International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Physicochemical Investigations on the Interaction of Surfactants with Drugs: A Mini Review

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ABSTRACT

All vertebrates, including human beings, naturally contain steroidal anionic amphiphiles, such as bile salts/biosurfactants/bile acids. Pharmaceutical products are developed using bile salts that are present in the intestines of humans as well as the animals. Surface-active substances known as surfactants can be made chemically or biologically. Surfactants, both bile salts and conventional, generate micelles, A sort of molecular arrangement that organises itself, above their critical micelle concentration (CMC). The chemical nature of hydrophilic and hydrophobic molecules, structure, temperature, the presence of electrolytes or non-electrolytes, the solvent, the type of counter ions, pH, and other factors all affect the CMC value of surfactants. When a drug is absorbed and becomes available to the body, its pharmacological activity is observed. Therefore, understanding their interactions with other substances in the system is important for understanding their role in biological systems. Before a medicine reaches its intended organ, it must first pass through a cellular membrane during use.

Several physicochemical techniques have been used to investigate the interactions of numerous pharmaceutical drugs with amino acids, carbohydrates, peptides, surfactants, and salts, among other substances, in both aqueous and non-aqueous media. The aim of this paper is to increase our understanding of the basic ideas regarding surfactant-drug interactions in order to help develop more stable and efficient pharmaceutical formulations.

Keywords: Amphiphiles**;** Micelles; Drug; Critical micelle concentration (CMC); Pharmaceutical

INTRODUCTION:

All vertebrates, including human beings, naturally contain steroidal anionic amphiphiles, such as bile salts/biosurfactants/bile acids. The human body primarily contains three types of bile acids: chenodeoxycholic, deoxycholic, and cholic acids. Their molecular makeup, however, sets them apart from other amphiphiles found in the body, such as phospholipids and the extensively researched head-tail surfactants. They are the primary by-products of the liver's breakdown of cholesterol. The gallbladder stores them, and the bile duct secretes them into the small intestine. The main route by which the body gets rid of cholesterol is through the production of bile salt [1]. Pharmaceutical products are developed using bile salts that are present in the intestines of humans as well as the animals [2].

Amphiphilic molecules, like surfactants, have both hydrophobic and hydrophilic groups on them, at critical micelle concentration (CMC) aggregates to form micelles.

Surfactants are useful in a variety of industrial and household applications due to their tendency to generate micelles. Surface-active substances known as surfactants can be made chemically or biologically. Nonetheless, the capacity to produce micelles persists regardless of the source of their synthesis, even though it may occur through many mechanisms. Scientists interest in bile salts, has recently increased considerably due to biocompatibility, environmental friendliness of these molecules. Additionally, they have been acknowledged as a better option to traditional surfactants in various industrial applications including pharmaceutical sector, bile salts are employed in the pharmaceutical industry as a penetration enhancer to address one of the complications faced by the sector right now, the low solubility/permeability of medicinal molecules. In order to provide a therapeutic effect, the drug molecule should have a high/reasonable solubility/permeability to enter bodily fluids and eventually target tissues. Therefore, researching the drug-bile salt system's interactional behaviour could be both fascinating and beneficial [1].

The technique known as hydrotropy was first described by the scientist Carl Neuberg in 1916. It involves addition of a significant amount of a secondary solute to water, that will improve the aqueous solubility of primary solutes in magnitude. An example of this would be a medicine that is poorly soluble. An anionic group plus a hydrophobic aromatic ring will act as a hydrotrope, a weakly amphiphilic chemical molecule in this case. Arginine act as hydrotrope for Lovastatin a cholesterol-lowering drug, that is specific competitive inhibitor of 3-hydroxy 3-methylglutaryl-coenzyme A (HMGCoA) [3].

Surfactants:

Surfactants are substances that reduce the surface tension that exists between two liquids or a solid and a liquid. These are a class of compounds that tend to form aggregates of different types due to the presence of polar and non-polar groups present in the same molecules. They can function as detergents, emulsifiers, and wetting agents. Surfactants are organic molecules that are amphiphilic chemically, meaning that their heads and tails include hydrophobic and hydrophilic groups respectively. Most surfactants have somewhat identical tails, made up of a hydrocarbon chain that might be aromatic, linear, or branched. As a result, surfactant molecule contains both water insoluble and water-soluble components. This characteristic enables surfactants to get absorbed at air-water interfaces and diffuse into the water. The capacity of amphiphilic surfactant molecules to combine in solution is a crucial characteristic. The type of amphiphilic molecule and the solvent that is used to dissolve determine how both aggregate at a specific surfactant concentration in solution. The aggregation of surfactant molecules leads to the formation of a micelle. Micelle creation is referred to as micellization, and the critical micelle concentration (CMC) is the precise concentration of surfactant molecules in solution for its formation. Surfactants, both bile salts and conventional, generate micelles, a kind of self-organized molecular assembly, above their critical micelle concentration (CMC).

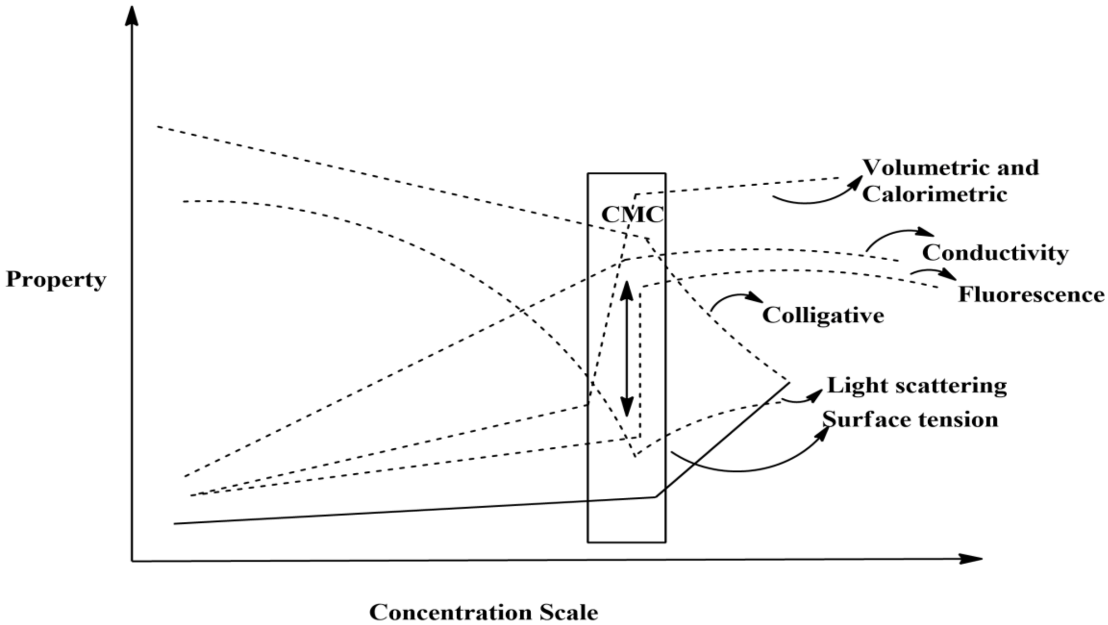

Figure 1: The variation in physical properties with concentration of surfactants.

The fundamental force responsible for this self-assembly is the hydrophobic effect, although hydrogen bonding, Vander Waals, and electrostatic interactions also play a vital role in determining how the self-association occurs [4]. When any physicochemical parameter is plotted against the concentration of surfactant molecules, the lowest concentration at which the molecules begin to aggregate, visible in graph as an inflection point (Figure 1) is known as the critical micelle concentration (CMC) [5].

The chemical nature of hydrophilic and hydrophobic molecules, Structure, temperature, the presence of electrolytes or non-electrolytes, the solvent, the type of counter ions, pH, and other factors all affect the critical micelle concentration (CMC) value of surfactants [6].

When a sufficient quantity of salts (inorganic or organic chemicals) is added, surfactant molecules can form a variety of self-aggregates in aqueous media, including rod-like and worm-like micelles, vesicles, and liquid crystals (hexagonal, lamellar, and cubic structure). When an anionic surfactant is present, the surface of a surfactant aggregates each polar head group is also highly dependent on the presence of the counterion and, more precisely, on its ability to attach to the surfactant aggregate. On the other hand, additional counterions decrease the effective area per head group by reducing the repulsive interaction between the head groups, making them a suitable means of stimulating morphological transition in surfactant aggregates [7].

On the basis of dissociation of surfactants in water, they are classified into four types: anionic, cationic, non-ionic, and zwitterionic. The most widely used surfactants are anionic surfactants, which dissolve in water to form an amphiphilic anion and a cation. These consist of fatty acid soaps, lauryl sulphate (foaming agent), lignosulfonates (dispersants), and alkylbenzene sulfonates (detergents) etc. About half of all surfactants produced worldwide are anionic. In water, cationic surfactants separate into an anion (usually halogen) and an amphiphilic cation. This class includes a significant amount of nitrogen compounds, such as quaternary ammoniums and fatty amine salts, which have one or more long alkyl chains and often derived from naturally occurring fatty acids. Second place goes to non-ionic surfactants, which account for roughly 45% of total industrial production. Since their hydrophilic group is of nondissociable type such alcohol, ester, phenol, ether, or amide they do not ionize in aqueous solution. A significant amount of these non-ionic surfactants has a polyethylene glycol chain, which is produced by polycondensing ethylene oxide, which makes them hydrophilic. They are known as non-ionic polyethoxylated polymers. Due to their low toxicity, glucoside head group that are based on sugar, have been brought to the market in the last ten years. When it comes to the lipophilic group, it is often alkyl or alkylbenzene based, with the former originating from naturally occurring fatty acids. Amphoteric or zwitterionic surfactant refers to a molecule, which exhibits both anionic and cationic dissociations. This is true for both natural and synthetic materials, such as phospholipids and amino acids, as well as betaines and sulfobetaines [8].

Bile Salts (Sodium cholate and Sodium deoxycholate):
Bile salts are endogenous surfactants that exist naturally and have exceptional biological compatibility, biodegradability, and low toxicity. By increasing drug solubility or changing the permeability of cellular membranes, bile salts can also improve transport through biological membranes.
Sodium cholate (NaC) molecular formula $C_{24}H_{39}O_5Na$ and sodium deoxycholate (NaDC) molecular formula $C_{24}H_{39}O_4Na$ are the bio-surfactants (Figure 2).

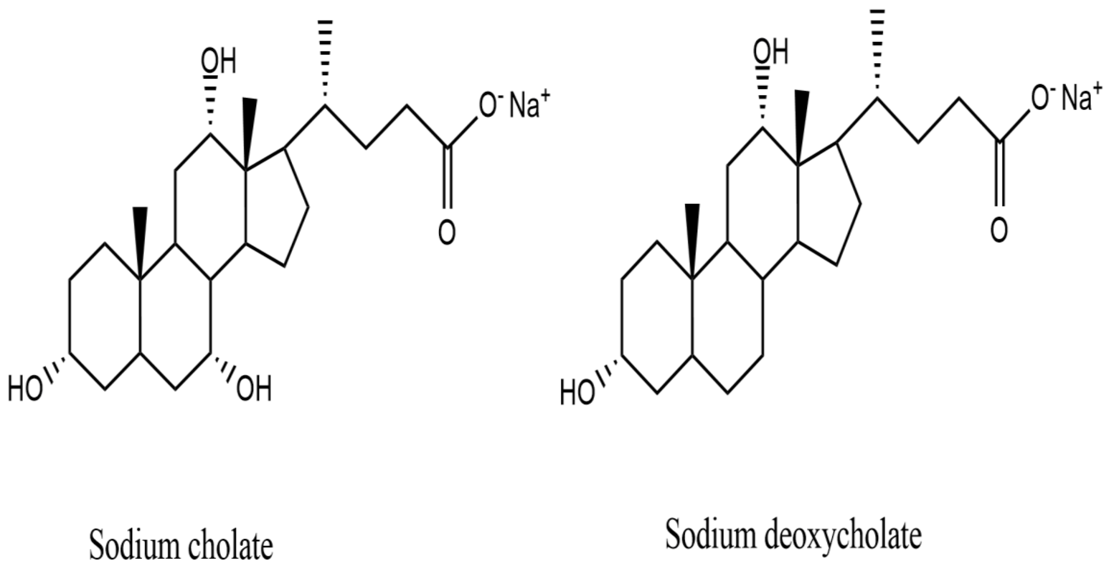

Figure 2: Chemical structure of sodium cholate and sodium deoxycholate

The molecular weight of sodium cholate is 430.6 g/mol and sodium deoxycholate is 414.6 g/mol. The NaC and NaDC, CMC value has been experimentally observed as 14.1 mmol/kg and 5.4 mmol/kg respectively [9]. Unlike other surfactants, the salt of bile acids creates small size micelles in aqueous solutions [10]. Bile salts are highly important in medicines since they are biocompatible and physiologically relevant compounds. Water soluble bile salts NaC and NaDC have good acceptability for use in medicinal applications [11].
At various temperatures, the aggregation of various bile salts in aqueous solution is being investigated both with and without NaCl (0.15 mol kg^{-1}). The findings indicate that micellization is favoured by both an increase in side chain length and a decrease in ring hydroxyls, both in the presence and absence of salt. This is because the bile salt molecules hydrophobic/hydrophilic balance has increased, favouring the movement of the hydrophobic portions of the molecules through the aqueous phase towards the micellar interior. Micellizations is favoured when NaCl (0.15 mol kg^{-1}) is present in the aqueous phase because it

lowers the CMC since fewer electrostatic repulsions exist among the negatively charged groups of the bile salt molecules that form the micelles [12].

Drug:

"Drug" refers to any chemical substance when absorbed into the body of a living organism, modifies normal body function. In fact, the human body makes several attempts to cope with this foreign molecule. When a drug is absorbed and becomes available to the body, its pharmacological activity is observed. To comprehend the physiological action, however, one must understand the importance of drug absorption through the gastrointestinal tract, as well as pharmacokinetics-the biological system's reaction to the medication and pharmacodynamics-the drug's reaction to the biological system.

The physical form of the drug (tablet, topical ointment, and capsule etc.) as well as the route of administration (oral or injectable etc.) as well as the anatomical and physiological characteristics of the application site, the expected pharmacodynamic effect (e.g., immediate or prolonged activity), the physicochemical properties of the drug molecule, the nature of the product's excipients, and the manufacturing process, among other factors, determine the physiological action of the drug. Drug absorption, however, is controlled by a perception that characterizes the purpose of the dose taken, that is, the interaction of the drug molecules solubility, dissolving rate, and permeability. The drug compounds solubility and permeability in bodily fluids can vary.

The drug's bioavailability and the rate of its absorption are mainly determined by the drug's solubility and the permeability in gastrointestinal tract. Macromolecules play a crucial role as fundamental cellular elements in biological systems, carrying out numerous functions essential for the growth and survival of living organisms. These are called as biomolecules. A biomolecule is a molecule generated by living organisms, predominantly consisting of organic molecules. The major classes of these biomolecules include proteins, lipids, bile salts and carbohydrates [13]. Based on the solubility and permeability of drugs molecules BCS (Biopharmaceutical Classification System (Figure 3)) is one of the most widely used scientific classification systems. Aqueous solubility and intestinal permeability are two important parameters that control the rate and extent of drug absorption [14].

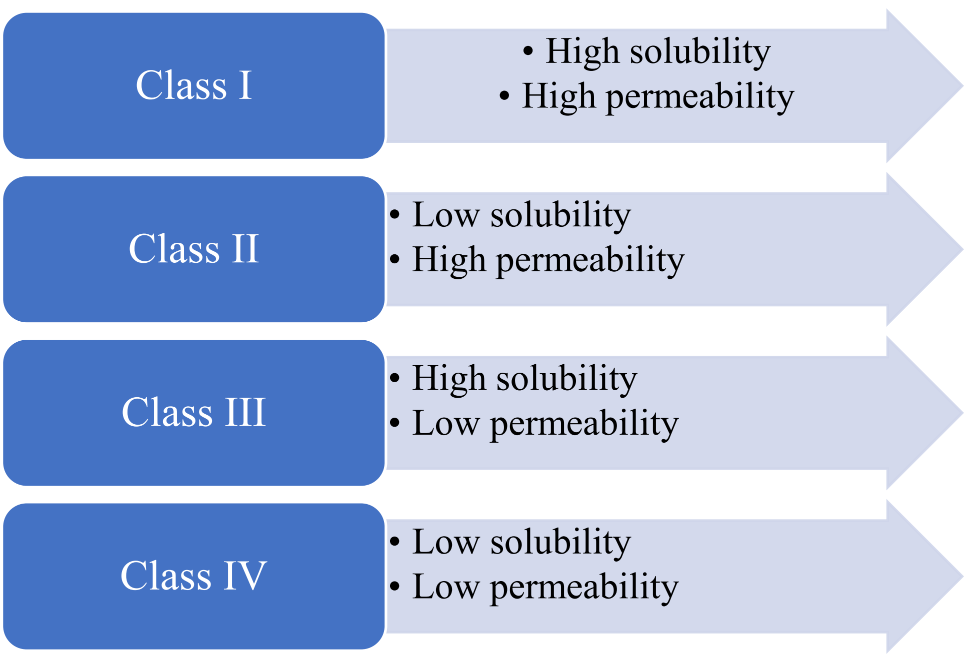

Figure 3: Biopharmaceutical classification of Drugs

Recent Developments on Surfactants Drug Interaction:

Researchers conducted a detailed physicochemical analysis of the interaction between sodium dodecyl sulphate (SDS) and the globular protein trypsin in an aqueous medium utilizing tensiometric, conductometric, calorimetric, fluorimetric, viscometric, and circular dichroism techniques. According to the findings, aggregates of SDS-trypsin begin to form when the concentration of surfactant above the critical micelle concentration of pure SDS micelle. On the other hand, trypsin causes a decrease in counterion binding. The interaction phenomena are entropy regulated and endothermic, as evidenced by the free energies and enthalpies of micellization, interfacial adsorption, and micellization entropy related with the interaction values. Only for the SDS-trypsin cluster system over the critical micelle concentration of SDS micelle is an increase in viscosity reported. When compared to the results of micelles without protein, the interface polarity and aggregation number decreases. Due to substantial electrostatic repulsion in the case of biopolymer-surfactant complexes, circular dichroism spectra reveal the high R-helical content and unfolded structure of trypsin in the presence of SDS, likely supporting the "necklace and bead" concept [15].

From a physicochemical perspective it was observed that, the interaction between a polymer and a surfactant with opposite charges is far more complex than the interaction between an ionic surfactant and a non-ionic polymer. In the former case, hydrophobic effect predominates, while electrostatic and hydrophobic interactions coexist in the latter. Researcher's investigated the interaction in an aqueous medium between a cationic amphiphile, cetyltrimethylammonium bromide (CTAB) and a water-soluble polyanion, sodium salt of carboxymethylcellulose (NaCMC). The published experiments in NaCMC-alkyltrimethylammonium bromide showed numerous inconsistencies, which are thought to be the result of varying degrees of substitution. This, in turn, influences the charge density of the polymer chain. it was observed that the electrostatic forces-driven interfacial contact and bulk complexation operate simultaneously. This process increases the entropy of the solution [16].

Glycine's interactions with cationic, non-ionic and anionic surfactants at various temperatures have been investigated, using conductometric, volumetric, viscometry and refractive index measurements as well as fluorescence probe. Densities, refractive indices, viscosities, and specific conductivities data of glycine (0.02-0.10 m) in 0.01m aqueous sodium lauryl sulphate (SLS), cetyltrimethylammonium bromide (CTAB), and triton X-100 (TX-l00) solutions from 298.15 to 313.15 K with 5 K gap have been used to calculate a range of thermodynamic parameters, including apparent molar volumes, partial molar volumes, transfer volumes, Falkenhagen coefficients, Jones-Dole coefficients, free energies per mole of solute and per mole of solvent, molar refraction and limiting molar conductivity. It was discovered that the above-mentioned computed parameters were vulnerable to the interactions present in the examined systems of amino acids, surfactants and water. Additionally, pyrene has been used as a photophysical probe in a fluorescence investigation, the results of which validate the findings from previous methods [17].

Various studies are shown in table 1 given below.

Table 1: Various Drugs and Surfactant studies

S. No.	Drug/ Molecule Name	Surfactant Name	Technique Used	Year of publication	Reference
1	Trypsin	Sodium dodecyl sulphate (SDS)	Tensiometry, conductometry, calorimetry, fluorimetry, viscometry, and circular dichroism	2002	[15]
2	Sodium carboxymethyl cellulose (NaCMC)	Cetyltrimethylammonium bromide (CTAB)	Tensiometry, conductometry, microcalorimetry, and turbidimetry	2006	[16]
3	Glycine	Sodium dodecyl sulphate, cetyltrimethylammonium bromide, and triton X-100 (TX-l00)	Conductometry, volumetry, viscometry, refractive index measurements and fluorimetry	2008	[17]
4	Pravastatin sodium	Sodium cholate (NaC), sodium glycholate (NaGC), sodium taurocholate (NaTC), sodium taurodeoxycholate (NaTDC), and sodium deoxycholate (NaDC)	Differential scanning calorimetry (DSC), high-performance liquid chromatography (HPLC)	2012	[18]
5	Promethazine hydrochloride (PMT)	Sodium cholate (NaC), sodium deoxycholate (NaDC), and sodium taurocholate (NaTC)	Conductometry and tensiometry	2013	[19]
6	Simvastatin	Sodium cholate (NaC), sodium deoxycholate (NaDC), and sodium salt of 12-Monoketocholic acid.	Distribution coefficient method, computational studies and high-performance liquid chromatography (HPLC)	2016	[20]
7	Metformin hydrochloride	Sodium cholate (NaC), sodium deoxycholate (NaDC)	Densimetry and sound speedometry, viscometry, and ^{1}H NMR Spectrometry	2018	[21]

8	Myoglobin	Sodium N-dodecanoyl sarcosinate (SDDS)	Tensiometry, viscometry, UV–visible spectroscopy, fluorimetry, circular dichroism (CD) method, fourier transform infra-red (FT-IR) method, differential scanning calorimetry (DSC), isothermal titration calorimetry (ITC)	2019	[22]
9	Asthalin-4	Water, ethanol	Densimetry	2021	[23]
10	Ceftriaxone sodium and metformin hydrochloride	Sodium cholate (NaC), Sodium deoxycholate (NaDC)	Surface tension method	2022	[24]
11	Glycyl glycine	Sodium cholate (NaC), sodium deoxycholate (NaDC)	Densimetry and sound speedometry, viscometry	2022	[25]
12	Clindamycin hydrochloride	Deoxycholic acid and cholic acid	pH meter, UV–visible spectroscopy, dissolution method	2022	[26]
13	Piroxicam	Sodium taurocholate (NaTC) and hydroxypropyl methylcellulose (HPMC)	Dynamic light scattering (DLS), nanoparticle tracking analysis (NTA), cryogenic-transmission electron microscopy (Cryo-TEM), cytotoxicity studies, cellular drug uptake studies and high-performance liquid chromatography (HPLC)	2023	[27]
14	Clindamycin hydrochloride	Deoxycholic acid and cholic acid	UV–visible spectrocopy	2024	[28]
15	Emtricitabine and Lamivudine	Sodium cholate (NaC), Sodium deoxycholate (NaDC)	Densimetry and sound speedometry, Viscometry	2024	[29]

16	Emtricitabine and Lamivudine	Sodium dodecylsulfate (SDS) and cetyltrimethylammonium bromide (CTAB)	Conductometry, UV–visible spectroscopy, fluorimetry	2024	[30]

The purpose of this study was to investigate how bile salts and formulations affect pravastatin's limited bioavailability during its absorption through the gastrointestinal tract. Several bile salts were used to generate solid dispersions and physical blends containing pravastatin sodium. Differential scanning calorimetry (DSC) was used to examine the physicochemical properties and penetration profiles of pravastatin sodium-bile salt physical mixes and solid dispersions. While pravastatin in the solid dispersion achieved a complete conversion to an amorphous state, it did not reach this state in the physical combination. While over 97% of the pravastatin sodium was dissolved in 5 minutes at pH 6.8, the rates of pravastatin dissolution from solid dispersions at pH 1.2 were much lower than those from physical mixes and commercial products. The findings led to the conclusion that bile salt-containing pravastatin sodium solid dispersions may improve drug absorption. Bile salts added to pravastatin sodium may improve medication absorption through a number of pathways, including P-gp inhibition and increased penetration via the paracellular pathway [18].

The study published in 2013, shows a broad conductometric and tensiometric investigation of the mixed micellization process of bile salts, promethazine hydrochloride (PMT), and a phenothiazine medication. Since bile salts are a natural part of the human body, their presence may change a drug's propensity to micellize when combined with additives to form mixed micelles. As a result, understanding how bile salts affect drug micelle production and the related energetics is crucial. The large size of taurocholic acid, which causes impediment, deoxycholic acid is more effective than cholic acid and taurocholic acid in lowering the CMC of drugs, even though in this investigation we utilized the same concentration for all types of bile salts. The hydrophobicity of cholic acid is reduced when it has an additional hydroxyl group on it. The number of hydroxyl groups have an inverse relationship with hydrophobicity. Deoxycholic acid, which has been solubilized in the outer part of the micelle core where it is subjected to lateral pressure, hence has the tendency to push them into the inner part of the micellar core. Because of the neutralizing and screening properties, deoxycholic acid binds firmly to the positively charged drug ions, reducing the head group area. Consequently, micelles are formed at lower concentrations [19].

The results show that the simvastatin distribution coefficient values are reduced at both of the pH levels, when bile salts are added to the n-octanol/buffer system. This could be the outcome of hydrophilic complexes forming and making simvastatin more soluble, which could then affect the drug's pharmacokinetic characteristics and the patient's overall response to treatment. Bile salts are known to cause micelle formation, which can solubilize medications that would otherwise be insoluble when present at concentrations higher than CMC. The distribution coefficient of both simvastatin forms decreased after the addition of sodium cholate, sodium deoxycholate, and sodium 12-ketocholate. This shows that in the presence of bile salts increases the simvastatin's concentration and solubility in the buffer layer. Bile salts may increase the solubility and absorption of simvastatin, as we know that it is highly lipophilic molecule with low bioavailability. This may bring an effect on the therapeutic response of simvastatin [20].

It was studied that bile acid's primary benefit is their dual function as agents that regulates the permeability and solubility of drugs. As a result, bile acids can be used to increase the bioavailability of medications with low membrane permeability or poor water solubility. Furthermore, bile acids have the potential to tolerate gastrointestinal obstructions and facilitate the carrier-mediated absorption of chemically or physically conjugated medicinal molecules [31].

It was discovered in that sodium cholate (NaC) and sodium deoxycholate (NaDC) in aqueous solutions of an antidiabetic drug metformin hydrochloride exhibit hydrophilic-hydrophilic interactions at lower concentrations of the bile salts that shifts to hydrophobic-hydrophobic nature as the concentration of bile salt increased. The characterization of these interactions in the system may be useful for the safe trials using bile salts in the pharmaceutical industry [21].

Horse myoglobin is a monomeric water soluble heme protein. Conformational and physicochemical studies have been conducted at various pH levels using surface tension, viscosity, UV-Visible and fluorescence spectroscopy, isothermal titration calorimetry, circular dichroism, and differential scanning calorimetry (DSC) to examine the interaction between horse myoglobin and sodium N-dodecanoyl sarcosinate (SDDS), an anionic surfactant based on amino acids. When they examined the relationship between a protein and an amino acid-based surfactant, they discovered that the protein displayed denaturation at greater surfactant concentrations, which results in the disappearance of the protein's original structure. It was also discovered that with increased protein concentrations, binding capacity weakens [22].

According to the study done regarding, limiting molar expansibilities and molar volumes shows that, at various temperatures, the interactions between the solute (Asthalin-4) ions and the solvent molecules in the solution are larger than those between the ions in the drug solutions. Furthermore, it has been discovered that the particular bronchospasm medication, Asthalin-4, functions as a structural modifier in both water and the ethanol binary aqueous solution. When the amount of ethanol grows from 5% (w/w) to 50% (w/w), the drug Asthalin-4 affinity increases [23].

Researcher's discussed number of physicochemical studies of protein-surfactant interactions. Furthermore, the review article provided an explanation of the effects of many factors on the structure, binding, critical micelle concentration (CMC) of surfactant, thermodynamic features and stability. These factors included cosolvent, chain length of surfactants, temperature, pH and salt [32].

This review highlights the chemical characteristics of a number of surfactants that are important due to their physicochemical interactions with biological macromolecules that includes hydrophobic and electrostatic interactions [13].

Using a standard method, the aggregation mechanism of two structurally distinct bile salts in the presence and absence of medicines has been examined. This experiment was conducted using the bile salts sodium cholate (NaC) and sodium deoxycholate (NaDC) in the presence of an antibiotic medication, ceftriaxone sodium and an antidiabetic medication, metformin hydrochloride. The surface tension has been examined at various temperatures and concentrations of both components to study the impact of temperature and the hydrophobicity of the constituents. CMC values decreased when these medications were present. Thermodynamic characteristics are used to identify energetic spontaneity in the micellization process in the study [24].

How aqueous glycyl glycine affects the micellization of biosurfactants like sodium deoxycholate (NaDC) and sodium cholate (NaC), researchers carried out the viscometric, sound speed, and density analysis of these substances at different temperatures. Using experimental speed of sound and density data, apparent molar volume, apparent molar isentropic compression, and isentropic compressibility were calculated. When glycyl glycine is present, biosurfactants sodium deoxycholate (NaDC) and sodium cholate (NaC) showed a great shift in their apparent molar volume and in the compressibility properties of the monomer

in comparison to water. The findings demonstrate that the glycyl glycine's zwitterionic end group interacts significantly with sodium deoxycholate (NaDC) and sodium cholate (NaC) to promote micellization. Variations in water-water interactions are most likely responsible for the observed concentration-dependent variations in apparent molar volume and apparent molar adiabatic compression, since the addition of glycyl glycine causes the bio-surfactant molecules to lose their hydrophobic hydration [25].
The main drawback of the commonly used topical antibiotic clindamycin hydrochloride is its limited skin penetration. Thus, it is crucial to create innovative approaches for clindamycin topical formulations. The objective was to examine how the type of gelling agent (sodium carmellose and carbomer) and the type and concentration of bile acids (cholic and deoxycholic acid, 0.1% and 0.5%, respectively) as penetration enhancers affected the rate of clindamycin release and permeation in an in vitro model using a cellulose membrane. Eight clindamycin hydrogel formulations were prepared by researchers, and their permeability, drug content, release, pH, and physical appearance were all assessed. Clindamycin hydrochloride released at substantially higher rates and permeated carmellose sodium hydrogels, even though formulations including carbomer as the gelling ingredient exerted the best sensory qualities. In carbomer gels, bile acid enhancement factors were higher and the permeation-enhancing effects of cholic acid were more pronounced. It is preferable to include cholic acid at a lower concentration because the variations in the permeability properties of hydrogels containing it at different concentrations were not statistically significant. The preferred formulation is a hydrogel with 0.1% cholic acid as a penetration enhancer and carmellose sodium as a gelling agent [26].
Drug solubility has been improved by making drug formulation with polymers in the form of solid dispersions in case of poorly soluble drugs. The solubilization of lipids and poorly soluble medications in the gut has been demonstrated to be significantly aided by endogenous surface-active species found in the gut, including bile salts, lecithin, and other phospholipids. The possibility of interactions between a model bile salt, sodium taurocholate (NaTC), and model spray-dried solid dispersions containing piroxicam and hydroxypropyl methylcellulose (HPMC), a hydrophilic polymer was studied. The crystalline drug exhibited a good solubilization effect as studied using solubility measurements. Drug absorption tests revealed that the combination of lecithin and bile salt, along with the drug being administered through solid dispersion, greatly enhanced drug absorption. The significance of biorelevant media in solid dispersion investigations as well as the critical function of the colloidal species produced during dissolution processes in drug absorption and solubilization are illustrated by findings. [27]
Although topical clindamycin formulations are often utilized in clinical settings, their therapeutic efficacy is significantly hampered by their limited skin penetration and poor absorption. A sensible and promising approach to overcoming the limitations of traditional topical medicinal formulations is penetration enhancement. By using in vitro skin parallel artificial membrane permeability assay the impact of cholic acid (CA) and deoxycholic acid (DCA) on the permeability of clindamycin hydrochloride was evaluated. Clindamycin hydrochloride's permeability through the skin-PAMPA membrane was enhanced by both DCA and CA at the highest investigated concentration of 100 µM in the tested solutions. At a pH value of 6.5, which is typical of the majority of dermatological indications treated with topical clindamycin formulations, this impact was more noticeable for CA. As per result of this study in future research may be done by the use of clindamycin hydrochloride along with bile acids acting as penetration-enhancing ingredient [28].
Using conductometry, fluorometry, and UV-visible spectroscopy, the aggregation behaviour of conventional surfactants, sodium lauryl sulphate (SLS) and cetyltrimethylammonium bromide (CTAB),

in aqueous solutions was studied in the presence of anti-HIV drugs, emtricitabine (ECT) and lamivudine (LMV) at various temperatures. The CMC values obtained from the traditional investigation closely matched with spectroscopic methods, such as fluorometry and UV-visible spectroscopy. The CMC values have been utilized to calculate thermodynamic parameters involving standard changes in enthalpy of micellization, entropy of micellization, and free energy of micellization. The surfactant, water, and drug ternary system's hydrophobic-hydrophilic interactions have been examined. The thermodynamic analysis shows that both medications favour the micellization of the two ionic surfactants under study (CTAB and SLS) in aqueous medium, with lamivudine having greater effects. This investigation of the interactions between anti-HIV drugs and surfactants has encouraging affect for improving pharmaceutical formulations in relation to HIV infection. The CMC of SLS and CTAB are lower in the presence of anti-HIV medications (lamivudine and emtricitabine) than in pure water. Although the two medication's structures are quite similar, emtricitabine distinguishes itself due to the inclusion of a fluoro group. The CMC values for SLS and CTAB decrease more in case of Lamivudine, suggests that it has a greater hydrophobic nature as compared to Emtricitabine [30].
Using a variety of techniques, including compressibility, volumetry, and viscometry, researchers investigated the solute–solute as well as solute–solvent interactions of bile salts sodium cholate (NaC) and sodium deoxycholate (NaDC) with anti-HIV drugs *i.e.*, Emtricitabine (ECT) and Lamivudine (LMV) at a temperature range (298.15 K-313.15 K) with a regular gap of 5 K. A variety of physicochemical metrics, including isentropic compressibility, apparent molar volume, and apparent molar adiabatic compression, have been assessed using experimental density and speed of sound data. They have also analyzed the CMC values of bile salts in pure water and in an aqueous solution of ECT and LMV at 298.15 K using speed of sound data, and these results agree well with our previous conductivity investigation on these surfactants. Strong solute-solvent interactions are evident in the system under study based on the trends of isentropic compressibility, apparent molar volume, and apparent molar adiabatic compression values for both NaC and NaDC with temperature and in the presence of medicines (ECT/LMV). The cosphere overlap model confirms that the results are explained in terms of electrostatic and hydrophilic-hydrophobic interactions in the bile salt-drug-water system. Because NaC is more hydrophilic than NaDC, it interacts with both medications more strongly. Comparably, ECT exhibits stronger solute-solvent interactions among the two bile salts than LMV because it is more hydrophilic. The foregoing conclusions are further supported by the relative viscosity parameter that is derived from viscosity measurements. Their research indicates that by using bile salts as a drug delivery vehicle, pharmacists might improve the efficacy and permeability of anti-HIV medications. This interactional knowledge regarding bile salts with ECT and LMV would be helpful in this regard [29], [33].

Research Gap Identification:
Numerous molecules with pharmacological activity are organic in nature and contain both hydrophobic and hydrophilic groups. In a biological system, their behaviour involves complex interactions with other molecules through interactions that include hydrogen bonding, hydrophobic, hydrophilic, and electrostatic forces. Therefore, understanding their interactions with other substances in the system is important for understanding their role in biological systems. However, at molecular level measurement of these interactions is necessary for a thorough understanding of the mechanism of action of pharmacological compounds in living systems. Before a medicine reaches its intended organ, it must first pass through a cellular membrane during use. Additionally, because this wetting effect of surfactant would allow the drug

to release more quickly, reducing surface tension is another element that helps water to penetrate into drug molecules. It is reasonable to anticipate a direct physiological contribution from surfactant molecules in this area.
Numerous studies have been done on the interactions of drug systems in aqueous solutions. Several physicochemical techniques have been used to investigate the interactions of numerous pharmaceutical drugs with amino acids, carbohydrates, peptides, surfactants, and salts, among other substances, in both aqueous and non-aqueous media. The interactions of bile salts (biosurfactants) with drugs in aqueous medium have only gotten minimal research attention.

Conclusion:
After reviewing the literature, we have found that the research gap and came to conclusion that physicochemical parameters of some of the drugs has not been studied in presence of bile salts. So, studying these parameters may help to determine these drugs and bile salts interaction with each other.

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