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Original research article

Micellar Solubilization of Some Poorly Water Soluble Steroids and Benzodiazepines Drugs and its Evaluation

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Abstract
Solubilizations of the poorly drugs soluble is one among the most important physicochemical characteristics for the drug development process as from the available drugs one-third of drugs are poorly water soluble or insoluble. Most of the approaches used to increase the solubility of poorly soluble drugs are used of many solvents, increase of main surface area by reduction of it size, salt form selection, change of crystal form, complex formation with the excipients as hydrophyllic polymers and change in preparation of solid dispersions
Keywords: DM,SDS, BCS, DTAB

Introduction

Micellar solubilization is one of the powerful alternative for increasing solubility by dissolving hydrophobic drug in aqueous medium[1,3]. Micelles play a vital role in various process to apply in both applied and fundamental sciences [4-6]. The simple miceller system solubilizes the poorly soluble drugs which increase it bioavailability.it can also be used as drug carriers for various drug delivery and targeting system. Micelles can also be called to have an anisotropic water distribution within their structure [7]. Other than this, water concentration decreases from the surface towards the core of the micelle, with a completely hydrophobic (water-excluded) core [8]. A partly, the abstraction position of the solubilized drugs in a very particle depend upon its nature of polarity: non-polarity molecules are going to be solubilized within the miceller core, and substances with intermediate polarity are going to be distributed on the wetter molecules in sure intermediate positions [9, 10]. Surfactants basically used as sodium dodecyl sulfate (SDS), Cationic dodecyl tri methyl ammonium bromide (DTAB), Nonionic dodecyl -D-maltoside (DM)used as excipients and are added into a formulation to make possibility of preparation, dosage form, patient acceptability also [11].

The drugs used in the present study belong to class II (poor solubility and high permeability) are 4 steroids (progesterone, testosterone, 17 beta hydroxyprogesterone 11 alpha hydroxyprogestrone), 4 benzodiazepines (diazepam, temazepam, oxazepam and α11 prazepam) of the biopharmaceutical classification system (BCS). Apartly, the studies on surfactant solubilization of a various range of drugs have not been reported yet. Along with this, to increase the solubility and improve the bioavailability of drugs, various studies shows that the uses of micelle as drug carriers shows acceptability that enhance permeability and also residence time in the system [12-16]. Many techniques such as UV. IR. NMR etc. had been employed to study the location of drug substances in difference micelle systems [17, 18]. In

this study, a thermodynamics based model was employed so as to evaluate the location of the drug and to provide quantitative partitioning information of the drug in different regions. In the present paper an attempt has been made to show the increase in solubility of eight drugs that are progesterone, testosterone, 17 beta hydroxyprogesterone 11 alpha hydroxyprogestrone, diazepam, temazepam, oxazepam and α11 prazepam, by using cationic, anionic and non-ionic surfactants.

Material and method

Material

All the drugs Progesterone (>99%), testosterone (-estradiol (β>98%), 17>98%), diazepam, temazepam, oxazepam, prazepam, sodium dodecyl sulfate (>99%), dodecyltrimethylammonium bromide (>99%) -D-maltoside (βand dodecyle >98%) were obtained from Sigma-Aldrich (St. Louis, MO). hydroxyprogesterone (α11>95%) was obtained from Janssen Chimica (New Brunswick, NJ).

Solubility measurements in aqueous solutions

By using conventional shake-flask method the solubility of all model drugs in aqueous solutions in the presence and absence of surfactant was measured: An excess amount of drugs was placed into aqueous solution with known concentration of surfactants and the system was rotated for 3 to 5 days at room temperature (24±1^{o}C) to reach equilibrium and hydrophilic PTFE filter (Millipore Inc.) Solutions were filtered using 0.2 filtrates were diluted appropriately and assayed for drug concentration determinations by reverse phase HPLC methods.

Solubility determination in hydrocarbon solutions:

As a model hydrocarbon medium Dodecane was used. The solubility was measured by using conventional shake –flask method. The unused amount of drugs was kept into the dodecane and for 3-5 days it is rotated at room temp to reach equilibrium. PTFE filter was used to filter solution and filtrate is diluted to estimate the drug conc. By normal phase HPLC method.

Micelle/water partitioning coefficient determinations

In a micelle-containing solution, drugs are dissolved both in the aqueous phase and in the micelle solutions and estimated.

Water/ Hydrocarbon partitioning coefficient determination

The direct partition method were employed for determination

Direct partitioning coefficient determination

The measured amount of drug was placed into 1:1 (v/v) mixture of dodecane and water. The system was rotated for 2 days and all the solid material was dissolved. The drug concentrations in aqueous solutions and dodecane solutions were analyzed using reverse phase HPLC and normal phase HPLC methods respectively.

HPLC methods

Waters HPLC system including 717 plus auto-sampler, 610 pump and 486 UV detector was employed in the reverse phase experiments. Waters LCMod1 HPLC system was employed to run the normal phase measurements. SRI Peak Simple V3.21 software was utilized to analyze the collected chromatograms. Column and samples were all held at room temperature

(24±1oC). All mobile phases were pre-mixed and degassed before use. The assay protocols used in reverse phase and normal phase HPLC for all model drugs. All the assays were validated for precision and linearity test by standard protocols. The measured drug concentrations were all within the linear range of the respective calibration curves. The majority of the chromatograms the peaks of the interested compounds exhibit symmetric shapes. Only the normal phase HPLC assays for temazepam and oxazepam result in significant tailing. These assays were not optimized in terms of the peak shape because there was only one interested compound and no peak overlaps from other components as seen.

Result and Discussion

Solubility measurements in aqueous solution:

The aqueous solubility of all model drugs steroids, benzodiazepines and parabens are shown in Tables 1 to 3. In all, the aqueous solubility results were in good agreement. The least soluble was 17- β estradiol.

The solubility results in dodecane for the three solute sets are also shown in Tables 1-2. For progesterone, testosterone, diazepam, prazepam solubility in dodecane is greater than in water. The data in Tables 1-2 clearly show that in all cases micelle/water partitioning coefficients, Km/w, are much larger than hydrocarbon/water partitioning coefficients, $K_{h/w}$. In most cases, Km/w is at least 2 orders of magnitude larger than $K_{h/w}$, which suggests there is less than 1% of the solutes are exclusively solubilized in the micellar core. The closest agreement between $K_{h/w}$ and $K_{m/w}$ is when progesterone is solubilized in DM micelles with the ratio $K_{m/w}/K_{h/w}$=25. When the Laplace pressure effect is taken into account the differences between $K_{h/w}$ and $K_{m/w}$ are even greater.

Table 1: The aqueous solubility of selected steroid class of drug in three micelle systems

	Progesterone	**Testosterone**	**17β-estradiol**	**11α-hydroxyprogesterone**
$logP_{oct}$	3.75	3.34	3.81	2.50
Aqueous Solubility (M)	$(2.69\pm0.20)x10^{-5}$	$(8.54\pm0.27)x10^{-5}$	$(6.45\pm0.34)x10^{-6}$	$(1.94\pm0.10)x10^{-4}$
Solubility in dodecane (M)	$(8.94\pm0.49)x10^{-3}$	$(1.86\pm0.08)x10^{-3}$	$(7.8\pm1.9)x10^{-6}$	$(5.41\pm0.50)x10^{-5}$
$K_{h/w}$	$(3.59\pm0.20)x10^{3}$	45.3±2.1	9.21±0.8	3.41±0.41
κ (SDS)	0.274±0.007	0.251±0.008	0.0289±0.0004	0.0295±0.021
$K_{m/w}$ (SDS)	$(4.12\pm0.20)x10^{5}$	$(1.69\pm0.08)x10^{5}$	$(2.72\pm0.15)x10^{5}$	$(7.10\pm0.48)x10^{4}$
κ(DTAB)	0.089±0.005	0.074±0.005	0.051±0.0014	0.269±0.0023
$K_{m/w}$ (DTAB)	$(1.69\pm0.16)x10^{5}$	$(6.02\pm0.28)x10^{4}$	$(5.01\pm0.21)x10^{5}$	$(3.15\pm0.17)x10^{4}$
κ (DM)	0.0612±0.004	0.0451±0.0015	0.0229±0.0024	0.0369±0.0023
$K_{m/w}$ (DM)	$(9.69\pm0.20)x10^{4}$	$(3.84\pm0.110)x10^{4}$	$(2.04\pm0.27)x10^{4}$	$(1.89\pm0.14)x10^{4}$

Where $logP_{oct}$ is aqueous solubility, solubility in dodecane, hydrocarbon/water partitioning coefficient (Kh/w), solubilization capacity (κ), Anonic sodium dodecyl sulfate (SDS), Cationic dodecyltrimethylammonium bromide (DTAB) Nonionic dodecyl -D-maltoside (DM).

Table 2: The aqueous solubility of selected Diazepam (BCA class-II) drugs in three micelle systems

	Diazepam	**Temazepam**	**Oxazepam**	**Prazepam**

$logP_{oct}$	2.94	2.30	2.41	3.52
Aqueous Solubility (M)	$(1.69\pm0.20)x10^{-4}$	$(4.54\pm0.27)x10^{-4}$	$(6.45\pm0.34)x10^{-5}$	$(1.41\pm0.10)x10^{-5}$
Solubility in dodecane (M)	$(3.94\pm0.49)x10^{-3}$	$(4.86\pm0.08)x10^{-4}$	$(2.4.8\pm1.9)x10^{-7}$	$(4.41\pm0.50)x10^{-3}$
$K_{h/w}$	297±14	15.3±2.1	0.0421±0.024	$(3.59\pm0.20)x10^{3}$
κ (SDS)	0.374±0.015	0.475±0.017	0.241±0.004	0.162±0.008
$K_{m/w}$ (SDS)	$(7.12\pm0.20)x10^{4}$	$(3.69\pm0.08)x10^{4}$	$(1.72\pm0.15)x10^{5}$	$(3.10\pm0.48)x10^{5}$
κ(DTAB)	0.089±0.0018	0.174±0.005	0.051±0.0021	0.0269±0.0018
$K_{m/w}$ (DTAB)	$(2.67\pm0.16)x10^{4}$	$(1.02\pm0.28)x10^{4}$	$(4.01\pm0.21)x10^{4}$	$(6.55\pm0.17)x10^{4}$
κ (DM)	0.0654±0.0010	0.0551±0.0022	0.0291±0.0014	0.0269±0.0005
$K_{m/w}$ (DM)	$(1.69\pm0.20)x10^{4}$	$(7.84\pm0.20)x10^{3}$	$(1.04\pm0.20)x10^{4}$	$(5.89\pm0.20)x10^{4}$

Where $logP_{oct}$ is aqueous solubility, solubility in dodecane, hydrocarbon/water partitioning coefficient (Kh/w), solubilization capacity (κ), Anonic sodium dodecyl sulfate (SDS), Cationic dodecyltrimethylammonium bromide (DTAB) Nonionic dodecyl -D-maltoside (DM).

Micelle/Water partitioning coefficient determinations

The solubilization results of 8 model drugs in SDS, DTAB and DM surfactant systems at room temperature are shown in Figures 1- 6.

The solubilization profiles expected in the presence of surfactants were obtained: at low surfactant concentration the drug solubility was constant and equal to the aqueous solubility. At surfactant concentrations above the CMC (critical micelle concentration) the solubility increased linearly as a function of surfactant concentration.

From the solubilization profiles, two critical parameters could be extracted: the aqueous solubility and the solublization capacity by the slope of the ascending line. The micelle/water partitioning coefficient could be calculated from the solubilization capacity and aqueous solubility.

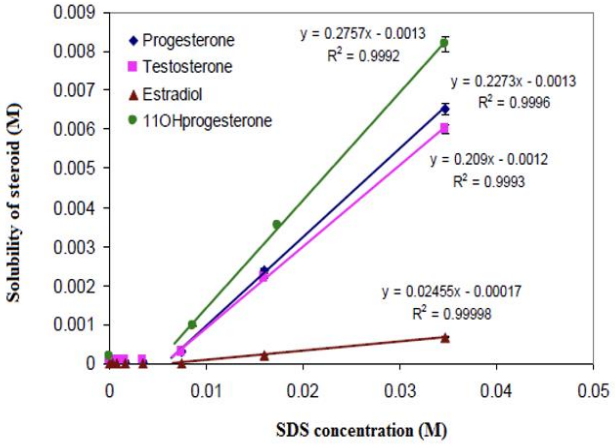

Figure 1: Solubility of selected steroid in Anionic sodium sulfate (SDS)

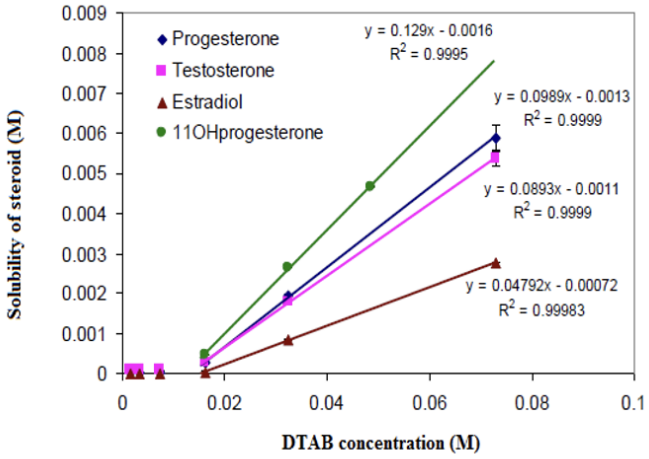

Figure 2: Solubility of selected steroid in cationic dodecyltrimethyl ammonium bromide (DTAB)

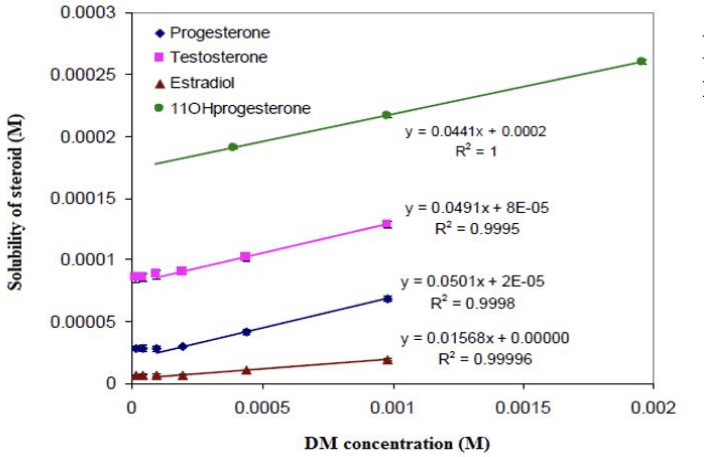

Figure 3: Solubility of selected steroid in non-ionic dodecyl D maltoside (DM)

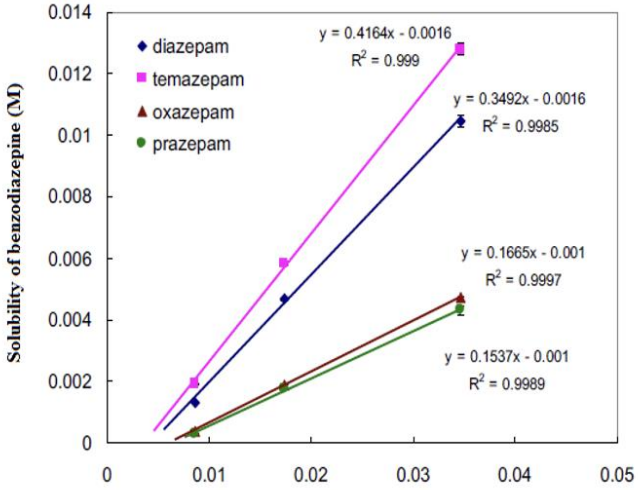

Figure 4: Solubility of selected benzodiazepines (BCA class-II) in anionic sodium sulfate (SDS)

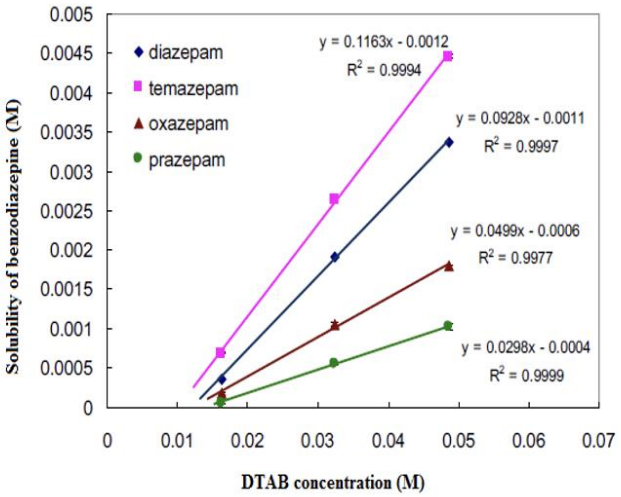

Figure 5: Solubility of selected benzodiazepines (BCA class-II) in cationic dodecyltrimethyl bromide (DTAB)

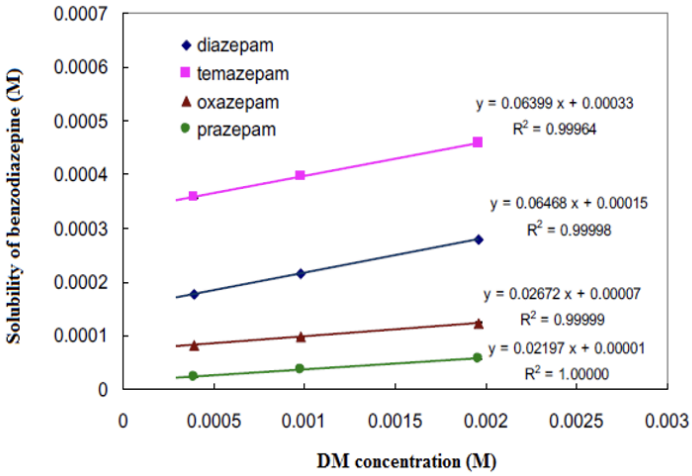

Figure 6: Solubility of selected benzodiazepine (BCA class-II) in non ionic dodecyl –D-maltoside (DM)

Micelle/Water partitioning coefficient determinations

Two model drugs, progesterone and diazepam each representing a series of solutes, were solubilized in SDS, DTAB and DM micelle systems in the presence of 0.15M NaCl to study the effect of the salts on the micelle/water partitioning coefficients.

The results are given in Figure 7. The quantitative results of aqueous solubility, solubilization power of micelles, and micelle/water partitioning coefficient for three model drugs are summarized. In anionic SDS solutions, for all three model drugs, the solubilization power shows a significant decrease in the presence of salt compared to that in the absence of salt. The aqueous solubilities of progesterone and diazepam in 0.15M NaCl solutions were not significantly different from the measured solubilities in the absence of salt. The decreasing solubility could be attributed to salting out effect. In cationic DTAB solutions, the solubilization power toward all three model drugs was significantly decreased by adding 0.15M NaCl. The micelle/water partition coefficients of progesterone and diazepam were reduced by 22% and 12% respectively in the presence of salts.

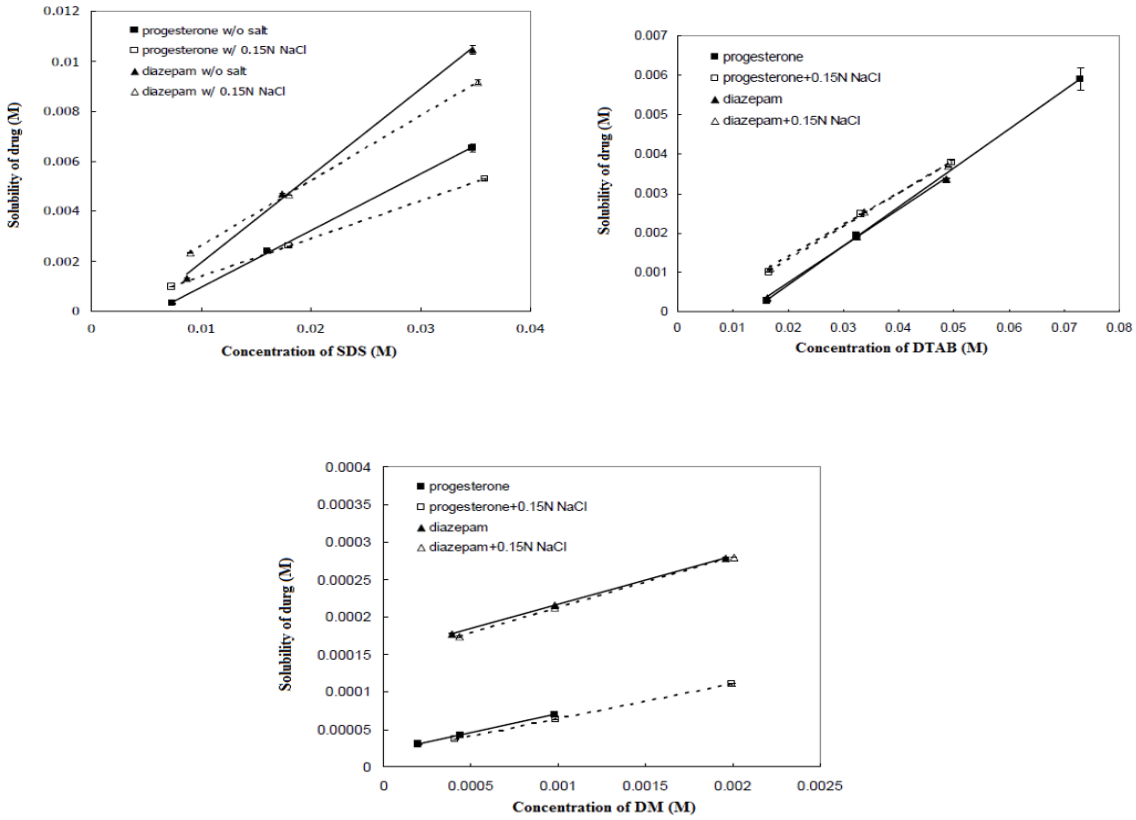

Figure 7: Solubility of progesterone and diazepam in SDS, DTAB and DM concentration in the absence and presence of 0.15 M NaCl

Drug solubility in anonic sodium dodecyl sulfate (SDS) micelles

Progesterone and diazepam were chosen as representatives of the two model drug series. The concentration of SDS was fixed at 15mg/mL. The measured diffusivities of drug molecules as a function of drug concentration are shown in Figure 8.

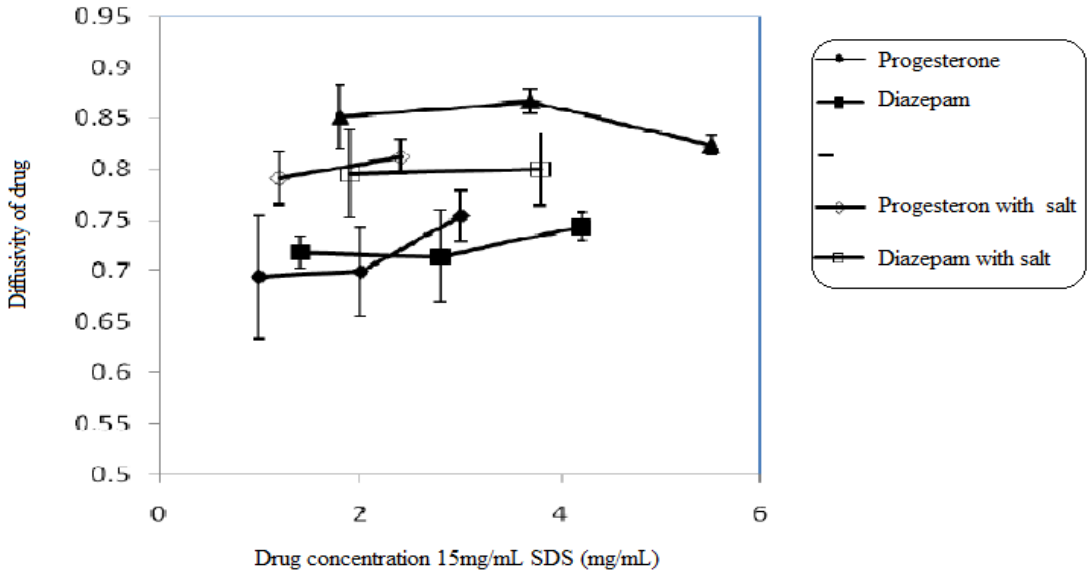

Figure 8: Diffusivity of selected drugs in SDS solution in the absence and presence of 0.15M NaCl

Drug solubility in cationic dodecyltrimethylammonium bromide (DTAB) micelles

Progesterone, diazepam and butylparaben were solubilized in 20mg/mL DTAB solutions. The diffusivities of drug molecules were measured as a function of drug concentration with results shown in Figure 9.

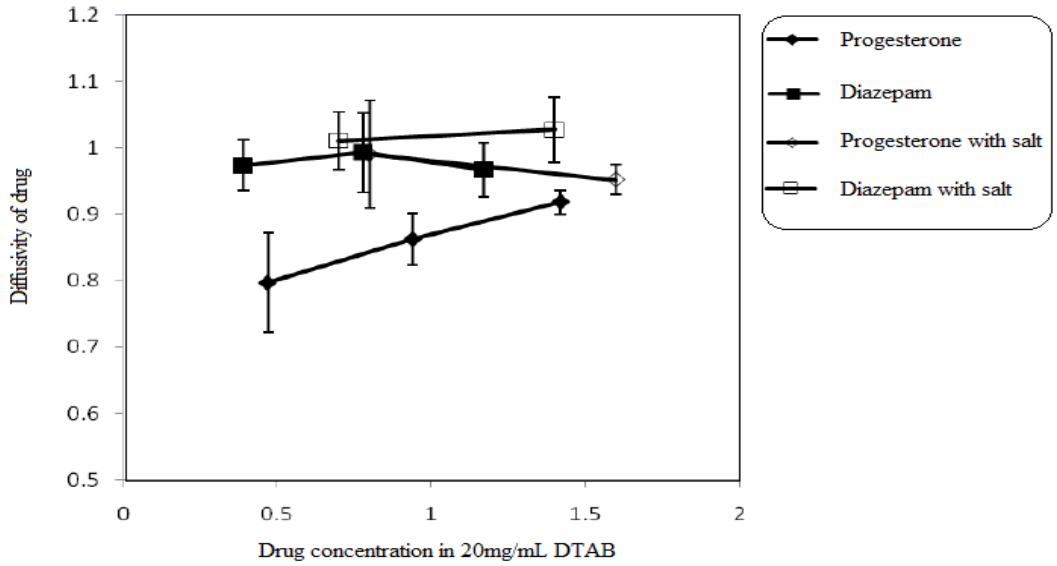

Figure 9: Diffusivites of progesterone and diazepam in 20mg.mL DTAB solutions in the absence and presence of 0.15M NaCl

Drug solubility in nonionic dodecyl -d-maltoside (DM)

The diffusivities of dodecyl β-D-maltoside (20mg/mL) as a function concentration selected drugs, progesterone and diazepam. Due to the low solubilization capacity of DM micelles, the concentration of solubilized drugs is much lower than the surfactant concentration. The results are shown in Figure 10.

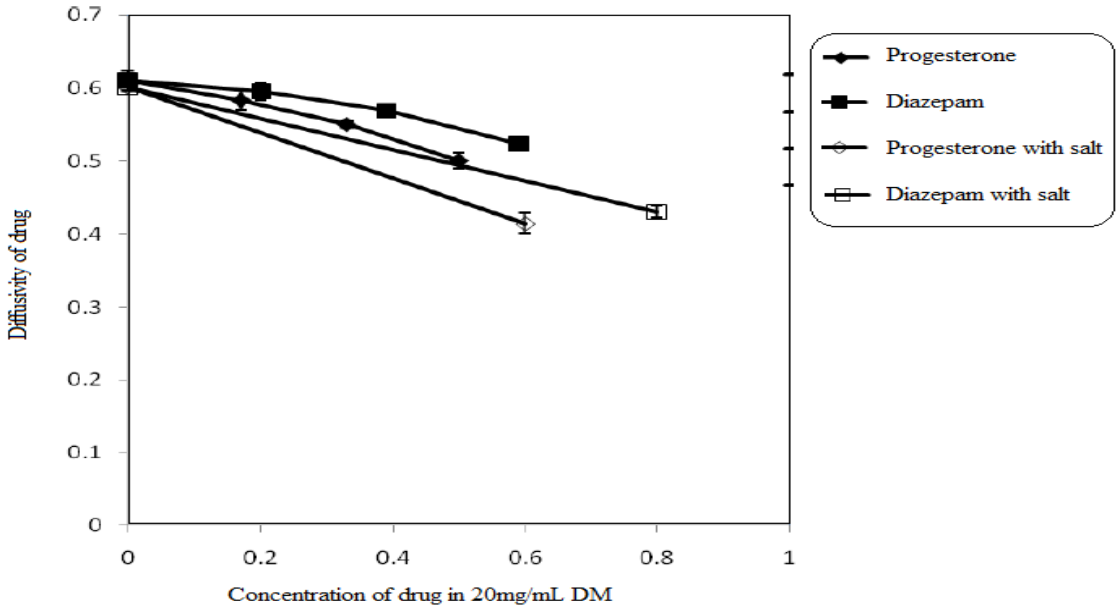

Figure 10: Diffusivities of drug concentration in 20mg/mL DM solutions in the absence and presence of 0. 15M NaCl

Conclusion:

In the present study, the micelle/water partition co-efficients was measured much larger than the hydrocarbon/water partition constants that shows that the core region of micelle was much insufficient to solubilize the model hydrophobic drugs based on the thermodynamic model. The micelle/water partitioning coefficients using surface localized model shows that the hydrophobic drugs are located at the surface of the micelles, the main mechanism of the miceller solubilization was co-adsorption to the micelle surface by drugs and surfactants and improve the solubilization of poorly water soluble drugs. The growth of the mechanistic understanding and quantitative predictions on drug solubilization in micelle systems will shows a pathway for improvement of drug development process and analyzing the solubilizing agents.

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