SYNOPSIS

A Study on Micellization behaviour of Pharmaceutical Drugs in Aqueous Electrolytic Solutions

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1. Introduction

Surface science is a fascinating scientific subject that defines the issue of amphiphiles and more specifically micellar and thermodynamic characteristics of surface active substances called surfactants$^1$. This branch has inputs from many disciplines including green chemistry, biochemistry and food chemistry. The surfactants have wide spread applications in the field of drug delivery$^2$, detergency$^3$, pharmaceutical formulations$^4$ and solubilization of drugs$^5$. Out of these applications, applications in the field of drugs are of paramount importance in the present scenario of struggle for existence of human beings.

A drug is any substance which when consumed causes a physiological change in the body. A pharmaceutical drug or medicine is a chemical substance used to treat, cure, prevent or diagnose a disease. Traditionally drugs were obtained through extraction from medicinal plants, but more recently also by organic synthesis. Physicochemical properties of drugs are of great interest to understand ‘drug action’ at the molecular level$^6$. Thus, knowledge of the physicochemical properties of drugs plays an important role to understand their physiological actions which is highly dependent upon the solution behaviour of drugs$^7$. In this context, the pharmaceutical drugs can be classified in two different categories i.e. surface active drugs and surface inactive drugs and majority of these pharmaceutical drugs are surface active. Surface active drugs are key components in pharmaceutical processes, thereby, account for immense utility in pharmaceutical formulations and drug delivery.

Surface active drugs are amphiphilic in nature. The term was coined by Paul Winsor 50 years ago$^8$ and comes from the Greek words; amphi, mean both and phillos expresses friendship, and the term relates to the fact that all surface active molecules (surfactants) consists of at least two parts. When the fluid is water one usually talks about the hydrophilic and hydrophobic parts respectively. The hydrophilic part is referred to polar head group and the hydrophobic is the non-polar tail$^9$.

Drugs because of their surfactants like nature assemble to form small organized aggregates such as micelles, micro-emulsions, vesicles, used as models to stimulate life system at a concentration known as critical micelle concentration (CMC). Micelles can mimic biological cells to study functions of bioactive substances in life systems. Micelles provide important functional properties to drugs which in turn change in the presence of additives (electrolytes and non-electrolytes). Addition of electrolytes in drug solution is another way of reducing CMC of
drug. In general, repulsive forces between the head groups of ionic surfactants are fighting against the aggregation. In the presence of salt, the repulsive forces of head group of drug monomer decreases due to the electrostatic shielding effect resulting in the formation of micelle at lower CMC\textsuperscript{10,11}. The effect of additives on the CMC of drugs in aqueous systems has been well documented in literature by using different experimental techniques. Though, the effect of electrolytes like sodium chloride, potassium chloride, calcium chloride, etc. on the micellization behaviour of surface active drugs still have not been investigated, especially by using density, speed of sound, surface tension, viscometric, conductance, fluorescence and ultraviolet studies. Moreover, micellization and surface properties of the system are the fundamental characteristics of surfactant solution which are very sensitive to temperature, pH, ionic strength, concentration and the presence of additives.

1.1 Electrolyte

Any substance which can conduct electricity in fused state or in its aqueous solution is known as an electrolyte. Electrolytes when dissolved in fluid tend to break into ions, creating an electrically-conductive solution. For example, table salt (NaCl) dissolved in water dissociates into positive ion of sodium (Na\textsuperscript{+}) and negative ion of chloride (Cl\textsuperscript{-}). Many electrolytes are found in the human body, each serves a specific and important role. Basically electrolytes play important role in maintaining the balance of fluids between the intracellular and extracellular environments. This balance is critically important for various physiological phenomenon like hydration, nerve impulses, muscle function, pH level, etc.

An electrolyte imbalance, whether too much or too little, can be proved fatal to one’s health. Muscle contraction, for example, requires calcium, potassium and sodium and their deficiency may result in muscle weakness or severe cramping. Too much sodium, on the other hand, can cause high blood pressure and consequently increase the risk of heart disease. Some biologically important electrolytic ions found in the human body and which are to be investigated in present study have been listed in following table along with their functions.
<table>
<thead>
<tr>
<th>Atomic Number</th>
<th>Element</th>
<th>Fraction of Mass (kg)</th>
<th>Mass (kg)</th>
<th>Essential in Humans</th>
<th>Negative Effects of Excess</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Lithium</td>
<td>31×10⁻⁹</td>
<td>7.0×10⁶</td>
<td>Yes (intercorrelated with functions of enzymes, hormones and Vitamins)</td>
<td>Toxic in higher amounts</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Sodium</td>
<td>1.5×10⁻³</td>
<td>0.10</td>
<td>Yes (e.g. Na⁺/K⁺-ATPase)</td>
<td>--</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>Potassium</td>
<td>2.0×10⁻³</td>
<td>0.14</td>
<td>Yes (e.g. Na⁺/K⁺-ATPase)</td>
<td>--</td>
<td>1</td>
</tr>
<tr>
<td>37</td>
<td>Rubidium</td>
<td>4.6×10⁻⁶</td>
<td>6.8×10⁻⁴</td>
<td>No</td>
<td>--</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>Magnesium</td>
<td>500×10⁻⁶</td>
<td>0.019</td>
<td>Yes</td>
<td>(e.g. binding to ATP and other nucleotides)</td>
<td>--</td>
</tr>
<tr>
<td>20</td>
<td>Calcium</td>
<td>0.014</td>
<td>1.0</td>
<td>Yes</td>
<td>(e.g. Calmodulin and Hydroxylapatite in bones)</td>
<td>--</td>
</tr>
<tr>
<td>38</td>
<td>Strontium</td>
<td>4.6×10⁻⁶</td>
<td>3.2×10⁻⁴</td>
<td>Yes</td>
<td>(in collagen formation)</td>
<td>2</td>
</tr>
<tr>
<td>56</td>
<td>Barium</td>
<td>310×10⁻⁹</td>
<td>2.2×10⁻⁵</td>
<td>No</td>
<td>Toxic in higher amount</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>Chlorine</td>
<td>1.5×10⁻¹</td>
<td>0.095</td>
<td>Yes(Cl transporting ATPase)</td>
<td>--</td>
<td>17</td>
</tr>
</tbody>
</table>

1.2 Streptomycin

It is one of the most effective and safe medicine needed in health system and is recorded in World Health Organization's (WHO) List of Essential Medicines. In veterinary medicine, streptomycin (Fig. 1) is the first-line antibiotic to be used against gram negative bacteria in large animals (horses, cattle, sheep, etc.). It is commonly combined with procain.

![Streptomycin molecule](image)

**Fig.1.** Chemical structure of drug streptomycin sulphate.

Streptomycin discovered in 1943 from *Streptomyces griseus*, is an antibiotic used to treat a number of bacterial infections. This includes tuberculosis, mycobacterium avium complex,
endocarditis, brucellosis, burkholderia infection, plague, tularemia, and rat bite fever. It is given as injection into a vein or muscle. Streptomycin sulphate is one of the most clinically useful aminoglycoside antibiotic, an oligosaccharide with basic properties that also possess antimicrobial activity against a wide range of gram-negative and gram-positive bacteria and mycobacteria, predominantly mycobacterium tuberculosis. One of the major disadvantage behind its use as antibiotic is its prominent oto- and nephron-toxicity\textsuperscript{12,13}. The manner in which electrolytes affect the physiochemical properties especially the micellar behaviour of streptomycin was studied.

\textbf{1.3 Diphenhydramine Hydrochloride}

Diphenhydramine (DPH) (Fig. 2) is a first generation antihistaminic (H1-receptor antagonist) possessing anti allergic, antitussive, antiemetic and sedative properties that is mainly used to treat allergies. It is a class of drugs that block histamine release from histamine-1 receptors and is used to relieve symptoms of allergy, hay fever, and the common cold. These symptoms include rashes, itching, watery eyes, itchy eyes/nose/throat, cough, runny nose and sneezing. It is also used to prevent and treat nausea, vomiting and dizziness caused by motion sickness. This medication works by blocking a certain natural substance (histamine) that our body makes during an allergic reaction. It is found in various pharmaceutical preparations\textsuperscript{13}.

![Chemical structure of drug diphenhydramine hydrochloride](image)

**Fig.2.** Chemical structure of drug diphenhydramine hydrochloride.

DPH has been found to have a higher efficacy in the treatment of allergies than some second-generation antihistamines such as Desloratadine\textsuperscript{14}. Several analytical methods have been recorded for determination of DPH in pharmaceutical formulations. Most of these studies focused on titrimetry\textsuperscript{15}, fluorimetry\textsuperscript{16}, HPLC\textsuperscript{17}, HPTLC\textsuperscript{18}, capillary electrophoresis\textsuperscript{19}, gas
chromatography\textsuperscript{20}, voltammetry\textsuperscript{21}, spectrophotometry\textsuperscript{22} and conductometric analysis\textsuperscript{15}.

2. Literature Review

In order to understand different approaches that have been successfully applied to investigate various drug-electrolyte aqueous micellar systems in terms of intermolecular interactions, the relevant representative studies that appeared in literature during the recent past have been summarized in following paragraphs.

Kim and Shah\textsuperscript{24} studied cloud point phenomenon in amphiphilic drug, amitriptyline (AMT) solutions. They investigated the influence of electrolytes on the micellar behaviour of AMT by using CP and dye solubilization techniques. The binding effect of anionic counter ions was in the order: \( \text{Br}^- > \text{Cl}^- > \text{F}^- \). The effect of cations was insignificant compared to anions.

Alam et al.\textsuperscript{25} studied effect of KCl on the micellization and clouding phenomenon of the amphiphilic phenothiazine drug promethazine hydrochloride. They reported the micellization at different fixed temperatures (293.15, 303.15, 313.15, and 323.15) K and the clouding behavior of the phenothiazine hydrochloride (PMT) in the absence and presence of KCl. The critical micelle concentration (CMC) of PMT was measured by the conductivity method. The cmc values decrease with increasing the KCl concentration, whereas with increasing temperature, the cmc values increase.

Mondal et al.\textsuperscript{23} studied physicochemical properties of an anticonvulsant drug sodium valproate in aqueous and in mixed aqueous solutions at different temperatures. Various parameters have been obtained for aqueous binary mixtures of sodium valproate and for the ternary mixtures of sodium valproate in aqueous solutions of sodium chloride and in aqueous solutions of dextrose in the concentration range (0.01 to 0.1) mol/ kg as a function of temperature.

Schreier et al.\textsuperscript{24} studied Surface active drugs their self-association and interaction with membranes and surfactants. It is seen that drug–membrane interactions are analogous to the interactions between membranes and classical detergents. Phenomenon such as shape changes, vesiculation, membrane disruption, and solubilization have been observed are described. The mechanisms of drug solubilization by surfactants are reviewed from the physicochemical point of view and in relation to drug carrying and absorption by the organism.
Ayad et al.\textsuperscript{25} worked on conductometric determination of certain pharmacological drugs using silver and bismuth. Two simple, rapid and accurate conductometric methods were developed for determination of losartan potassium, pantoprazole sodium, sumatriptan succinate, rabeprazole sodium and lomefloxacin HCl in pure form as well as in their pharmaceutical formulations.

Patil and Dudhe\textsuperscript{26} studied thermodynamic properties of streptomycin aqueous solutions from $T = (298.15$ to $308.15)$ K. Densities, viscosities, and the speed of sound. The influence of concentration and also the temperature upon some physico-chemical properties such as acoustic impedance, adiabatic compressibility, free length, relaxation time, internal pressure, absorption coefficient, free volume, Rao’s constant, Wada’s constant, cohesive energy, Gibb’s free energy, relative association and Van der Waal’s constants have also been studied.

Dhondge et al.\textsuperscript{27} conducted volumetric and acoustic study of aqueous binary mixtures of quinine hydrochloride, guanidine hydrochloride and quinic acid at temperatures $T = (278.15,$ $288.15$ and $298.15$) K. They reported the fundamental thermodynamic properties like volumetric and compressibility.

Bharate et al.\textsuperscript{30} studied interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients. The present review covers the literature reports of interaction and incompatibilities of commonly used pharmaceutical excipients with different active pharmaceutical ingredients in solid dosage forms. Examples of active drug/excipient interactions, such as transacylation, the Maillard browning reaction, acid base reactions and physical changes are discussed for different active pharmaceutical ingredients belonging to different therapeutic categories viz antiviral, anti-inflammatory, antidiabetic, antihypertensive, anticonvulsant, antibiotic, bronchodilator, antimalarial, antiemetic, antiamoebic, antipsychotic, antidepressant, anti-cancer, anticoagulant and sedative/hypnotic drugs and vitamins.

Bhattacharya et al.\textsuperscript{28} studied solvation behaviour of an antihelmintic drug piperazine in aqueous solutions of sodium chloride and glucose at different temperatures. The experimental values of densities ($d$), speeds of sound ($u$) and relative viscosities of piperazine citrate in aqueous solution and in 0.06 mol/kg of sodium chloride and D-glucose as a function of concentration have been obtained at $T = (293.15,$ $303.15$ and $313.15$) K. The thermodynamic parameters of solute, piperazine citrate in water and in aqueous solutions of sodium chloride and D-glucose have been computed using the density and speed of sound data.
Yu Li et al.\textsuperscript{29} studied densities and viscosities of cefodizime sodium in water and normal saline from (278.15 to 313.15) K. Density and viscosity were measured for the binary mixtures of cefodizime sodium + water and the ternary mixtures of cefodizime sodium + 0.9 mass % normal saline at the temperatures (278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15, and 313.15) K and at atmospheric pressure. The dependence of density and viscosity on temperature and concentration has been correlated with V–T–F equation. The results are used to analyze the nature of solute-solute interactions.

Taboada et al.\textsuperscript{30} studied self-association of amphiphilic Penicillins in aqueous electrolyte solution. Self-association of the penicillin, cloxacillin, dicloxacillin, and flucloxacillin in water and in the presence of added electrolyte (0.025–0.40 mol.kg\textsuperscript{-1} NaCl) at 30 °C has been examined by light-scattering and NMR techniques. Inflections in the data from both techniques were observed at a single critical concentration for solutions of cloxacillin and at two critical concentrations for dicloxacillin and flucloxacillin. Aggregation numbers and effective micellar charges were calculated from the static light-scattering data for the stable aggregates formed at the first critical concentration.

Khatun et al.\textsuperscript{31} studied apparent molar volume, adiabatic compressibility, and critical micelle concentration of Flucloxacillin Sodium in aqueous NaCl solutions at different temperatures. Densities, ρ, and speeds of sound, u, of flucloxacillin sodium in water and aqueous NaCl solutions were measured at T = (298.15, 303.15, 308.15, 313.15, 318.15, and 323.15) K and atmospheric pressure using a high precision vibrating U-tube digital density and sound velocity analyzer (DSA 5000, Anton Paar, Austria). The results were interpreted in terms of solute-solvent and solute-solute interactions and structure making/breaking ability of the solute in the aqueous environment.

Pichel et al.\textsuperscript{32} studied solute and solvent structure effects on the volume and compressibilities of some colloidal Penicillins in aqueous solution. The apparent molal volumes and adiabatic compressibilities of aqueous solutions of the sodium salts of the amphiphilic anionic penicillins, cloxacillin, dicloxacillin, and nafcillin have been determined from density and ultrasound velocity measurements at 298.15 K. Critical concentrations were obtained from both techniques, confirming the existence of a second critical concentration for dicloxacillin, as had been previously reported.
Yan et al.\textsuperscript{33} studied intermolecular interactions of four $\alpha$-amino acids and three glycyl dipeptides with drug domiphen bromide (DB) as the function of temperature and DB molality have been investigated by combination of volumetric and UV–vis spectroscopy methods. The standard partial molar volume, standard partial molar transfer volumes, hydration number, partial molar expansibility and Hepler’s factor are calculated from the density data. The above parameters are used to interpret the solute-solvent interactions in ternary systems. The dependence of these parameters upon concentration, temperature and hydrocarbon chain length of the amino acids/dipeptides clearly suggest the roles of amino acids/dipeptides and domiphen bromide in solute-solvent interactions.

Malik et al.\textsuperscript{34} studied mixed micellization between amphiphilic drug promethazine hydrochloride and cationic surfactant (conventional as well as gemini). It has been investigated conductometrically at different concentrations and temperatures. The micellar mole fractions of the surfactant calculated by different proposed models, show greater contribution of surfactant in mixed micelle and increases with the increase in concentration of the surfactant.

Nain et al.\textsuperscript{35} studied (solute + solute) and (solute + solvent) interactions of homologous series of some $\alpha$-amino acids in aqueous streptomycin sulfate solutions at different temperatures by using physicochemical methods. Densities, $\rho$, ultrasonic speeds, $u$, and viscosities, $\eta$ of solutions of glycine-alanine-valine-isoleucine in water and aqueous streptomycin sulfate \{1\% (0.0069 mol kg$^{-1}$) and 2\% (0.0137 mol kg$^{-1}$) streptomycin sulfate in water\} mixed solvents were measured at $T$ (293.15, 298.15, 303.15, 308.15, 313.15, and 318.15) K and atmospheric pressure. The results are interpreted in terms of (solute + solvent) and (solute + solute) interactions in these systems.

Dhote and Bedare\textsuperscript{36} studied acoustic parameters of streptomycin solution at different concentration. Experimental measurements of ultrasonic velocity, density have been carried out on aqueous solution of Streptomycin at different concentrations at 303 K temperature and 2 MHz frequency. Ultrasonic studies may throw more light on the molecular interaction to know the behaviour of solute and solvent molecules in liquid mixtures and solutions.

Brattty et al.\textsuperscript{15} carried out conductometric determination of the antihistaminic diphenhydramine hydrochloride using silver nitrate as a titrant. The study developed and validated a conductometric method for determination of Diphenhydramine HCl (DPH) in its pure form and in a syrup formulation using silver nitrate ($\text{AgNO}_3$). Conductometric titration method
was achieved by using AgNO₃. The method is built on the reaction of chloride ions coming from the DPH with AgNO₃ yielding silver chloride precipitate. Conductance of the solution is measured as a function of the volume of titrant.

Lima et al. studied how alkali-metal cations affect the inclusion of decanoic acid in beta-cyclodextrin. An equimolar mixture of decanoic acid (Dec) with a concentration approximately 18 times above its critical micellar concentration (cmc) and beta-cyclodextrin (beta CD) in deuterated water have been studied by H-1 NMR, and the beta CD CH protons (H3, H4, H5, H6) have been used as probes for assessing the effects of varying the concentration of various alkali-metal chlorides (LiCl, NaCl, KCl, CsCl) on guest inclusion and aggregation processes. The observed chemical shift variations are consistent with the progressive aggregation of decanoic acid induced by an increase in [NaCl]. When the different salts were considered and their concentrations varied, Na⁺,K⁺, and Cs⁺ displayed a similar and common slope while Li⁺ showed a smaller gradient.

Sartori et al. carried conductometric determination of propranolol hydrochloride in pharmaceuticals. In this paper the conductometric titration of propranolol hydrochloride in pharmaceutical formulations using silver nitrate as titrant is proposed. The method was based on the formation of an insoluble salt (AgCl(s)) between the chloride of propranolol hydrochloride molecule and Ag(I) ions of the titrant AgNO₃. The effect of the PROP-AgNO₃ concentrations and the interval of time between the successive additions of the titrant on the shape of the titration curve were studied.

Sharma et al. determined ultrasonic velocity and carried viscosity studies of tramacip and parvodex in binary mixtures of alcohol and water. The viscosity and ultrasound velocity of narcotic analgesic drugs in aqueous mixtures of methanol, ethanol and 1-propanol have been studied. Various acoustical parameters have been obtained which include viscous relaxation time (Γ), free volume (Vf), internal pressure (πi) and molar cohesive energy (MCE). Temperature-dependent volumetric and viscometric properties of amino acids in aqueous solutions of an antibiotic drug were also studied.

Chauhan et al. studied temperature-dependent volumetric and viscometric properties of amino acids in aqueous solutions of an antibiotic drug amikacin sulphate (antibiotic drug) aqueous solution with the molality range of 0.025 mol kg⁻¹ – 0.25 mol kg⁻¹ were measured over the temperature range of 20 – 40 °C at the interval of 5 °C. Different parameters like apparent
molar volume ($\phi_v$), apparent molar adiabatic compression ($\phi_\lambda$), isentropic compression ($\kappa_S$) along with other acoustical parameters were calculated. The $\phi_v$ values are positive in both cases, but with higher magnitude observed in methionine.

Kaur and Kumar\textsuperscript{41} conducted viscometric measurements of L-serine with antibacterial drugs ampicillin and amoxicillin at different temperatures: (305.15 to 315.15) K. The viscosities, $\eta$ of L-serine with drug ampicillin (AMP) and amoxicillin (AMX) have been measured as a function temperature at $T = (305.15, 310.15$ and 315.15) K. The viscosity data have been utilized to determine viscosity B-coefficients employing the Jones–Dole equation. The trends of variation in viscosity values of amino acid with an increase in molal concentration of AMP and AMX solutions and also with an increase in temperature have been ascribed to the solute–solvent interactions operative in the solutions.

Rub et al.\textsuperscript{42} studied mixed micellization between amphiphilic drug promethazine hydrochloride and cationic surfactant (conventional as well as gemini) The micellization behaviour of an amphiphilic drug (promethazine hydrochloride (PMT)) in the presence of cationic surfactants (conventional as well as gemini) has been investigated conductometrically at different concentrations and temperatures. The micellar mole fractions of the surfactant(X1Rub, X1 M, X1 Rod, and X1 id), calculated by different proposed models, show greater contribution of surfactant in mixed micelle and increases with the increase in concentration of the surfactant. Although $\alpha_1$ (mole fraction of surfactant) is higher for DTAB than that of 12-4-12, the contribution of 12-4-12 is almost equal to that of DTAB.

Sharma et al.\textsuperscript{43} studied of partial molar volumes of some narcotic-analgesic drugs in aqueous-alcoholic mixtures at 25°C. Partial molar volumes of the drugs Parvon Spas, Parvon Forte, Tramacip, and Parvodex in aqueous mixtures of methanol (MeOH), ethanol (EtOH), and propane-1-ol (1-PrOH) have been determined. The data have been evaluated using the Masson equation. The parameters, apparent molar volumes ($\phi_v$), partial molar volumes and $S_v$ values (experimental slopes) have been interpreted in terms of solute-solvent interactions.

Syal et al.\textsuperscript{44} studied ultrasonic velocity studies of drug Parvon-spas in mixed alcohol-water solvent systems at 25 °C. Ultrasonic velocities and densities of the drug Parvon-spas in binary mixtures of water with methanol (MeOH), ethanol (EtOH), and propane-1-ol (1-PrOH) have been measured over the complete solvent composition range at 10mol% intervals at 298 K. Various acoustic parameters such as the acoustic impedance $(Z)$, adiabatic compressibility ($\beta$),
intermolecular free length (L_f), relative association (R.A.), molar volume (V_m), and molar sound velocity (R_m) have been calculated.

3. Research Gap Identification

Researchers have done lot of work on interactions of aqueous solutions of drug systems. Many pharmaceutical drugs and their interactions with amino acids and carbohydrates present in body fluid have been studied. However, a little work has been done on surface active drugs and their interactions with various electrolytes present in body fluid in terms of their micellar behaviour. There is no previous study reported about analysis of streptomycin and diphenhydramine in the presence of electrolytes with the help of conductometric, viscometric and volumetric studies in the term of self aggregation behaviour of these drugs. Therefore, we propose to investigate the drug-electrolyte interactions thermodynamically and consequently the effect of electrolytes on the aggregation behaviour of the amphiphilic drugs in aqueous medium.

4. Objectives

In light of above discussion, in the present study we propose to investigate the effects of different electrolytes viz. sodium chloride, potassium chloride, rubidium chloride, magnesium chloride, calcium chloride and strontium chloride on micellar behaviour of some surface active drugs namely, streptomycin sulphate and diphenhydramine hydrochloride in terms of electrostatic and hydrophobic interactions. Therefore, our objectives to investigate different drug-electrolyte aqueous systems are:

1. To calculate the CMC values and different thermodynamic parameters of micellization like \( \Delta H_m^o \), \( \Delta S_m^o \), \( \Delta G_m^o \), etc. by employing conductivity, UV Visible and Flourescence techniques.
2. To calculate the apparent molar volumes (\( \phi_v \)), isentropic compressibilities (\( \kappa_v \)), apparent molar isentropic compressions (\( \phi_\kappa \)) and different acoustical parameters by applying density and speed of sound measurements.
3. To calculate relative viscosity (\( \eta_r \)) and viscous relaxation time (\( \tau \)) by using viscosity measurements.
4. To calculate surface excess ($\Gamma_{\text{max}}$), minimum area per molecule ($A_{\text{min}}$), surface film pressure ($\Pi_{\text{CMC}}$), etc by implementing surface tension measurements.

5. Proposed Methodology

5.1 Materials
Doubly distilled water with conductivity $\sim 1-2 \times 10^{-7}$ s cm$^{-1}$ and pH of 6.8–7.0 at 298.15 K has to be used for all experiments. Diphenhydramine hydrochloride, streptomycin sulphate and electrolytes sodium chloride, potassium chloride, rubidium chloride, magnesium chloride, calcium chloride and strontium chloride of high purity have been purchased from Himedia Laboratories Pvt limited.

5.2 Methods

5.2.1 Conductivity Studies
The conductivity ($\kappa$) values of surface active drugs in aqueous solution of different electrolytes will be obtained in temperature range (298.15-313.15K) at an interval of 5 K using a calibrated conductivity meter, Cyberscan CON-510. The $CMC$ values will be determined from intersection point of plots of $\kappa$ versus concentration of drug$^{44}$. The $CMC$ values will be converted into mole fraction units ($X_{\text{CMC}}$) and then will be used to estimate the following standard thermodynamic parameters of micellization:

$$\Delta H_m^o = -RT^2(2 - \alpha)[d(\ln X_{\text{CMC}})/dT]$$

(1)

where $\Delta H_m^o$ is standard change in enthalpy of micellization, T is temperature in Kelvin, R is gas constant and $\alpha$ is counter–ion dissociation which is evaluated by using equation as

$$\alpha = \frac{S_2}{S_1}$$

(2)

here $S_2$ and $S_1$ are the slopes of conductivity curve in the post and pre micellar regions, respectively. The standard free energy change of micellization ($\Delta G_m^o$) and standard entropy change of micellization ($\Delta S_m^o$), will be estimated as follows$^{45}$:

$$\Delta G_m^o = (2 - \alpha)RT \ln(X_{\text{CMC}})$$

(3)

$$\Delta S_m^o = \frac{\Delta H_m^o - \Delta G_m^o}{T}$$

(4)
5.2.2 Surface Tension Studies
Surface tension of surface active drugs in presence of electrolytes will be carried out by using Man Singh Survismeter at different temperatures (298.15-313.15K) with an interval of 5 K. The surface tension ($\gamma_s$) will be calculated by using the relation\(^{46}\):

$$\gamma_s = \gamma_w \frac{n_s \rho_s}{n_w \rho_w}$$  \hspace{1cm} (5)

where $\gamma_s$ and $\gamma_w$ are surface tension of the solution and solvent respectively, $n_s$ and $n_w$ are the number of drops of solvent and solution respectively, $\rho_s$ and $\rho_w$ are the density of solvent and solution, respectively.

The surface active properties of pure surfactant, effectiveness ($\pi_{cme}$), maximum surface excess ($\Gamma_{max}$), minimum area per molecule ($A_{min}$) will be calculated using the following equations\(^{46}\):

$$\Gamma_{max} = -\frac{1}{2.303nRT} \frac{\delta \gamma}{\delta \log C}$$  \hspace{1cm} (6)

$$A_{min} = \frac{10^{38}}{[\Gamma_{max}.N_A]}$$  \hspace{1cm} (7)

$$\pi_{cme} = \gamma_0 - \gamma_{cme}$$  \hspace{1cm} (8)

where $\frac{\delta \gamma}{\delta \log C}$ is the slope calculated from the graph plot between $\gamma$ vs $\log C$, $n = 2$ in all the cases. $\gamma_0$ is the surface tension measured for pure solvent at the appropriate temperature and $\gamma_{cme}$ is the surface tension at CMC.

5.2.3 Viscometric Studies
Viscosity ($\eta_s$) of drugs in presence of electrolytes solution at different temperatures (298.15-313.15K) with an interval of 5 K will be carried out by using Ostwald viscometer. The $\eta_s$ values will be calculated by using the relation

$$\eta_s = \eta_w \frac{t_s \rho_s}{t_w \rho_w}$$  \hspace{1cm} (9)
where $\eta_s$ is viscosity of solvent, $t_w$ and $t_s$ are time of flow of solvent and solution respectively, $ho_w$ and $\rho_s$ are density of solvent and solution respectively. The viscosity values will be further used to calculate relative viscosity ($\eta_r$) and viscous relaxation time ($\tau$) using the relations:

$$\eta_r = \eta_s / \eta_o$$  \hspace{1cm} (10)

$$\tau = \frac{4\eta_s}{3u^2 \rho}$$  \hspace{1cm} (11)

### 5.2.4 Volumetric, Compressibility and Acoustical Studies

Density ($\rho$) and speed of sound ($u$) of surface active drugs in aqueous solution of electrolytes will be performed with a high-precision digital Density and Sound Velocity Analyzer–5000 (DSA–5000) at different temperatures (298.15-313.15K) with an interval of 5K. The apparent molar volume ($\phi_v$), isentropic compressibility ($\kappa_s$) and apparent molar adiabatic compression ($\phi_\kappa$) values of surface active drug would be calculated using the following relations:

$$\phi_v = \frac{M}{\rho} + \frac{[\rho_o - \rho]}{m\rho\rho_o}$$  \hspace{1cm} (12)

$$\kappa_s = 1/u^2 \rho$$  \hspace{1cm} (13)

$$\phi_\kappa = \phi_v \kappa_s + \frac{[\kappa_s - \kappa_o]}{m\rho_o}$$  \hspace{1cm} (14)

where, $m$ is the molality of the solution, calculated as amount of drug per unit mass of solvent where solvent is either pure water or 0.01 mol·kg$^{-1}$or 0.002 mol·Kg$^{-1}$ aqueous solutions of electrolytes and $M$ for relative molar mass of drug, $\rho$ and $\rho_o$ are the densities of the solution and pure solvent, respectively.

In addition, following acoustical parameters will be evaluated from the density and speed of sound data, which are expected to give significant information about the solvation behaviour of the surface active drug in aqueous solutions of electrolytes.

- Specific acoustic impedance, $Z = u \times \rho$  \hspace{1cm} (15)
- Intermolecular free length, $L_f = K \times \sqrt{\kappa_s}$  \hspace{1cm} (16)
  where, $K = [(93.875 + 0.375T) \times 10^{-8}]$
- Relative association, $RA = \left(\frac{\rho}{\rho_o}\right) \times \left(\frac{u_o}{u}\right)$  \hspace{1cm} (17)
Sound velocity number, 
\[ U = \frac{(u - u_o)}{u_o} \times m \]  \hspace{1cm} (18)

Using experimental density, speed of sound and viscosity, different thermo-acoustical parameters viz. free volume \( V_f \), molar volume \( V_m \), internal pressure \( \pi_i \) and molar cohesive energy \( MCE \) will be calculated:

\[
V_f = \left[ \frac{M_u}{K' \eta} \right]^{\frac{1}{2}} \hspace{1cm} (19)
\]

\[
V_m = \frac{M}{\rho} \hspace{1cm} (20)
\]

\[
\pi_i = \frac{bRT (K' \eta / u)^{\frac{1}{2}} \times \rho^{\frac{2}{3}}}{M^{\frac{7}{6}}} \hspace{1cm} (21)
\]

\[
MCE = \pi_i V_m s \hspace{1cm} (22)
\]

where \( \eta \), \( \rho \) and \( u \) are the viscosity, density and speed of sound of the solution. \( K' = 4.28 \times 10^9 \) is constant and is independent of nature of liquid. Packing factor \( b \) is assumed to be 2 in liquid systems. \( \bar{M} \) is the average molecular weight of the solutions which is defined as follows:

\[
\bar{M} = \bar{M}_{12} + \text{Weight of solute} \hspace{1cm} (23)
\]

where \( \bar{M}_{12} = x_1M_1 + x_2M_2 \) is average molecular weight of solvent, here \( M_1 \) and \( M_2 \) are the molecular weights, and \( x_1 \) and \( x_2 \) are mole fractions of the solvent components (electrolyte + water).

### 5.2.5 Fluorescence Probe Studies

Pyrene has to be used as fluorescence probe to obtain \textit{CMC} values of surface active drugs in the presence of electrolytes. This method is based upon the solvent dependence of vibrational band intensities in pyrene monomer fluorescence. There are five emission peaks at 373, 379, 383, 389 and 393 nm for monomer fluorescence emission spectra of pyrene \( (2 \times 10^{-6} \text{mol} \cdot \text{kg}^{-1}) \) in aqueous electrolytic solution of drugs \( ^{49,50} \). The ratio of \( I_1 \) to that \( I_3 \) is related to the polarity of the microenvironment around the pyrene, lower value of \( I_1/I_3 \) indicates apolar environment \( ^{50} \). In the absence of micelles (below \textit{CMC} ) pyrene senses the polar environment of water molecules and results in higher \( I_1/I_3 \) values. However, above \textit{CMC} , when micelles are present, pyrene molecules are solubilized in the interior of micellar phase owing to their high hydrophobicity.
This is a hydrophobic–like solvent, so the environment sensed by pyrene is less polar thereby resulting in the decrease of $I_1/I_3$ values. It clearly shows that the pyrene senses the polar environment of solvent system pertaining to electrovalent interaction between drugs and electrolytes. Thus this technique will also be used to calculate CMC values.

5.2.6 UV–Visible Probe Studies

UV-Vis spectroscopy provides supporting evidence about the formation of micelles in the solution. The spectra with varying concentration of drugs will yield important information regarding the interaction between pyrene and surface active drugs. Simple UV-Vis absorbance spectrum of pyrene in water gives four strong peaks at 242, 272, 320 and 336 nm due to multiple rings. The total absorbance, $A_T$ i.e. the sum of absorbance of all the four strong peaks is plotted against the concentration of drug. At the low drug concentration, there is very small increase in the absorbance as pyrene resides in polar environment of water molecules. But when the concentration reaches CMC value, there is sudden increase in absorbance because of tendency of hydrophobic pyrene to reside in a non-polar environment provided by the micelles. Also the lack of hydrophilicity of pyrene helps it to stay at the interface. This reduces the hydrophobic repulsions between water and pyrene. It also reveals the importance of ionic interactions between the pyrene molecules and ionic head group of drug. The absorbance-drug concentration profiles will be used to calculate the CMC of the ionic surface active drugs in aqueous solutions of electrolytes.

5. Thesis Outline

CHAPTER 1 (Introduction): A brief introduction of surfactants, amphiphilic drugs, electrolytes and the aggregation beaviour of amphiphilic drugs will be presented in this chapter.

CHAPTER 2 (Literature Review): This chapter will give the overview of literature on research work done in the field of drugs, their interactions with various co-solutes and effect of interactions on physiochemical properties.

CHAPTER 3 (Materials and Methods): All the details of materials and methods used for present research work will be included in this chapter.

CHAPTER 4 (Results and Discussion): This chapter will include results and discussion of various studies conducted and their interpretations in terms of solute-solute and solute-solvent interactions.
CHAPTER 5 (Summary and Conclusions): This chapter concludes the work on the physiochemical properties of drugs especially aggregation behaviour in terms of drug-electrolyte interactions in aqueous system.

Research Plan Schedule

<table>
<thead>
<tr>
<th>Research Activity</th>
<th>Progress in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course work, extensive literature survey or design of work</td>
<td>Jan 2015 to Dec 2015</td>
</tr>
<tr>
<td>Research gap identification and development of methodology</td>
<td>Jan 2016 to July 2016</td>
</tr>
<tr>
<td>Experimental Work and Publications</td>
<td>August 2016 to August 2018</td>
</tr>
<tr>
<td>Thesis writing and publications</td>
<td>August 2018 to Dec. 2018</td>
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References


(46) Kumar, K.; Chauhan, S. Surface Tension and UV-Visible Investigations of


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