along the surfactant molecules in certain intermediate positions[1].

Micellar systems can solubilize poorly soluble drugs and thus increase their bioavailability, they can stay in the body (blood) long enough to provide gradual accumulation in the required area, and their sizes permit them to accumulate in areas with leaky vasculature[2].

A surfactant, when present at low concentrations in a system, adsorbs onto surfaces or interfaces significantly changing the surface or interfacial free energy. Surfactants usually act to reduce the interfacial free energy, although there are occasions when they are used to increase it. When surfactant molecules are dissolved in water at concentrations above the critical micelle concentration (CMC), they form aggregates known as micelles. In a micelle, the hydrophobic tails flock to the interior in order to minimize their contact with water, and the hydrophilic heads remain on the outer surface in order to maximize their contact with water. The micellization process in water results from a delicate balance of intermolecular forces, including hydrophobic, steric, electrostatic, hydrogen bonding, and van der Waals interactions. The main attractive force results from the hydrophobic effect associated with the nonpolar surfactant tails, and the main opposing repulsive force results from steric interactions and electrostatic interactions between the surfactant polar heads. Whether micellization occurs and, if so, at what concentration of monomeric surfactant, depends on the balance of the forces promoting micellization and those opposing it[3]

Ketoconazole a poorly water soluble antifungal agent with superficial and systemic action that can be incorporated in to several pharmaceutical forms. It acts by binding to the fungal cytochrome P-450 dependent 14-α-demethylase enzyme, that is responsible for the demethylation of lanosterol to ergosterol. The ergosterol synthesis is therefore hindered, which results in damaged leaky fungal cell membrane.

In the present investigation non-ionic surfactant have been used to improve the solubility of the selected drug. The non-ionic surfactant have been considered in this work as they are more stable and less toxic as compared to cationic, anionic or ampholitic surfactant, also in this work an attempt has been made to investigation the locus of drug in the micelles of Brij-35 and Tween-80.

MATERIALS AND METHODS

Materials

Ketoconazole was obtained as a gift sample from Lincoln pharmaceuticals Ltd. Ahmedabad. Iodine, Potassium iodide and Brij- 35 were procured from Loba chem. Pvt. Ltd. Mumbai. Tween- 80 was purchased from S.D. Fine chemical Ltd. Mumbai. All the other chemicals and reagents were of analytical grade.

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Methods

Solubility studies and Dose/ Solubility ratio:

The solubility of ketoconazole was assessed in various dissolution media. Saturated solutions of drug were prepared in 0.1 N HCl, distilled water, phosphate buffer 6.8 and 7.4 in a close container at 37 ± 0.5˚C.Excess amount of drug was added to ensure saturation and solutions were equilibrated for 47 hours. The saturated solutions were filtered through Whatman filter paper No. 41. The concentration of drug was determined by UV visible spectrophotometer at 269 nm. The dose solubility ratio was also obtained because the drug ketoconazole is listed in class II in biopharmaceutical classification system (BCS). A dose solubility ratio (D:R) of less than 0.25 litters at all pH of interest indicates that dissolution would not limit drug absorption[4].

CMC determination by Iodine Probe method:

The CMC of both the non-ionic surfactant Tween-80 and Brij-35 was determined by iodine probe method. Iodine 2.6 gm and potassium iodide 3 gm was dissolved in 100 ml distilled water this solution was scanned from 200 to 400 nm to determined the wavelength of maximum absorption. The stock solution of iodine was diluted to obtained iodine solution having 80 % transmittance (T)[5].

A series of solution of both the surfactant were prepared by diluting with the iodine solution having 80 % transmittance (T). Solubilised I_2 prefers to participate in the hydrophobic micro environment of the surfactant system causing the conversion of I_3 to I_2 from the excess potassium iodide in the solution in order to maintain the saturated aqueous concentration of I_2. The absorption intensity of I_2 was plotted as a function at surfactants. The break point in the plot was taken as CMC of tween 80 and brij 35 surfactants. The experiment was carried out in triplet to check reproductively.

Determination of solubility descriptors of surfactants:

The solubility of ketoconazole was determined in both Tween-80: water and Brij-35: water solution. Tween-80 and Brij-35 were taken in the concentration range of 0.001M to 0.006 M (The concentration range chosen for both the surfactant was above their CMC). Excess amount at drug was added to each of the surfactant water mixture. The resulting mixture was gently agitated for 48 hours. After equilibrium the solutions were centrifuged and filter through Whatmen filter paper No. 41. The amount of drug solubilised was determined spectrophotometrically at 269 nm.

Molar solubilisation capacity (χ):

The molar solubilisation capacity (**χ**) is defined as the number of moles of solute that can be solubilised by one mole of micelle surfactant.

$$\chi = \frac{(S_{tot} - S_w)}{(C_{surf} - cmc)} \qquad (1)$$

Where

S_{tot} - total drug solubility
S_w - Solubility in water
C_{surf} - molar Concentration of surf
cmc - critical micelle concentration

Above CMC the surfactant monomer concentration is approximately equal to CMC. Therefore equation (1) can be written as-

$$\chi = \frac{S_{tot} - S_w}{C_{surf}} \quad (2)$$

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Equation (2) can be further rearranged in the form of equation of straight line (equation-3) with the slope of the line equal to **χ.**

$$S_{tot} = \chi \cdot C_{surf} - S_w \qquad (3)$$

The molar solubilisation capacity of each surfactant was determined from the plot of stot versus concentration of each surfactant used (Tween-80 and Brij-35). The value of *χ* was then obtained from equation- (3).

Micelle –water partition coefficient *(K_m):*

It is defined as the ratio of solute concentration in the micelle to the solute concentration in water for a particular concentration of surfactant.

$$K_m = \frac{S_{tot} - S_w}{S_w} \qquad (4)$$

According to equation (2) $S_{tot} - S_w = X \,.\, C_{surf}$
Substitute the value from equation (2) in equation (4) we get

$$K_m = \frac{\chi \cdot C_{surf}}{S_w} \qquad (5)$$

According to equation (5) when the *Km* is plotted as the function of C_{surf}, the idea of the amount of drug partition into micelle can be obtained.

Molar Micelle water partition coefficient *(K_m^n):*

In order to eliminate dependence of K_m on surfactant concentration, a molar micelle-water partition coefficient *(K_m^n)* corresponding to the partition coefficient when C_{surf} = *1M* can be defined as follows.

$$K_m^n = \frac{K_m}{S_w} \qquad (6)$$

RESULTS AND DISCUSSION

Solubility of Ketoconazole:

The solubility studies in different dissolution medium showed that ketoconazole has varying solubility in different medium (Table-1). The D/S ratio was found to be highest in water i.e. 14.28 litter, however the D/S ratio is smallest in 0.1N HCl (0.005 litter). But the D/S ratio was found > 0.250 litter in the intestinal pH 6.8 and pH 7.4 suggesting that drug would be poorly absorbed through intestine. To improve the drug solubility use of surfactants (Tween-80 and Brij-35) was done.

CMC determination:
Iodine-Probe Method:

In Iodine Probe Method, the formation of micelles was monitored by using iodine as a hydrophobic probe. As discussed previously I_2 refers to partition in the hydrophobic micro environment of the micelles. It was observed that as the concentration of Tween-80 and Brij-35 was increased respectively the amount of I_2 present in the solution also increased, as shown in the Fig. 1 and 3. When the absorption intensity of I_2 was plotted as function of the amount of surfactant concentration the absorbance was found to be increased linearly up to a certain concentration of surfactant after which a break point was observed. The CMC was determined as the intersection point between the two straight lines as shown in Fig. 2 and 4.
The CMC of Tween-80 and Brij-35 were found the 0.01337603 mM and 0.008947 mM receptively. The CMC of Brij-35 was found to be less than that of Tween-80. This suggests that the micelles of Brij-35 are expected to

show more *in vitro* and *in vivo* stability as compared to the micelles of Tween-80. Also the low CMC value of Brij-35 suggests that its micelles would be spontaneously formed. The difference in the CMC of both these surfactant can be attributed to their difference in polyoxyehtylene chain length[6].

Solubility descriptors of surfactants:

An important property of micelles that has particular significance in pharmacy is their ability to increase the solubility of sparingly soluble substance in water. From the thermodynamic point of view the micellisation can be considered as a normal partitioning of the drug between micelles and aqueous and the standard free energy of micellisation.

Molar solubilisation capacities (χ):

Molar solubilisation capacity of both the surfactant was calculated from the slope of phase solubility curve. The phase solubility profile of drug in presence of different micelles concentration of Tween-80 and Brij-35 is shown in Fig. 5 and 6. The correlation coefficient of linear relationship suggests that a liner relationship exist between the total drug solubilised and the molar concentration of each surfactant and also that the amount of drug solubilised increases with the increase in the concentration of each surfactant (Table 2 and 3). The molar solubilisation capacity of Tween-80 and Brij-35 were found to be 183 µg/mole and 100.11 µg/mole. This suggests that micelles of Tween-80 have a greater efficiency to solubilise the selected drug as compared to Brij-35.

Micelle water partition coefficient *(K_m):*

The amount of the hydrophobic drug partitioned into the micelle was found to increase as the micellar concentration of both of the surfactants was increased. Almost linearly relationship was observed between the amount of drug portioned into the micelles *(K_m)* and the molar concentration of each surfactant (Fig 7 and 8; Table 2 and 3). The rate of partitioning of drug into the micelles for Tween-80 and Brij-35 was found to be 18.3228×10^4 µg/mole and 10.1053×10^4 µg /mole. These data of ratio partitioning suggested that the partition of drug is favoured in the micelles of Tween-80 as compared to Brij-35. The standred free energy of solubilisation (ΔG_s^0) can be calculated by ($\Delta G^o s = RT \ln Ks$) .The standard free energy of solubilisation with Tween-80 and Brij-35 was negatives, indicating spontaneous solubilisation (Table-4). The lowest value was observed for Brij-35 micelles system confirming that the solubilisation process of negatively charged drug is energetically more favourable in non-ionic micellar system, due to electro static interaction.

Table: 1 Solubility of Ketoconazole

S.No.	Molar conc. of surfactant (Tween 80)	Drug solubility *(S_{tot})*	Micelle water partition coefficient *(K_m)*
1	0.002	0.026	12.80
2	0.003	0.273	179.32
3	0.004	0.435	321.75
4	0.005	0.611	487.25
5	0.006	0.772	640.12

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Table: 2 Drug solubility and Micelle water partition coefficient at different concentration of Tween-80

DISSOLUTION MEDIUM	SOLUBILITY (g/ml)	D/S (Litter)
Water	0.000014	14.280
pH 1.2	0.039040	0.005
pH 6.8	0.000372	0.537
pH 7.4	0.000460	0.434

Table: 3 Drug solubility and Micelle water partition coefficient at different concentration of Brij-35

S.No	Molar conc. of surfactant (Brij-35)	Drug solubility (S_{tot})	Micelle water partition coefficient(K_m)
1	0.001	0.0156	14.60
2	0.002	0.0568	55.81
3	0.003	0.1332	123.68
4	0.004	0.2650	264.02
5	0.005	0.3781	377.05
6	0.006	0.4972	495.96

Table: 4 Solubilisations and thermodynamic parameters

Surfactants	Solubilisations and thermodynamic parameters	
	Molar solubilization capacity (χ) (µg/ml)	ΔG_s^0=(kjmol-)
Tween 80	180.0	-9.035
Brij 35	101.5	-7.982

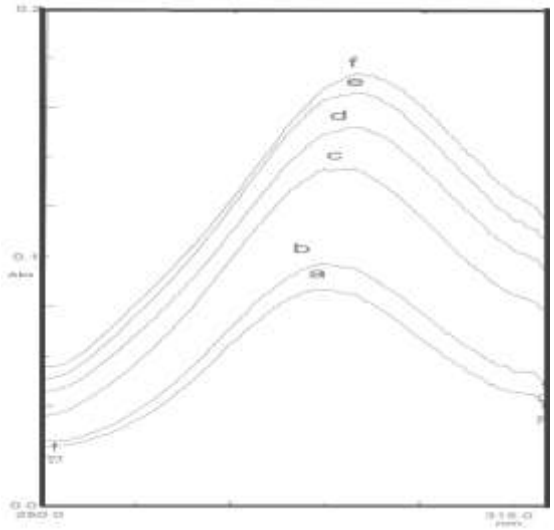

Fig: 1 U.V. Spectra of solubilised iodine (λ_{max}= 289.95) in tween 80 solution with different concentration. a = 0.0008 mM, b = 0.0009 mM, c = 0.001 mM, d = 0.0015 mM, e = 0.002 mM, f = 0.003 mM.

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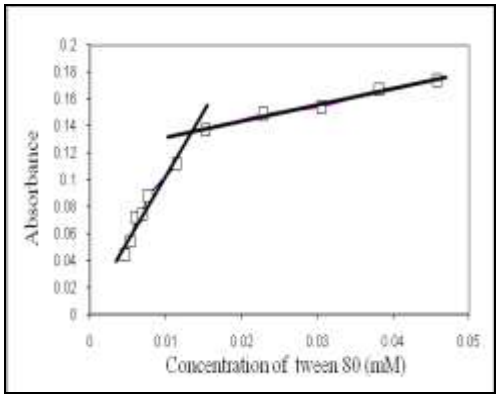

Fig: 2 CMC Determination of Tween 80

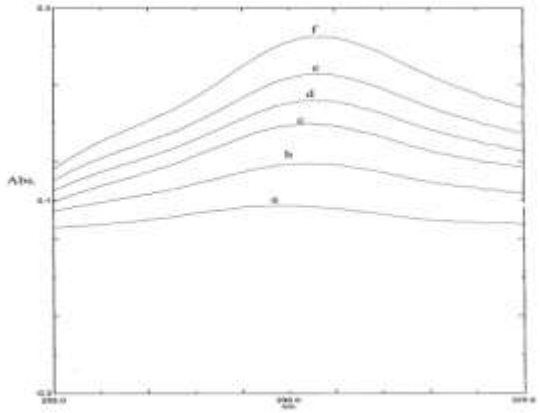

Fig: 3 U.V. Spectra of solubilised iodine (λ_{max}= 289.95) in brij 35 solution with different concentration. a = 0.0008 mM, b = 0.0009 mM, c = 0.001 mM, d = 0.0015 mM, e = 0.002 mM, f = 0.003 mM, g = 0.004 mM.

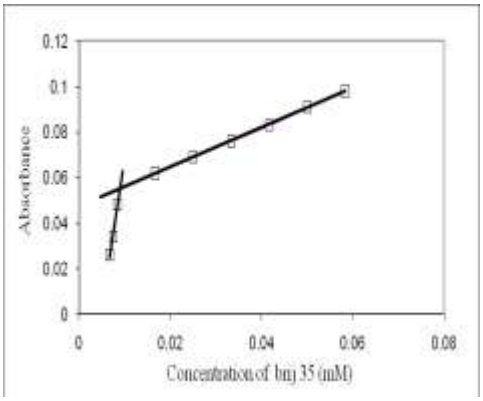

Fig: 4 CMC Determination of Brij 35

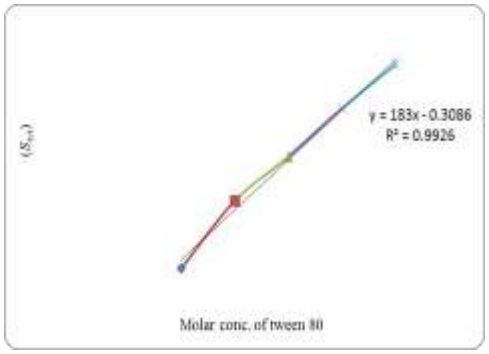

Fig: 5 Graph between the drug solubility verses molar concentration of tween 80

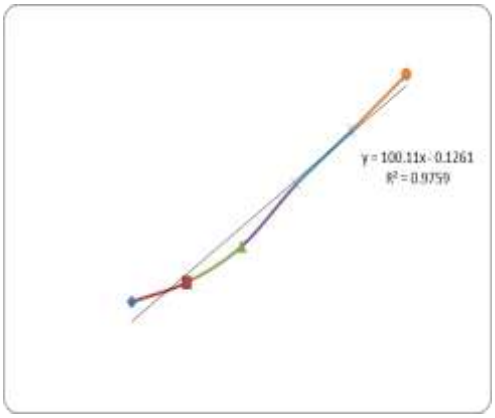

Fig: 6 Graph between the drug solubility verses molar concentration of brij 35

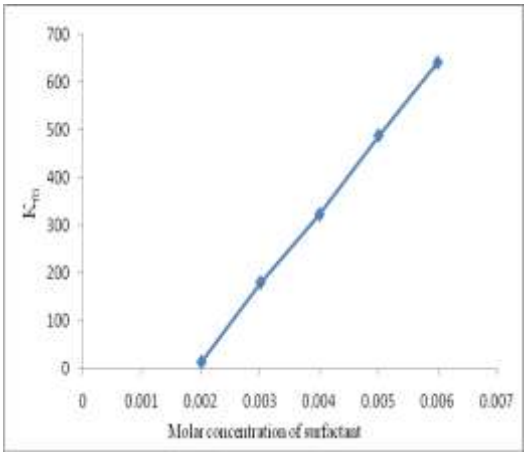

Fig: 7 Graph between the Micelle water partition coefficient *(K_m)* verses molar concentration of Tween 80.

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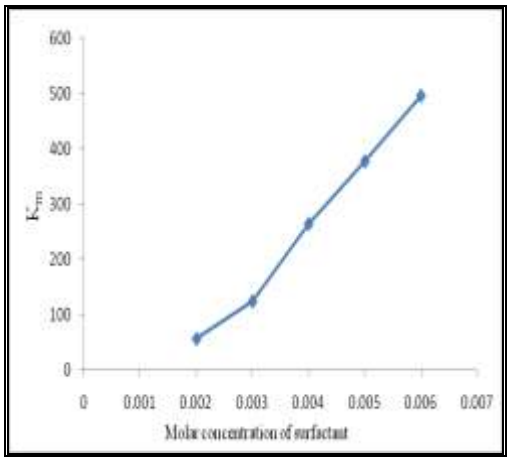

Fig: 8 Graph between the Micelle water partition coefficient (K_m) verses molar Concentration of Brij 35.

CONCLUSION

In this work, the influences of the surfactant head group on the extent of ketoconazole solbilization were investigated. The non-ionic surfactant (tween-80 & Brij-35) could be considered the best alternative for the solubilization of ketoconazole. This class of surfactants provide a reasonable molar solubilization capacity (**χ**) combined with the CMC value, resulting in increased solubility of ketoconazole.

The low CMC of Brij-35 suggested that the micelles would be formed spontaneously and is expected to show the more *in-vitro* and *in-vivo* stable as compared to Tween- 80. However the molar solubilization capacity (**χ**) of Tween-80 is higher as compared to Brij-35. This could be due to higher alkyl chain length of Tween-80 as compared to Brij-35. The molar solubilization capacity of the drug in surfactants also depends on its molecular characteristics. The negative value of free energy of solubilization for ketoconazole indicates spontaneous solubilization process by the both surfactants.

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