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SOLUBILITY ENHANCEMENT OF DIURETIC DRUGS IN DIFFERENT SURFACTANT SYSTEM- A COMPARITIVE STUDY

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ABSTRACT

The most common challenges faced by pharmaceutical industry to develop a drug with good aqueous solubility. The poor solubility and permeability through bio-membrane leads poor bio availability of drugs which affect the drug delivery system. Thus, a full knowledge of the mechanism of the interactions of drugs with other foreign materials is required before the actual application in human body. This is due to the fact that drugs are always used in the presence of a variety of additives. The present investigation aimed to determine solubilization of diuretic drug (furosemide, acetazolamide and spironolactone) using different ionic surfactants by means of UV-visible spectroscopy. Various solubility parameters such as molar solubilization ratio (MSR), micelle-water partition coefficient (K_m) and Gibb's free energy of solubilization ($\Delta G°_s$) for all the three drugs has been evaluated in aqueous media. This type of study emphasizes the importance of development of the better mixed system which can be frequently used for drug delivery purpose

Keywords: Solubilization, surfactants, furosemide, acetazolamide, spironolactone.

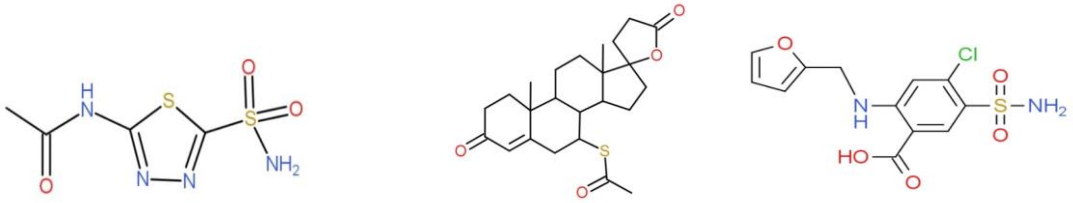
INTRODUCTION

In pharmaceutical industries, solubility of drugs is an important factor for the early drug development. The oral bioavailability of drugs depends on several factors including aqueous solubility, drug permeability, metabolism etc. The major causes of low oral bioavailability are poor solubility. One of the most important aspects associated with this phenomenon is the relative participation of hydrophobic and electrostatic interactions between the drug and surfactant molecule. Solubility plays an important role in drug delivery and effective absorption of drugs. It is one of the parameter for deciding the desired concentration of drugs required for pharmaceutical response. But due to low aqueous solubility, high doses of drugs are required to reach the therapeutic concentration after oral administration. Thus, a full knowledge of the mechanism of the interactions of drugs with other foreign materials is required before the actual application in human body. This is due to the fact that drugs are always used in the presence of a variety of additives.

EXPERIMENITAL

Material and Methods

Furosemide in the form of Lasix tablet were purchased from Sanofi Aventis Pharma, India.Spironolactone in the form of Aldactone tablets are purchased from Rpg Life Sciences Ltd., India. Acetazolamide in the form of Diamox tablets were purchased from Pfizer Ltd., India.Sodium dodecyl sulphate (SDS) and cetyltrimethylammonium bromide (CTAB) having purity >99% were obtained from Molychem laboratories, Mumbai (India).



Acetazolamide Spironolactone Furosemide

Figure 1- Structures of Diuretic Drugs

Sodium Dodecyl Sulphate (SDS) Cetyltrimethylammonium Bromide (CTAB)

Figure 2- Structures of Surfactants

Solubilization experiments

1 Molar Extinction Coefficient

For solubilization experiment, 1mM stock solution of each drug was prepared by dissolving them in pure methanol. For each experiment, 100µl of the stock solution was added to 5ml of pure methanol in cuvette. The absorption spectra were monitored over the range of 200-400 nm with UV-visible spectrophotometer equipped with a quartz cuvette at 300K. The solubilization of FUR, ACT and SPI were measured in different surfactant solutions at 250, 280 and 295 nm respectively.

2 Molar Solubilization Ratio

The solubility of furosemide, acetazolamide and spironolactone was measured in different ionic surfactant solution. Batch experiments for solubilization of various drugs in various different surfactant (SDS and CTAB) solutions were carried out consequently. Surfactant solutions were taken in 10 ml vials with various concentrations above the CMC and drugs were separately added to each vials in excess to obtained saturated solution. These mixtures were than kept for continuous shaking at 300K. Then 0.5 ml of stock solution was diluted in 5 ml in flask with 10% (v/v) methanol. The concentration of the solubilized drug was determined spectrophotometrically.

RESULTS AND DISCUSSION

The solubility of furosemide was found to increase with increasing the concentration of surfactants above critical micelle concentration (CMC). Figure 3 is the plot of absorbance versus the concentration of furosemide (FUR) which represents the molar extinction coefficient (Ɛ). Solubilization of drug in surfactant solution can be defined by molar solubilization ratio (MSR) and micelle-partition coefficient.A molar solubilization ratio (MSR) gives a quantify efficiency of a surfactant for solubilizing a given solubilizate. It also may be defined as the no. of organic compounds solubilized per moles of surfactant added to the solution and can be expressed as follows:

$$\mathbf{MSR = (S-S_{CMC}) / (C_s-CMC)}$$

Where, S is the apparent solubility of drug at surfactant concentration C_s (C_s > CMC) and $S_{CMC}$is the apparent solubility of drug at CMC.

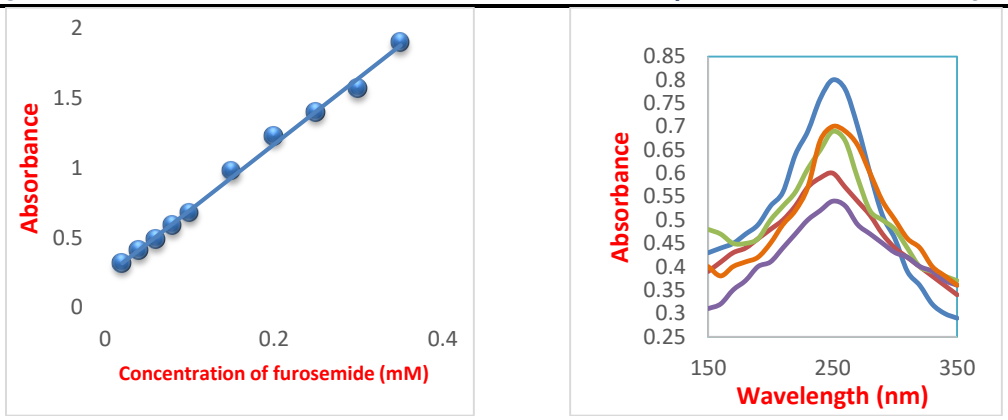


Figure 3- Plot of concentration of furosemide vs absorbance and Absorption spectra of Furosemide at different concentration of SDS.

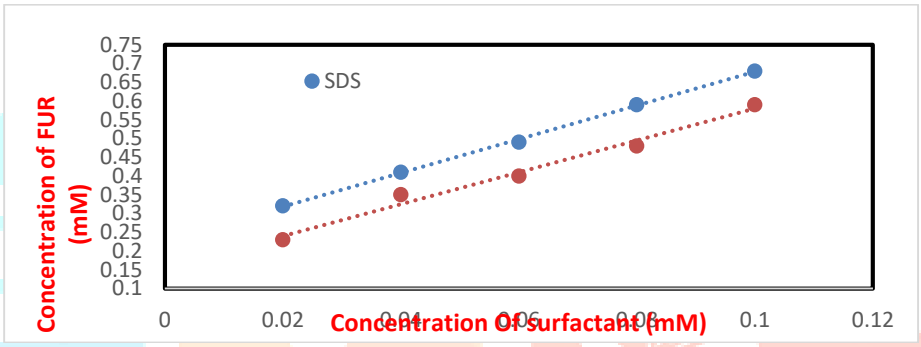


Figure 4- Variation of solubility of Furosemide (FUR) with ionic surfactants (SDS and CTAB)

In addition to MSR, micelle-water partition coefficient (K_m) is also an important parameter which may be defined as the effectiveness of solubilization of organic substance between micelle and aqueous phase. The value of Km is depend upon the nature of surfactant/ solubilizate and temperature. The partition coefficient can be expressed as:

$$K_m = X_m / X_a$$

Where, X_m = MSR/ (1+MSR) is the mole fraction of the solute in micelle, $X_a = S_{CMC}.V_m$ is the mole fraction of the solute in aqueous phase. V_m is the molar volume of water (V_m = 0.01805 L/mol.), then K_m can be rearranged as

$$K_m = MSR/S_{CMC}.V_m\ (1+MSR)$$

From conductivity and surface tension studies, it can be inferred that presence of furosemide as well as its concentration affects the micellization of both type of surfactants SDS and CTAB. The solubilization of furosemide in SDS was found to be effective as compared to tested CTAB. UV-visible studies in case of SDS support the conclusion drawn from these studies.

Figure 5 is the plot of absorbance versus the concentration of acetazolamide (ACT) which represents the molar extinction coefficient (Ɛ).Molar solubilization ratio (MSR) and micelle-partition coefficient (K_m) are the important factors for solubilization of drug in surfactant solution.

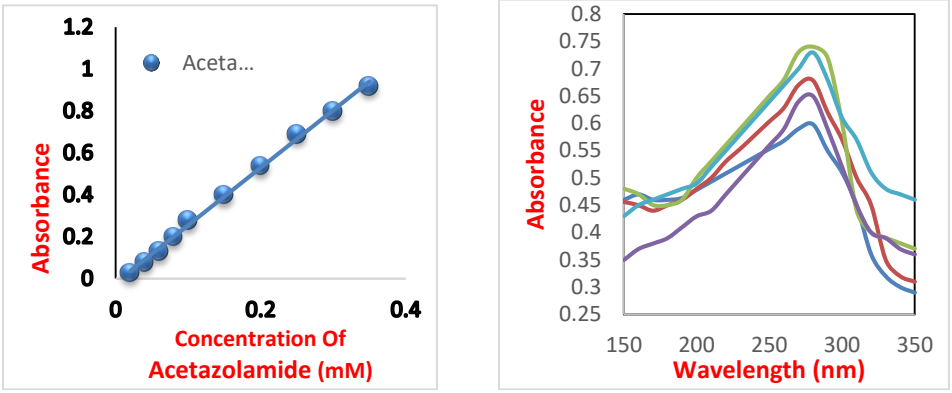


Figure 5- Plot of concentration of acetazolamidevs. absorbance and absorption spectra of acetazolamide at different concentration of CTAB

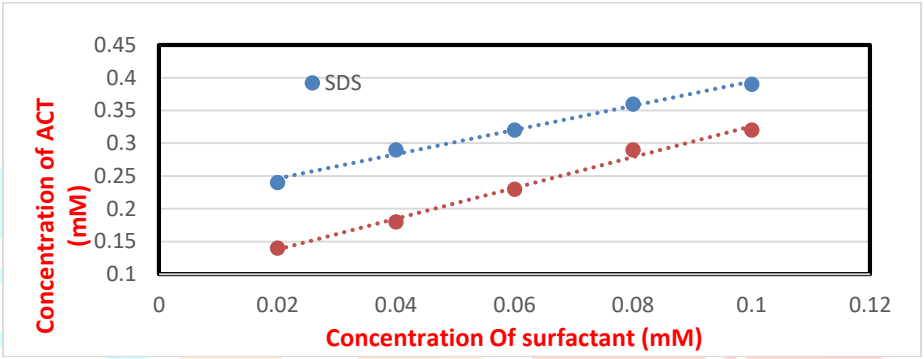


Figure 6- Variation of solubility of Acetazolamide (ACT) with ionic surfactants (SDS and CTAB)

In the present work, SDS and CTAB showed significant solubilizing ability of acetazolamide at room temperature. Results show that the solubility of ACT linearly increases with increasing concentration of surfactants. The best acetazolamide solubilization profile has sodium dodecyl sulphate (SDS). UV analysis of solubilized acetazolamide in SDS is display in Figure 6 indicates a strong interaction between the pharmaceutically active compound and surfactant, with increasing of concentration of SDS. The slope of each curve plotting acetazolamide solubility versus micellar concentration of different surfactant at 300K was used to calculate molar solubilization ratio. Table 1 gives values of molar solubilization ratio of all surfactants, the one that gives the highest solubilization of acetazolamide is SDS.

The absorbances of the drug of specified concentration were determined by measuring the molar extinction coefficient (Ɛ) in micellar solution. The UV spectra of SPI in aqueous SDS and CTAB solutions are illustrated in Figure 7. It is clear from graphs, that with the increasing surfactant concentration absorbance of spironolactone solubility also increases.

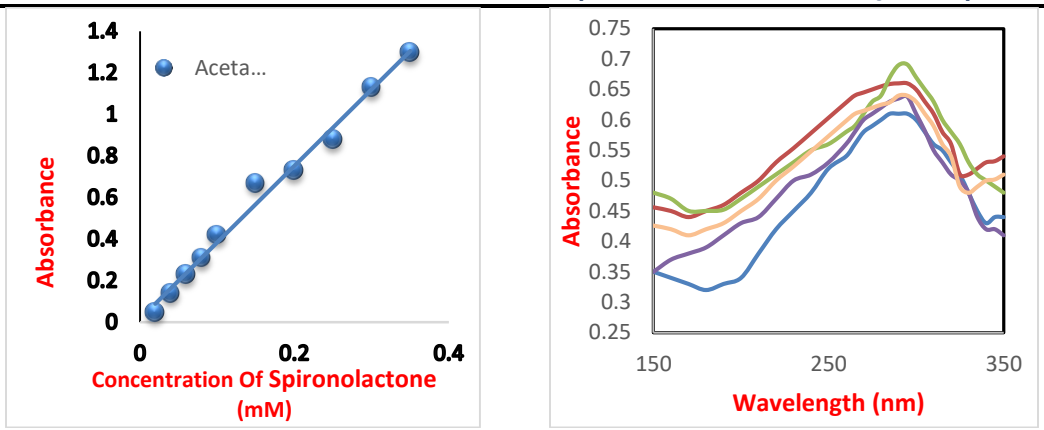


Figure 7- Plot of concentration of spironolactonevs absorbanceand absorption spectra of spironolactone at different concentration of SDS.

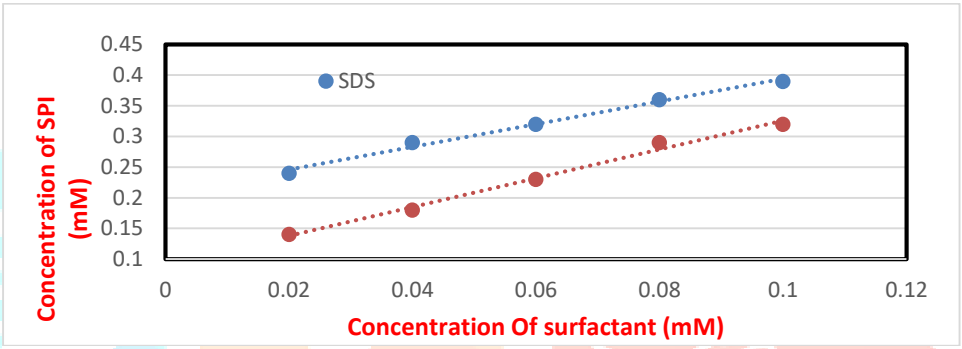


Figure 8- Variation of solubility of Spironolactone (SPI) with ionic surfactants (SDS and CTAB)

It is observed that the solubility of spironolactone were greatly enhanced with the application of surfactant systems and further increases with increasing surfactant concentration above CMC of each surfactant as shown in Figure 7. UV-spectra of SPI in aqueous SDS and CTAB solution are shown in Figure 8.

Table 1- Molar solubilization ratio (MSR), lnKm and the Gibb's free energy of solubilization ($\Delta G°_s$) of furosemide, acetazolamide and spironolactone in anionic (SDS) and cationic (CTAB) surfactant system at 300K

Surfactant	CMC (mM)	MSR	lnK_m	$\Delta G°_s$ (kJ/mol)
Furosemide				
SDS	2.2	0.512	12.0	-30.2
CTAB	0.25	0.854	11.4	-28.4
Acetazolamide				
SDS	2.6	0.186	11.7	-29.2
CTAB	0.29	0.417	12.0	-30.0
Spironolactone				
SDS	2.7	0.330	13.5	-33.7
CTAB	0.32	0.235	11.6	-28.4

CONCLUSION

An estimation of the interaction between the surfactants (SDS and CTAB) and diuretic drugs (FUR, ACT and SPI) are important to understand the role of these amphiphiles in biological processes. The CMC values for pure surfactants are found to be in good agreement with the literature value. The present investigation aimed to determine solubilization of diuretic drug (furosemide, acetazolamide and spironolactone) using different ionic surfactants by means of UV-visible spectroscopy. Sodium dodecyl sulphate (SDS) of anionic surfactant shows the higher solubilization towards all the drugs as compared to cationic surfactant CTAB. Various solubility parameters such as molar solubilization ratio (MSR), micelle-water partition coefficient (Km) and Gibb's free energy of solubilization ($\Delta G°_s$) for all the three drugs has been evaluated in aqueous media. This type of study emphasizes the importance of development of the better mixed system which can be frequently used for drug delivery purpose. Hence it is hoped that these findings will illuminate novel ways for researchers to further study in use of surfactants in pharmaceutical field and providing well characterized systems.

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