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A Review Conductometric Measurement of Interaction of Anionic Surfactant with Phenothazine Drug at Room Temperature

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Abstract

Prometizine Hydrochloride-PMZ is a first generation HI receptor antagonist, Antihistimine, and anti- emetic medication that can also have a strong sedative effect[11]. The incidence and severity of drug interractions are on the rise as more medications are brought to market. For a drug to get to its target soon as possible, the critical micelle concentration- cmc must be appreciably low. However, most drug's cmc are higher which generally leads to wastage of fund; It then means more drugs will be taken in to the biological system for effective delivery. This review aimed at the interaction of amphilphile with anionic surfactant which may usually helps in bringing down cmc as at when required. Conductometric measurement gives detailed picture of the interraction between Promazine [PMZ] and Sodiumduodecylsulphonate [SDS] using conductometric titration. Solid Promethazine hydrochloride is an odourless white faint yellow which can medically act sedatives, for combating hay fever and migraines, and to reduce nervousness and agitation.

Keywords: Amphiphilic, Surfactant, Critical Micelle Concentration.

Introduction

Amphiphile is a chemical compound with both hydrophilic and hydrophobic properties. Their interactions with different nature of pharmaceuticals is important for biological and pharmacological and clinical process. Amphiphilic compound bears an ionic (zwitterionic, anionic or cationic) or non polar head group and a hydrophobic portion [1]. A lots of insoluble drugs (hydrophobic)will require a carrier for its secure delivery to targeted organs, and the lower the critical micelle concentration- cmc, the better it is for the drug to get to get to its target, whereas, many membrane systems are encountered when drug make a way to its target site.[3]The measurement of partition coefficient of the drug in aqueous and micellar system can be used as a measure of the ease of movement of drug through these membrane systems[4].

Malik et al.,2017 showed that the association or micelles begin to form at the concentration corresponding to the intersection of lines; which means the break point of specific conductivity (k) versus the PMT- Promazine were used as the CMC value for the pure amphiphiles. Whereas, Abban khan et al.,2015 [79] emphasized that the measurement of specific conductivities provides more scientific technique to detect cmc of ionic surfactant, and this is also testified in [75-78]. Apart from this, his surface tension's measurement to determine cmc showed a gradual decrease in surface tension with an increase in surfactant concentration reflecting the surface activity of amphiphilic nature of SDS in his result. R.M.Martine et al.,2006 confirmed that due to the presence of salts in all body fluids, and to the potential applications in pharmaceutical formulations, interraction of various additives with surfactants are studied in the presence of salt [80]. Although, most of the surfactant used in practice are not pure compared to mixture of several surfactants.

The spatial separation between the polar and non polar moities as well as the molecular shape [34] and the hydrophilic-hydrophobic balance HHB [35] determines their tendency to form the different structure which eventually can interconverted as a function of pH, temperature, ionic strength, concentration. Drug's distribution in the body is majorly effected by molecular polarity [23]. Classes of amphiphilic drugs include phenothiazine [41-51] and benzodiazepine [52], tranquilizers, analgesic [53], peptide [54], and non peptide [55,56], antibiotics, tricyclic anti depressants[57-59], antihistimines[60], anticholinergics,[61] β -blockers [62] local anasthetics[40, 63-66], non steroidal antiinflammatory drugs [67], anticancer drug [68].

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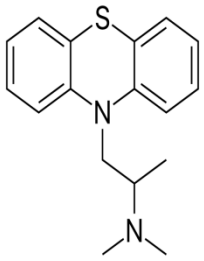
Drugs may be lipophilic or hydrophilic. Lipophilic drugs are non polar and distribute into adipose tissue as well as passing the brain blood barrier[7], whereas, polar drugs hydrophilic and are mainly distributed in lean body tissue. Sara *et al* , 1995 reported that large stable biomolecules can reach their destination easily but small biomolecules (with an upper moleculer weight of approximately 900g/mol^{-1}, are not able to reach their target in effective concentrations because of the dissociation in water/ acid prior to reaching the lipophilic target due to their high hydrophilicity. Introduction of surfactant could anyway curb this challenge.

Structure of Promethazine Drug



Prometizine inhibit the brain Napkp-ATPase and the mitochondrial permeability transition pore. Since its first introduction in 1946, it has been used for prevention and treatment of nausea and vomitting caused by narcotic therapy, migraine episodes, cancer chemotherapy[17]. The utilization of hydrotropes as drug vectors is beneficial relative to other substitutes because some drugs exhibits hydrotropism [12]. An hydrotrope is a compound that solubilizes hydrophobic compound in aqueous solutions. It typically consists of hydrophobic part and hydrophilic part. The chemical structure of the convectional Neuberg's hydrotropic salts consists generally of two essential parts, an anionic ring or ring system. To form hydrotropes, an aromatic hydrocarbon solvent is sulfonated creating an aromatic sulfonic acid. It is then neutralised with a base. Hydrotropes are in use industrially and commercially in cleaning and personal care products formulations to allow more concentrated formulation of surfactants. Hydrotropes have the ability to obstruct and or to manage the phase separation phenomenon as well as also have considerable micellization / solubilization improving capability of the compound [12].

According to Dileep and Malik(2016). The majority of the drugs are organic `molecules of distinct molecular structure having hydrophobicity, Several of these hydrophobic drugs have amphiphilic nature, and for this reasons, amphiphilic drug undergoes aggregation and adsorption in aqueous solution to surfactant. The spatial separation between the polar and non-polar moieties, as well as the molecular shape and the hydrophilic- hydrophobic balance (HHB) determines their tendency to form the different structures, which eventually can be inter-converted as a function of pH, temperature, ionic strength, concentration [34,35]. Surfactant have self aggregation properties, they interact with model and biological membranes, promoting lysis and tend to associate as micelles[2].

Micelle

Micelle formation is a stepwise process characterised by a series of equilibrial and equilibruim constant or as phase separation (all or none) process such that, once a critical concentration (cmc) is reached, further addition of the surfactant will result in aggregation [36]. It is a particle of colloidal dimension that exist in equilibrium with the molecules or ions in solution from which it is formed [22]. Polymeric micelles have a much lower critical micelles concentration (cmc) than soap or surfactant micelles, but are nevertheless at equilibrium with isolated macromolecules called unimers. Therefore, micelle formation and stability are concentration- dependent [26]. The micellar systems help in the transport of the drug to the specific site, and thus minimize drug degradation and increase bioavailability [28,29,30,31,32, 33]. Micelles are characterised by physicochemical parameters such as the cmc, aggregation number (N), Particle size (HHB) [1]. Shape of micelle is always spherical, but are known to grow with increasing in detergent concentration, becoming cylindrical shape[36].

The shape and size of a micelle are a function of the molecular geometry of its surfactant molecules and solution conditions such as surfactant concentration, temperature, pH, and ionic strength. Micellisation is the process of forming micelle which is as a result of when concentration of surfactant is greater than the critical micelle concentration (cmc), and the temperature of the system is greater than the critical micelle temperature or Krafft temperature. When surfactants are present and above the cmc, they can act as emulsifier that will allow a compound that is normally insoluble to dissolve. This occurs because the insoluble species can be incorporated into the micelle core, which itself solubilised in the bulk solvent by virtue of the head groups favourable interactions with solvent species. The most common example is detergent, which clean poorly soluble lipophilic material (oils, waxes) that cannot be removed by water alone. Micelle can rotate about their long molecular axes [37,38], diffuse laterally along the micellar surface [39] and, when formed by alkyl chain-containing surfactants, the chains, being highly flexible, can undergo segmental motions [37, 38] Micelle can be more loosely packed and less stable when compared with other aggregates such as bilayers[40].

Surface Active Drugs

Surface active drugs of quite different chemical structure are reported to self associate and bind to membranes, causing disruption and solubilization, in a detergent -like manner [1]. Drug is a substance which when taken into the body, alters the body function either physically and or physiologically. Drug may be legal

(alcohol, caffeine, tobacco) or illegal (cannabis, ecstasy, cocain, heroin). Drug must partition to a well-defined and energetically favourable environment, orientation, and conformation in the membrane layer before diffusing into intrabilayer receptor binding cell [19]. Some reports has shown that surface active drugs can be mixed with cationic surfactants to form cationic vesicles and micelles, which when incorporated into gels, were useful in slowing release rates of active pharmaceutical ingredient [15]

Surfactant

Surfactants possess a characteristics chemical structure that consists of (1) molecular component that will have a little attraction for one surrounding (i.e solvent) phase, normally called the lyophobic group, and (2) chemical units that have a strong attraction for that phase- the lyophilic group [25]. Surfactant have hydrophilic and hydrophobic moieties in their structures, and they function to adsorb at interface and effect solubilization [20].

Surfactant which may act as wetting agents, emulsifier, foaming agent are compounds that lower the surface tension between two liquids, between a gas and a liquid, or between a solid and a liquid [14]. The 'tails' of most surfactant are fairly similar, consisting of a hydrocarbon chain, which can be branched, linear, or aromatic. Many important surfactant include a polyether chain terminating in a highly polar anionic group.

Anionic Surfactant

Anionic surfactant carries a negatively charged head groups. In principle, any negatively charged functional group that can complex with a counterion may lend itself to be cationic surfactant. A non-ionic surfactant has no charged groups in its head. The head of an ionic surfactant carries a net negative or positive charge. If the charge is negative, the surfactant is more specifically called anionic, If the charge is positive, it is called cationic.[25]. Dauli *et al*., 2014 reported that some cationic surfactant are already in use in different drug formulations such as Cetalkonium chloride used to retard the release of an opthalmic drug. Surfactant (detergent) tend to associate as micelles; in these structures the hydrophobic portion is sequestered from the highly polar aqueous medium by a surrounding , approximately spherical, shell formed by the polar or ionic head groups. [1]

Conductometry

This is a measurement of electrolytic conductivity to monitor a progress of chemical reaction. It is a type of reaction in which the electrolytic conductivity of the reaction mixture is continuosly monitored as one reactant is added. The equivalent point is the point at which the conductivity undergoes a sudden change. Conductometry is used as a synonyms of conductometric titration while the, term conductimetric is used to describe non-titrative applications.

Partition or Distribution Coefficient

This is the ratio of concentration of a compound in a mixture of two immiscible phases at equilibrium (P) is useful in estimating the distribution drug within the body. Partition coefficient of a drug may be determined by shaking it with equal parts of two immiscible solvent (organic layer which is saturated with water and the aqueous drug solution) until the equilibrium is attained. The content of drug in one of the layers is determined and the value is calculated.

Binding Constant (Association constant)

This is a special case of the equilibrium constant K, and is the inverse of the dissociation constant. It is associated with binding and unbinding reaction of receptor R and ligands L molecule R+L= RL The reaction is characterised by the on rate constant K on and the off rate constant K off which have the unit of M^{-1} S^{-1} and S^{-1} respectively.

$$Kon\,[R][L] = Koff[RL]$$

$$Ka = \frac{Kon}{Koff} = \frac{[RL]}{[R][L]}$$

Binding Affinity

This is typically measured and reported by the equilibrium dissociation constant[KD], which is used to evaluate and rank the order of bimolecular interaction. Decrease in KD value increase the Binding affinity.

Dissociation Constant

This is a mathematical constant that describes the tendency of a large molecule to dissociate reversibly into smaller components. For an acid, the distribution constant is called Ka.

Bathochromic Shift

This is the shift of absorption to a longer wavelength due to substitution or solvent effect (a red shift). Longer wavelength, lower frequency. A covalently unsaturated group responsible for electronic absorption (for example C=C, C=O, and NO_2). Bathochromic shift is change of spectral band 0position in the absorption, reflectance, transmittance, or emission spectrum of a molecule to a longer wavelength .Because the red colour in the visible spectrum has a longer wavelength than most other colours, the effect is also commonly known as a RED SHIFT. It is a change that occur because of the red colour in the visible has a longer wavelength than most other colours.

Hypochromic shift

It is a change to a shorter wavelength (higher frequency). It can occur because of a change in environmental conditions. For example, a change in solvent polarity will result in solvatochromism. A series of structurally related molecules in a substitution series can also show a Bathochromic Shift. It is a phenomenon seen in molecular spectral, not atomic spectra. It is thus

more common to speak of the movement of the peaks in the spectral rather than lines. [10,5]
$\Delta\lambda = \lambda$ state 2 observed -λ state 1 observed
λ - the wavelength of the spectral peak of interest
state 2 is greater than state 1

Calculation and Parameters
Binding Constant

The values of the binding contant is obtained according to the methods described by Gokturk *et al.*,2003

$$kb = \frac{[SM]}{[SW][DM]}$$

S_W and S_M are substrate [PMZ] concentration in the aqueous phase and the micella pseudophase respectively.
D_M is the concentration of surfactant molecules in the micellar form
K_b is the associated equilibrium of binding constant
ε_m is the molar absorbtion coefficient
K_b and ε_m is determined using the Benesi- Hildebrand equation which is valid for high surfactant concentrations. [69,70]

$$\frac{l[PMZ]}{A0-A} = 1 + \frac{1}{\in m - \in 0} + \frac{1}{Kb[Sm](\in m - \in 0)}$$

Where [PMZ] and [Sm] are the initial molar concentration of PMZ and the micellized surfactant concentration respectively
Sm= Total SDS concentration - cmc
l= optical path length of the solution
A and A0 are the absorbance of PMZ in the presence and absence of surfactant like Sodiumduodecyl sufonate-SDS respectively.
The plot of $\frac{l[PMZ]}{A0-A}$ against $\frac{1}{Sm}$ is used to calculate Kb values at different temperatures from the slope and intercept.

Partition Coefficient K_x

Absorbance values obtained at λmax is useful to calculate K_X according to Sepulveda *et al*., 1986 and Kawamura *et al*., 1991

$K_X = X^m_{PMZ} / X^w_{PMZ}$

X^m_{PMZ} and X^w_{PMZ} are the mole fractions of the PMZ in the micellar and aqueous phases respectively.

$X^m_{PMZ} = C^m_{PMZ} / C^m_{PMZ} + C^m_{surfactant}$ 1

$X^w_{PMZ} = C^w_{PMZ} / C^w_{PMZ} + C^w_{surfactant} + n_w$ 2

Where $C^m_{surfactant}$ and $C^w_{surfactant}$ represent the concentration of surfactant micellar and monomeric states
n_w= 55.5moldm^{-3} is molarity of water.
Under the present experimental conditions, $C^m_{PMZ} + C^w_{surfactant} << n_w$
If Ks is expressed as K_X/n_w, we get the equation

$$KS = \frac{C^w_{PMZ} / (C^w_{PMZ} + C^w_{surfactant})}{C^w_{PMZ}} \quad .....3$$

Using equations 1 and 2, Equation 4 can be written in linear form

$$\frac{1}{\Delta A} = \frac{1}{\Delta A\infty} + \frac{1}{Ks\Delta A\infty(CPMZ + Csurfactant - CMC)}$$

Ks and kx are obtained from the slope of the plot of $\frac{1}{\Delta A}$ versus $\frac{1}{(CPMZ + Csurfactant - CMC)}$

Solvatochromism

This is the phenomenon observed when the colour due to solute is different when that solute is dissolved in different solvent. Solvatochromic effect is the way the spectral of a substance (solute) varies when the substance is dissolved in a variety of solvents. In this context, the dielectric contant and hydrogen bonding capacity are the most important properties of the solvent [13]. With the various solvents, there is a different effect on the electronic ground state and excited state of the solute, so that the size of the energy gap between them changes as the solvent changes. This reflected in the absorption or emission spectrum of the solute as the differences in the position, intensity and shape of the spectroscopic band. When the spectroscopic band occurs in the visible part of the spectrum, solvatochromism is observed as a change of colour. Negative solvatochromism corresponds to a hypsochromic shift (blue shift) with increasing solvent polarity. Example, 4-(4- hydroxystyryl)-N-methylpyridinium iodide. It is red in propanol and orange in methanol, yellow in water.

Positive solvatochromism corresponds to a bathochromism shift (red shift) with increasing solvent polarity. Example, 4,4-bis(dimethylamino) fushone. It is orange in toluene, red in acetone. [18].

Conclusion

From the above overview, it could be inferred that the addition of different additives could actually bring down CMC detailed in [79]. Decrease in surface tension with an increase in surfactant concentration would be a reflection of surface activity and amphiphilic nature of SDS, this can be attributed to fact that hydrogen(dodecyl) chain broke the intermolecular bond when SDS is dissolved in water. The more the surfactant, the lower the surface tension and the more the free energy of the system.

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