

Interaction of Sodium Dodecyl Sulfate with Anticancer Drug 6-Mercaptopurine

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Abstract

Background: 6-Mercaptopurine (6-MP) is used in the conventional chemotherapy of patients with acute lymphoblastic leukemia. **Materials and Methods:** Sodium dodecyl sulfate (SDS), an anionic surfactant that is commonly used to mimic hydrophobic binding environments such as cell membranes, micellization behavior of sodium dodecyl sulfate (anionic surfactant) has been studied in the presence of 6-MP (anticancer drug) at (1×10^{-5} M) concentrations with different time periods in micelle solution, studied at 37°C. **Results:** The results showed increase the absorbance values for the pharmaceutical compound (6-MP). Increase the absorbance values of pharmaceutical compounds with 1×10^{-2} critical micelle concentration values of surfactant increase of 6-MP concentrations in micelle solution, with decrease its concentrations in organic media, various thermo-dynamic parameters such as standard-free energy of micellization ΔG ($0.6216 \text{ k J.mol}^{-1}$), that have direct bearing on the consequences of such interactions at the molecular level have been calculated. Depend on K_{eq} and slope values for reversible reactions. **Conclusion:** The above-calculated parameters were found to be sensitive toward the interactions prevailing in 6-MP–SDS–hexane–water systems. After fixed the experimental optimum conditions at pH 7.4, 37°C, and λ_{max} 322 nm.

Keywords: 6-mercaptopurine, N. hexane, sodium dodecyl sulfate, thermodynamic parameters ΔG°

INTRODUCTION

6-Mercaptopurine (6-MP), sold under the brand name Purinethol®, is an immunosuppressive medication. It is used to treat acute lymphocytic leukemia, Crohn's disease, and ulcerative colitis.^[1,2] It is a thiopurine. Surfactants are soluble amphiphiles which play an important role in applied and fundamental science. In addition, treatment protocols have evolved with improved risk classification, leading to more accurate therapeutic stratification. Indeed, a more recent study demonstrated that the timing of 6-MP administration did not impact the risk of relapse.^[3] Above the critical micelle concentration (CMC), they self-associate to form thermodynamically stable and noncovalent aggregates called micelles.^[4,5] The most important property of surfactant solution that has significantly been used in pharmaceutical formulations is "Micellar Solubilisation," especially with respect to increasing the bioavailability of the drugs.^[6-9] Micelles are widely used as membrane mimetic systems to characterize.

MATERIALS AND METHODS

Prepared (8×10^{-4} M) by dissolve (0.0006) g of 6-MP (Sigma chemicals) in a small amount of solvent normal Hexane and complete the volume to the mark in a volumetric flask of 5 mL.

Micelle solution of sodium dodecyl sulfate (SDS) was prepared at a concentration of 1×10^{-2} molar (288.38 g/mL) weighed 0.0865 g then solubility at a 30 mL of regulated buffer solution (pH 7.4) at 37°C and then complete the volume to the mark in a 30 mL volume vial. Transfer mixture to snocater to get a cleaer and hemoginuse solution kept in digital water path provider thermostat regular temperature at 37°C, 0.1 mL of the pharmaceutical compound were withdrawn at a concentration of 1×10^{-5} molar mixed and completed with a micelle solution for (6-MP). The absorbance was measured at λ_{max} at 322 nm.

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Apparatus and measurements

Conductivity measurements were carried out with a calibrated digital conductivity meter (CM 180 Elico Ltd.) using a dip type conductivity cell. The reproducibility of the individual point was within $\pm 2\%$ of conductivity unit. The solution under investigation was taken in the jacketed measuring cell. A high precision water thermostat fitted with a digital temperature controlled device used for all experimental measurements was supplied by Narang Scientific Works – New Delhi. The temperature of the thermostat was maintained within $\pm 0.1^\circ\text{C}$ over the entire temperature range studied. DSA was calibrated before use with deionized water. The measurements were performed at 37°C . The temperature was maintained to $\pm 0.001^\circ\text{C}$. In all cases, the solutions were prepared very shortly before the experiments were carried out to avoid possible alterations in the surface agents and hence, changes in their properties over time. NaOH and HCl, supplied by Merck and Probus, respectively, were used as pH modifiers; in both cases, a concentration of 4 molaL-1 was used to reach the desired pH easily, and pH measurements were performed with a CRISON 2001 pH-meter.

RESULTS

Calibration curve of 6-mercaptapurine

Regarding calibration curve of 6-MP, Figure 1b shows that at the wavelength of the maximum absorption (322 nm) [Figure 1a] nanometers and compliance with the absorptive absorption law within the range (1×10^{-4} – 1×10^{-6}) molar and carried out by using buffer solution and the correlation coefficient $R = 0.9965$, obeys Lambert-Beer Law.^[10]

Study the permeability of pharmacokinetic compounds (6-mercaptapurine) in sodium dodecyl sulfate micelle solutions

The measurements mentioned showed results that could be used to discuss the behavior of 6-MP compound in SDS (micelle solutions). They were calculated at the wavelength of the maximum absorption of 322 nm 6-MP, at pH 7.4 as shown in Table 1. The spectral measurements recorded in Table 1 valid the change values of absorbance with time.

The increase in absorption values is due to the high concentration of materials in the phase of the solution relative to the phase of the solution. Based on the Beer's Lambert relationship (the positive relationship between concentration and absorption), absorption is increased by increasing concentration in SDS [Figure 2].

Find the residual concentration of pharmaceutical compounds (6-mercaptapurine) in the organic and aqueous media Corg., Caq.

Depending on the values established in Table 2.

$$\text{Caq. outside micelle} \xrightleftharpoons{K_{eq}} \text{C.org in side micelle} \quad (1)$$

$$\text{Atot.} = A_{aq.} + A_{org} \dots\dots\dots (2)$$

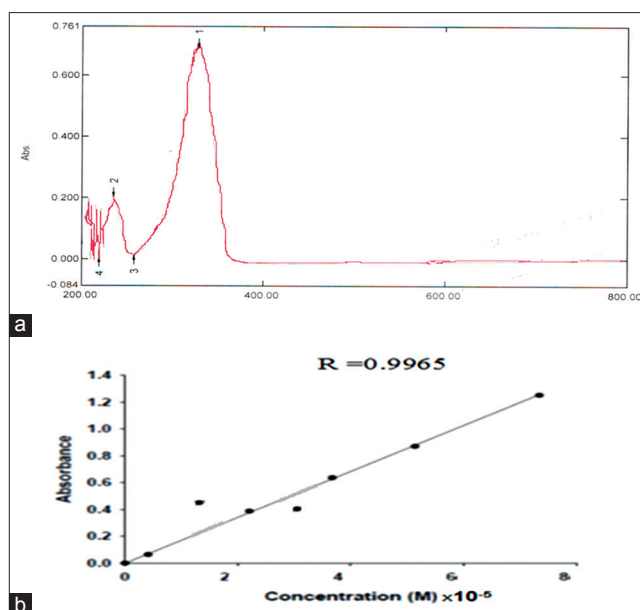


Figure 1: (a) Absorbance spectrum of 6-mercaptapurine. (b) Calibration curve for determination of 6-mercaptapurine at λ_{max} 322 nm

Table 1: Absorption coefficient values and the maximum wavelength of aqueous (buffer) and organic solutions and pharmacological membership

Drugs	ϵ org	ϵ aq.(buffer) pH 7.4	λ_{max} org	λ_{max} eq
6-MP	89600	46200	321	322

Table 2: Concentrations of 6-MP in aqueous and organic media (micelle) with ($1 \times 10^{-5}\text{M}$) 37°C , pH 7.4 and λ_{max} 322 nm at different time periods

Time (min)	Atot 6-MP	C aq./10-5	C org./10-5
1	0.4742	0.9723	0.0274
5	0.4753	0.9701	0.0291
10	0.4915	0.9332	0.0669
15	0.5272	0.8503	0.1498
30	0.5313	0.8411	0.15899
45	0.5334	0.8365	0.1636
60	0.5870	0.7111	0.2881
75	0.6103	0.6590	0.3911
90	0.6137	0.6528	0.5605
105	0.6205	0.6355	0.3641
120	0.6205	0.6355	0.3641

$$\text{Atot} = \epsilon_{aq} \text{Caq} + \epsilon_{org} (\text{C initial} - \text{C aq.}) \dots\dots\dots (3)$$

From Table 1 the values were offset in equation (3) to obtain the Caq. of the drug compound.

$$\text{Atot} = 46.200 \text{Caq.} + 89.600 (\text{C initial} - \text{C aq.}) \dots\dots\dots (4)$$

Moreover, thus give the following values. In addition, the absorbance peak shift to higher wavelength in the ultraviolet (UV) spectral measurements of SDS confirms some transition occurred in the micellar range [Figure 3].

By plotting the relation between $\ln (X_e/[X_e-X])$ and time [Figure 4], we obtained a straight line with a slope equal to $(k_1 + k_{-1})$.

$$\text{Slop} = 139.5 \times 10^{-3} \dots\dots (5)$$

$$\text{So: } k_1 + k_{-1} = 139.5 \times 10^{-3} \text{ Sec}^{-1} \dots\dots (6)$$

Determination the change of Gibbs-free energy (ΔG) for (6-mercaptopurine) compounds

By associating the kinetic behavior of the reaction with its thermodynamic properties, based on the K_{eq} 's value, we can find the diffusion voltage or change in free energy therefore Gibbs-free energy is a measure of chemical reaction spontaneity that could be directly accounted from the equilibrium constant according to Van't-Hoff equation:

$$\Delta G = -RT \ln K_{eq} \dots\dots\dots (7)$$

Depend on K_{eq} and slope values for reversible reactions as shown in Figure 4 and Table 3, where the free energy values that calculated and their results were reported in Table 4. Table 4 shows the values of the spontaneous process through the negative sign carried by each value.

DISCUSSION

The increase in absorption values is due to the high concentration of materials in the phase of the solution relative to the phase of the solution. This increase is attributed to the values of the large molar absorption factor in the organic media and their increasing melting due to the formation of hydrophobic interactions.^[11,12] These are typically series chains, which contains a large group of atoms. These chains usually overlap with each other almost randomly, and each series is associated with large numbers of solvent particles that are often small.

As these numbers of molecules (solvent molecules) are removed from the solution, the free volume of the solvent decreases significantly, resulting in an increase in the effective concentration of solubility. This results in an increase in the reciprocal effect of the distributed minutes. This causes the system to deviate significantly from The ideal behavior is to increase even when the concentration of minutes is low.^[13]

Table 3: Values of rate constants k_1 , k_{-1} , and K_{eq} of pharmacological compound (6-MP) permeability in aqueous and organic media

Drugs	k_1 (min^{-1})	k_{-1} (min^{-1})	K_{eq}
6-Mp	0.0079	0.0062	1.2725

Table 4: The free energy (ΔG) and K_{eq} values for 6- TG and 6-Mp

Drugs	K_{eq}	$\ln K_{eq}$	ΔG (kJ/mol)
6-Mp	1.2725	0.2409	-0.6216

Based on the Beer' Lambert relationship (the positive relationship between concentration and absorption), absorption is increased by increasing concentration in SDS [Figure 2].

Depending on the values established in Table 2 of the pharmacological compounds in the aqueous and organic

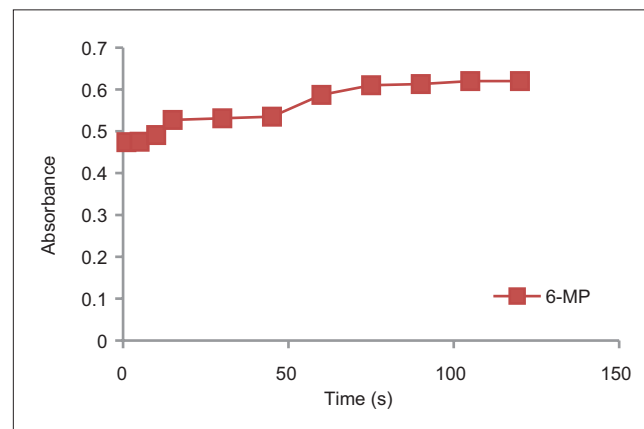


Figure 2: Plot of absorbance value of 6-mercaptopurine in aqueous solution of sodium dodecyl sulfate different time periods

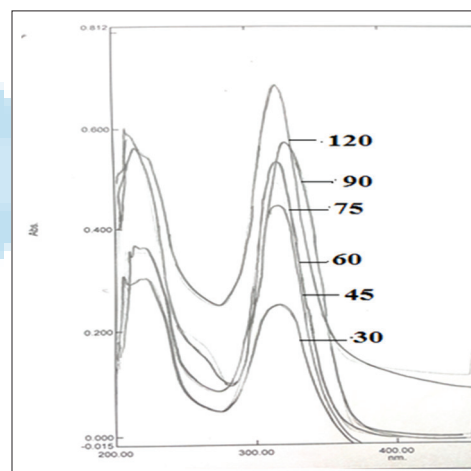


Figure 3: Total absorption spectra of 6-mercaptopurine with a aqueous solution of sodium dodecyl sulfate at different time periods

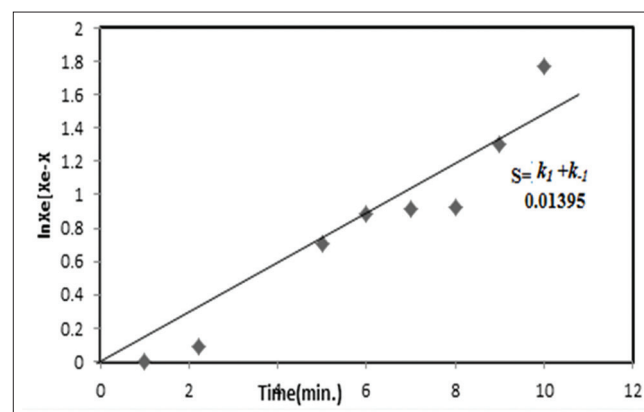


Figure 4: Diffusion (6-mercaptopurine) through sodium dodecyl sulfate micelles solution at different time periods

mediums were fixed in Table 2 refer to increase in concentration in the organic medium Corg. values compared with a decrease of concentration in the aqueous medium Caq. Moreover, the pharmacological compound (6-MP) indicating interaction of SDS with these drugs compatible with their chemical structures is initially electrostatic, binding to positively charged groups, and later followed by hydrophobic interaction. Thus, the characteristics of structure are consistent with the experimental results at a high molar concentration of (SDS).

In addition, the absorbance peak shift to higher wavelength in the UV. spectral measurements of SDS confirm some transition occurred in the micellar range. As shown in Figure 3, indicate the SDS molecules occupy the hydrophilic sites on the pharmacological compounds (6-MP) and allow the hydrophobic sites to be exposed to the solvent by expanding the molecule. This destabilizes the drug molecule and enhances the formation of intermolecular the hydrophobic parts in different molecules meet. By contrast, for structure, the hydrophobic segments, which are important initiators of formation, are buried in the micelles, inhibiting their interactions.^[14] At the same time, the charged nature of the micelle will also prevent aggregation. That fixed with a limited given set of experimental conditions, 37°C, pH 7.4 and 1×10^{-2} special concentration of SDS to get critical concentration CMC.^[15] However, the interaction between molecules in solution and other factors will destroy this linear relationship, such as the formation of intermolecular hydrogen bonds or the formation of micelles. The SDS-6-MP complexes are explained and hydrophobic interactions along with hydrogen bonding and suitably explain the earlier models too.

As the concentration factor of the materials in the phase Micelle and its height and low concentration of pharmacological compounds (6-MP). These results indicate the permeability and transfer of the bulk of these compounds to the inside of the mucus cavity micelles (which represents the organic medium). By plotting the relation between $\ln(X_e/[X_e-X])$ and time [Figure 4], we obtained a straight line with a slope equal to $(k_1 + k_2)$.

Regarding determination the change of Gibbs-free energy (ΔG) for (6-MP) compounds, By associating the kinetic behavior of the reaction with its thermodynamic properties, based on the K_{eq} 's value, we can find the diffusion voltage or change in free energy therefor Gibbs-free energy is a measure of chemical reaction spontaneity that could be directly accounted from the equilibrium constant according to Van't-Hoff equation:

$$\Delta G = -RT \ln K_{eq} \dots\dots\dots (7)$$

Free energy is used to handle the state of equilibrium in which the process moves, and its change (measured) measures the useful workpiece (chemical effort) obtained from an operation at a constant temperature 37°C, is a measure of spontaneous process. The very important result is that: the decrease in the free energy of the process is obtained at a constant

temperature (37°C) which is under study is a measure of the tendency to this process get spontaneously.

Depending on K_{eq} and slope values for reversible reactions (as show in Figure 4 and Table 3), the free calculated energy values and their results in Table 4 show that the values of the spontaneous process through the negative signal^[16] is often obtained in biologics.

However, the rate of access is likely to be slow. This is due to the penetration of the pharmacological compounds into the micelles. This permeability is reduced by the vacuum impedance caused by the interaction of the OH (ion) formed during the reaction, which gives it a negative charge causing some impediment to the permeation of this compound to the SDS, Which is often the spherical periphery of negatively charged ions.^[17]

The free energy values of this compound due to a number of factors, including temperature, equilibrium constant, the composition of solution, solubility, and the type of interactions between the compound and the solvent used. Depending on kind functional grope, it was found that the permeability of 6-Mp as the corresponding result to the present study.^[18] The behavior of drugs agree with the fact of the difference on their lipophilicity a lowest lipophilic of 6-Mp molecule given the highest rate of diffusion and the highest ΔG_o value refers to spontaneously of diffusion process with a low lipophilicity than 6-Mp Which is reflected on the value of diffusion rate, (ΔG_o value In biochemistry that deals to written G_o weld be recognize when physiological hydronium concentration at pH (7).

CONCLUSION

In summary, we can say that addition of nonaqueous solvent N. hexane has a profound influence on the micellar properties of ionic surfactant and it leads to the formation of charged complex between N. hexane and 6-MP preferentially due to the solubilization of drugs in the micellar core, which is reflected by spectroscopic studies. Moreover, the free energy of micellization G_{om} becomes more negative with 37°C and pH 7.4, as well as with increase in drug concentration which support the above observations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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