IMPORTANCE OF PHYSICOCHEMICAL PROPERTY IN DRUGS

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CERTIFICATE OF ORIGINALITY

This is to certify that the thesis entitled: **"IMPORTANCE OF PHYSICOCHEMICAL PROPERTIES OF DRUGS"** submitted by **Pranjal Kalia** and **Manu Sharma** in partial fulfillment of the requirement for the award of the degree of Bachelor of Technology in Biotechnology, Jaypee University of Information Technology, Solan has completed under the supervision and guidance of Dr. Poonam Sharma. This work has not been submitted to any other University or Institute for the award of this or any other degree or diploma.

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Pranjal Kalia

Manu Sharma

Abstract

Micellar systems possess great drug-delivering advantages due to their ability to dissolve a wide range of hydrophilic or hydrophobic compounds. A micellar production with anionic surfactant sodium dodecyl sulfate (SDS) and the fungal drug fluconazole (FLZ) has already been investigated at various temperatures during drug solvents addition with SDS in this work. A critical micelle concentration (CMC) was established by plotting specific conductance versus SDS concentration at different temperatures and specific conductance measured by a conductivity meter and the experimental data was utilized to compute various relevant thermodynamic parameters such as standard Gibbs free energy, standard enthalpy, and standard entropy of micelle formation. In this work, we observed specific conductance at four different temperatures (25°C, 30°C, 35°C, and 40°C) showing an increase in concentrations of the drug with SDS and Also study this parameter by using the Ostwald viscometer to check the density and viscosity of the drug with the addition of SDS in the solution. At four different temperatures (25°C, 30°C, 35°C, and 40°C) the significance of checking the viscosity show reduction in the rate of flow through the capillary tube under pressure.

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Pranjal Kalia Manu Sharma Dr. Poonam Sharma

(Signature of student) (Signature of Supervision)

CHAPTER – 1

INTRODUCTON

1. Introduction

1.1. General Introduction

The description of physicochemical properties has received a lot of attention in pharmaceutical businesses and is now the standard method. It is the primary stimulus for incorporating biological activity suitable for the physicochemical form into a pharmaceutically active agent in medicine. Physicochemical properties protect all aspects of a compound's function, including structural, biochemical, physiochemical, pharmacokinetics, and toxicity. Physical qualities of drug molecules such as solubility, particle size, lipophilicity, partition coefficient, and others are responsible for their activity and quantify the behavior and interaction of the medication. The chemical properties of pharmaceuticals define their absorption, metabolism, excretion, and toxicity characteristics, all of which influence the drug molecules' physiological activity. Drugs' physicochemical properties are supposed to be specific. The study of chemicals and their effects on living animals is referred to as pharmacology. It demonstrates what medicines are, what they do when they enter the body and perform a function, and what side effects a person may experience from a drug. A drug is defined as a substance that interacts with proteins in the body to affect physiological processes. A drug can be administered via inhalation, injection, ingestion, or absorption. The active ingredient of a medicine is the molecule that alters physiological activity. The active component is the molecule that allows the medicine to function. Most of the drugs we take include inactive chemicals that do not affect physiological function. The fillers, binders, and lubricants in the medication are inactive components, whereas active components are molecules that consist of a chemical that acts with the body that causes an effect... An agonist is a chemical that causes a change in the way cells behave. Antagonists are drugs that prevent a cell from operating normally. Pharmacokinetics is the study of how medications behave once they enter the body. It investigates the interaction of biological receptors and chemicals whereas the pharmacokinetic process, which investigates the chemical absorption, distribution, metabolism, and excretion from the biological system, is concerned with the biological system's activity on the medication.[1]

1.2 Surfactant

Surfactant is a chemical compound known as an active agent which consists of amphiphilic molecules. Surfactant is categorized according to the character of the polar head group. There are four such types: ionic, neutral, cationic, anionic, and non-ionic. The balance between hydrophilic and hydrophobic parts of the molecule is provided by the system its properties example accumulation of various interfaces and associations in the solution, called micelles These micelles are in dynamic equilibrium and may vary by order of magnitude, depending on the structure of the surfactant molecule One of the examples is an amphiphilic surfactant sodium dodecyl sulfate (SDS). It is composed of long-chain C-12 hydrocarbons(dodecyl) along with an accompanying Na counter ion, this group is linked to the polar sulfate head group. In the current research, sodium dodecyl sulfate (SDS) has been utilized for the topical delivery of the FLZ. The drug molecules find their way into biological systems through membranes. These membranes have lipid bi-layered patterns that nearly resemble surfactant molecules. Sodium dodecyl sulfate (SDS), a surfactant molecule has found broad application in various formulations in the drug exchange as it can act as a wetting agent, solubilizer, or emulsifier. They may improve the membrane permeability, resulting in the enormous absorption of a maximum of the medicines or helping in expanding the surface area for absorption. In this study, we worked and researched the surfactant SDS.[2]

The surfactant used:

1.2.1. Cationic Surfactant:

The dissociated component generates charged hydrophobic molecules. The positive character of cationic surfactants also has the fascinating property of disturbing the bacterium cell membrane. This means that cationic surfactants can be utilized as antimicrobial agents in disinfectants, for example. They also have great fat-dissolving abilities.

Example - CTAB (Cetyltrimethylammonium bromide) is shown in Fig 1.1.

Fig. 1.1 Structural illustration of CTAB

1.2.2. Non-ionic Surfactant: Nonionic surfactants are charge-free on their hydrophilic end. As a result, nonionic surfactants emulsify oils very well and remove organic soils/grease better than anionic surfactants. Nonionic and anionic surfactants are routinely used to make dual-action, multi-purpose cleansers capable of not only lifting and suspending particle soils but also emulsifying oily soils. Nonionic surfactants (emulsifiers and detergents), anionic surfactants, or a combination of both are commonly found in cleaning products.

Example - TWEEN twenty (522.676 g/mol) is shown in Fig 1.2 and triton X one hundred (647g/mol).

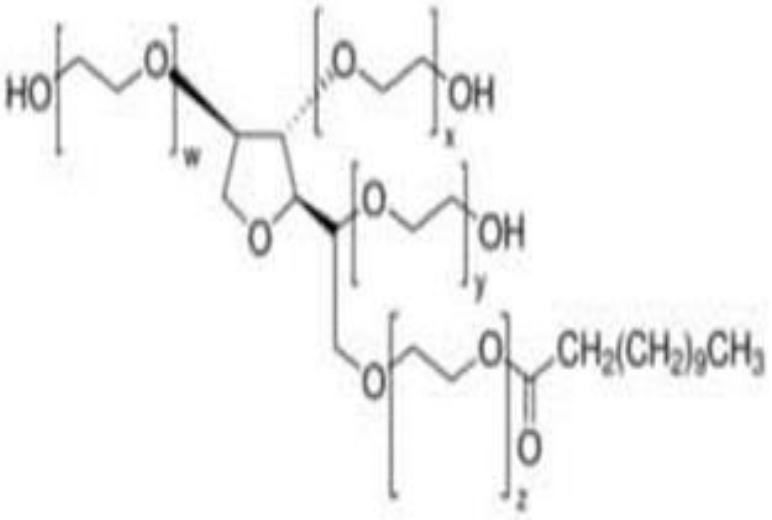

Fig 1.2.Structural illustration of TWEEN 20

1.2.3.Anionic Surfactant:

The hydrophilic end of an anionic surfactant has a negative charge. When these surfactants react with water, they produce negatively charged anions. One of its distinguishing properties is its incredible capacity to bond to positively charged particles like oils or dirt. These are then elevated and suspended in a micelle-like structure.

Example - Sodium dodecyl sulfate is shown in Fig 1.3.

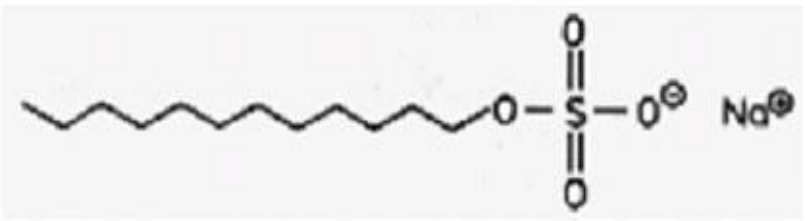

Fig 1.3. Structural illustration of SDS

1.3 Micellization

When surfactants are added to water, the surfactant molecules get dissolved in water. Further increasing the concentration of surfactant in water, aggregates of surfactant molecules are formed and the phenomenon of formation of aggregates is known as micellization. Micelles are the nano-sized stable aggregates of setting agent molecules, that kind of impromptu in wetting agent solutions. When the concentration of the surfactant is increased above the critical Micelle concentration (CMC) the reaction of micelles within the surfactants becomes nonetheless vital. The process of micellization is shown in fig 1.4.[3]

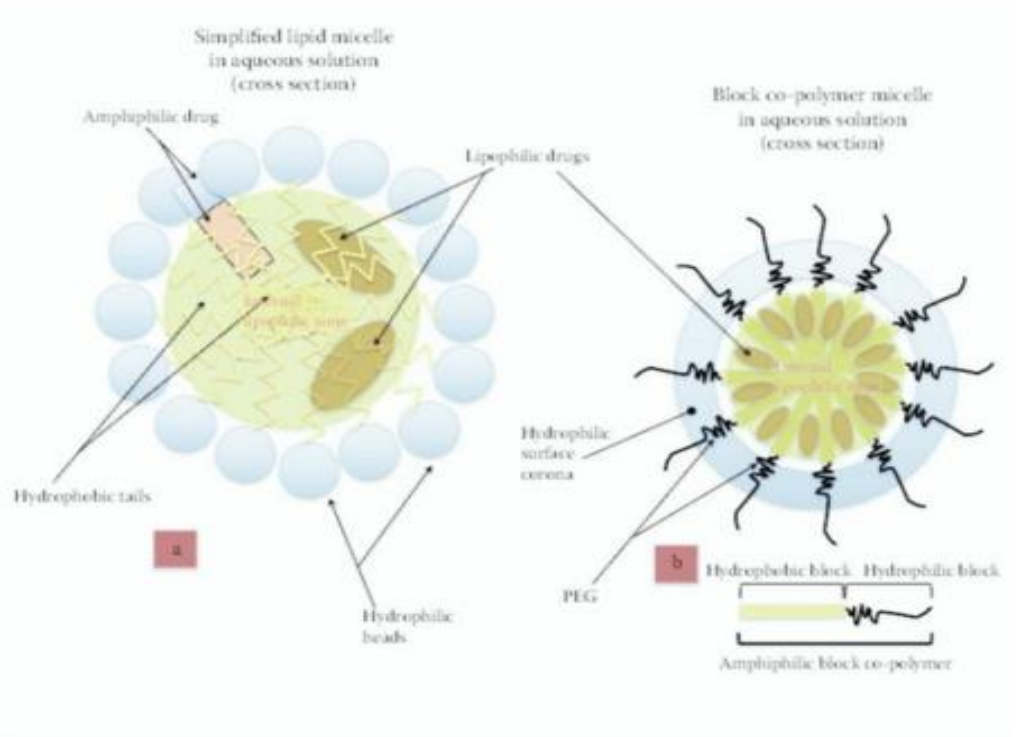

Fig 1.4. Process of micellization

1.4 Fluconazole

Fluconazole is an antibacterial drug that is used to treat a wide variety of fungal infections. Candidiasis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, dermatophytosis, and pityriasis Versicolor are also all types of fungal infections. It's used to treat candidiasis among those who are at high risk such as patients who've had transplants, infants with reduced birth weight, and people with low blood neutrophil counts. This can be taken by mouth or injected into a vein. Fluconazole belongs to the azole antifungal drug class. It is considered to work by interacting with the fungal cellular membrane Fluconazole has been demonstrated to exhibit high antimicrobial action against the majority of strains of Candida albicans, Candida glabrata (many strains are intermediately sensitive), Candida parapsilosis,

Candida tropicalis, and Cryptococcus neoformans, resulting in the cure of fungal infections and structure is shown in Fig 1.5. This is accomplished by interfering with cell wall formation, proliferation, and adherence in fungal cells, hence curing fungal infections and associated symptoms.

Fluconazole has also been shown to have growth inhibitory activity in regular or immunocompromised laboratory animals with systemic and intracranial Cryptococcus neoformans infections, as well as systemic Candida albicans infections. It's important to remember that fluconazole-resistant organisms have been identified in a variety of strains. This highlights the need for antimicrobial susceptibility.[4]

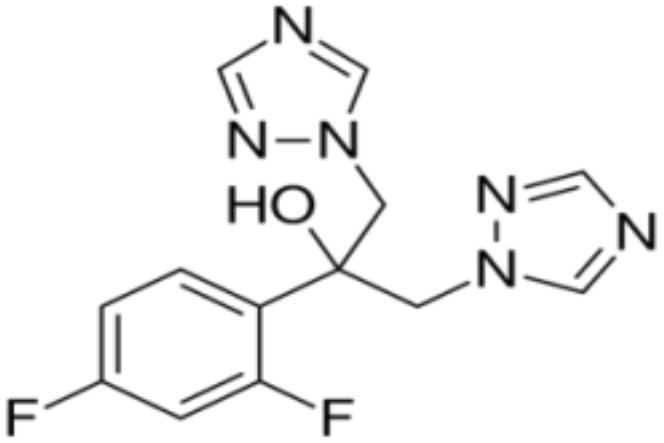

Fig 1.5. Structure of Fluconazole

1.5. Physicochemical Interaction:

A drug interaction is a change in a drug's activity or adverse effects caused by taking it with food, drink, supplements, or another medication. When a drug is used with another prescription medication OTC, we put ourselves at risk by using a potentially harmful medicine, food item, or herb, with harmful interactions. The likelihood of a drug-drug interaction rises as the dose increases the total number of medicines used. The "Object Drug" is the drug whose activity is affected by such an interaction. The "Precipitant" is the agent that causes such an encounter to occur. Drug interactions can be caused by a variety of factors. Drug interactions can also be caused by competition for a single receptor or signaling pathway. The main elements that influence medication interactions: Multiple drug treatments, Several prescribers,

Multiple medications pharmacological effects on multiple illnesses/diseases, Patient compliance is poor, and Patient age increases, when two pharmaceuticals are combined, their effects may be additive (the result is the same as if the effects of each drug were added individually), synergistic, or antagonistic (combining the results of the drug in a better result) a stronger effect than expected), or antagonistic (drugs used together)results in a smaller effect than anticipated). Occasionally there has been debate about whether medications are additive or synergistic. Individual medication effects may differ from patient to patient. Patients may benefit from synergistic interactions, but they can also be harmful. raise the likelihood of an overdose. During various stages of development, both synergy and antagonism can occur. The interaction of a medication with a living organism. In contrast, the compounds involved in antagonism are known as inverse substances. agonists. The many responses of a receptor to a drug's activity several classifications, such as "partial agonist," have resulted. in “competitive agonist," for example... These interactions have pharmacodynamic uses. When compared to the predicted behavior of each medication when given individually, differences in absorption, transport, distribution, metabolism, or excretion of one or both drugs cause alterations in their impact. The concentration of the drugs has been changed.[5]

CHAPTER -2

LITERATURE REVIEW

2. Literature Review

This section summarises the most current representative research on fluconazole, antifungal infection, surfactant, and physicochemical interaction that have appeared in the literature.

Vikrant abbot et al.[6] investigated the thermodynamic study of the flavonoids which specify the number of active ingredients used in pharmaceutical firms. Quercetin with sodium dodecyl sulfate (SDS) has been identified. Quercetin and its interactions with different surfactants were used to create a drug that included micelles. Sodium dodecyl sulfate helps in the formation of micelles and observed aspects of the micellar system. It shows different hydrophobic and hydrophilic interactions. It indicates various hydrophobic and hydrophilic interactions. The experiment was conducted in four various hydro ethanol concentrations used i.e., aqueous 30%v/v, 70%v/v, and absolute ethanol at five various temperatures (293.15K, 298.15K, 303.15K, 308.15K,313.15K). The specific conductivity calculates the micelle's concentration at five different temperatures. Many parameters such as density, viscosity, and conductivity are used to calculate the data from thermodynamic factors, specifically standard enthalpy change, standard entropy change, and standard Gibbs free energy of micellization. The exact position of quercetin in the surfactant's micelle structure was determined using the spectroscopic study of SDS and micelles using ^{1}H NMR spectroscopy. This paper helps in evaluating the amount of hydrophobic interface within the structure and is used in determining the flavonoids surfactant concentration in formulating in the pharmaceutical industry.

Varun Bhardwaj et al.[7] investigated the thermodynamic analysis of rutin trihydrate. CTAB (cetyl trimethyl ammonium bromide) is a cationic surfactant used with rutin trihydrate. It is exploited in formulation expansion at five different temperatures and hydroethanolic concentration is observed. The experiment was performed at five different temperatures (20°C to 40°C) and it analyse the influence of temperature on the nature and reactivity of rutin trihydrate four various ethanolic concentrations are used (aqueous, 30%V/V, 70%V/V, and absolute ethanol).

The (CMC) critical micelles concentration rate was attained by creating a variation study of specific conductivity about change in CTAB concentration. The micellization behavior of the surfactant flavonoid structure was used to evaluate the thermodynamics parameters such as standard enthalpy change, standard entropy change, and standard Gibbs free energy change. The thermodynamic parameters i.e., apparent molar volume and apparent molar compressibility computed from density and ultrasonic sound velocity analyses. In micelles formation, the position of flavonoids in the micellar structure of surfactant was observed through FTIR and ^{1}H NMR spectroscopic analysis. Overall, this research work analyses flavonoids' surfactant concentration acquired in pharmaceutical and cosmeceutical industries for manufacturing that is useful for formulations.

Wanwen Xu et al.[8] investigated the impact of drug physicochemical properties on the development impact of enhancers and it shows potent permeation enhancing drug-specific effect. Enhancer which directed the application of enhancers in various drug transdermal drugs. Polyglyceryl 3 dioleate was determined as an enhancer and its improvement consequence on ten drugs was analyzed in vitro skin permeation testing and an investigation of physicochemical properties of drugs was performed from the factors of partition and permeation. FT-IR, molecular docking, solubility parameter computation, ATR-FTIR, Raman research, and confocal laser scanning microscopy were used to demonstrate the connection of drug skin POCC (CLSM). The study found overall drug enchantment ratios varied from 2.23 to 7.45. POCC significantly increased the absorption of the drug having low polar surface area and polarizability because the drug interacts less with skin lipids than the others, and POCC had a higher chance of binding with skin lipids.

Gradzielski researched[9] the phase composition and features of a compound that included an anionic surfactant and medium-chain alcohol as a cosurfactant for a variety of counterions. The phase behavior differed significantly as a function of cosurfactant level, but the uniflagellar vesicle gels generated at high octanol content are strikingly comparable. This vesicle gel was so well stabilized that the counterion has only a minimal effect. The kinetics of vesicle production were also investigated when various salts were added.

With increasing ionic strength, the formation of the vesicle gel accelerates and tightly binds the counterion to the charged amphiphilic interface.

Bhalaria et al.[10] described the preparation and characterization of fluconazole (FLZ) encapsulated ecthosomes, they compared their clinical efficacy in the treatment of candidiasis patients to liposomal gel, a commercial product, and the drug's hydroethanolic solution, as well as how they combined them into an appropriate dermatological basis. The improved ethosomes and liposomes had vesicle sizes of 144.68nm and 82.68 percent, and drug entrapment efficiency of 216+9.2nm and 68.22 percent, respectively. In vitro, drug diffusion tests revealed that ethosomes diffused roughly twice as much as liposomes and three times as much as a hydroethanolic solution through rat skin. Unlike liposomal formulations, commercial hydroethanolic liquids, and formulations of the medication, the created new delivery method displayed increased antifungal activity in clinical trials.

Arezzo Moradi et al.[11] using UV–Vis spectrophotometric at 298.15 K, conductometric techniques used, the combined micellar activity of bile salt (sodium cholate, SCH), and two cationic surfactants (tetradecyltrimethylammonium bromide, TTAB, and cetyltrimethylammonium bromide, CTAB) in aqueous solution were investigated. The tautomer of 1-phenyl-1, 3-butanedione was used to identify the critical micelle concentration (CMC) of SCH-surfactant mixtures (or benzoyl acetone, BZA). The CMC values of the combinations were lower than the isolated surfactant at various mole fractions (Yi) (due to the strong electrostatic attraction between anionic and cationic components after mixing).

Using differential scanning calorimetry (DSC) and thermogravimetry, Lemsi et al. [12] investigated the thermal degradation of Fluconazole-active ingredient and tablet (TG). To characterize materials, thermal analysis was augmented with X-ray powder diffraction and infrared spectroscopy. Due to the inclusion of excipients in the medicine, the active ingredient in commercial samples had a slightly different thermogravimetric profile (tablet). Except for microcrystalline cellulose, DSC investigations of binary mixes, fluconazole, and excipients (lactose monohydrate, microcrystalline cellulose, and magnesium stearate) revealed that the drug's

endothermic peaks were expanded and shifted to a lower temperature. These changes could be due to minor interactions that FTIR spectroscopy has not validated. The activation energy for the breakdown process of Fluconazole was measured under non-isothermal circumstances.

Modha and associates[13] created fluconazole polymorphs with a faster dissolving rate and better bioavailability. Fluconazole polymorphs were crystallized in a single solvent and studied by x-ray diffraction, infrared absorption spectra, differential scanning calorimetry, melting point, and particle size measurement. Hard gelatin and hydroxypropyl methylcellulose capsules containing fluconazole polymorphs were manufactured and tested according to pharmacopeia guidelines. 0. IN HCI, distilled water, acetate buffer pH 5.0, and phosphate buffer pH 6.8 were used to test the discriminatory dissolution criteria provided in the biopharmaceutical classification of solvent recommendations. By stability recommendations, the expedited stability study was submitted for the possible formulation. According to the findings, the discovery, characterization, and selection of selective dissolving media might be a valuable tool in the development of fluconazole dosage forms.

Hajare et al.[14] investigated Fluconazole partition coefficient and adsorption. Fluconazole is an antifungal medication that is used to treat superficial and systemic fungal infections. It is extensively metabolized in the hepatic first pass. Adsorption experiments were carried out on hydrophobic adsorption, at temperatures of 25, 35, and 45°C with activated charcoal and Talc 1. P. Partition experiments were carried out utilizing several lipophilic solvents such as dichloromethane, dichloroethane, hexanol, and n-octanol at a constant temperature of 25°C. The shaking flask method was used to calculate the partition coefficient. Adsorption tests on talc and activated charcoal follow both the Freundlich and Langmuir isotherms, suggesting both monolayer and multilayer physical adsorption and demonstrating poor oral bioavailability. Increases in the carbon chain length of a lipophilic solvent diminish the drug's partition coefficient, according to partition studies. The fact that partition coefficient values are close to unity implies that the medicine may be able to pass the microorganism's biological membrane and function locally.

Adsorption and partition studies may be used to formulate fluconazole.

Parkinson et al.[15] described the case of infection with pre-and post-treatment isolates that were used to compare the mechanism of fluconazole resistance in Candida glabrata. The resistant, posttreatment isolate was cross-resistance to ketoconazole and itraconazole, just as other azole-resistant yeasts. Resistance was triggered by a reduction in [3H] fluconazole accumulation rather than alterations in ergosterol production. Using metabolic or respiratory inhibitors, researchers discovered that this phenomenon was caused by energy-dependent drug efflux rather than a barrier to the influx. Because energy-dependent efflux is a characteristic of multidrug resistance in bacteria, yeasts, and mammalian cells, they looked into the possibility that fluconazole resistance is mediated by a multidrug resistance-type mechanism. Fluconazole and benomyl competed for outflow from resistant Candida glabrata isolates, according to research indicating that these drugs have a shared efflux mechanism. Fluconazole efflux was unaffected by other conventional substrates or multidrug resistance protein inhibitors.

Bhardwaj et al.[16] investigated the presence of butylated hydroxyanisole, sodium dodecyl sulfate (SDS) self-aggregation, and solution characteristics (BHA), a lipophilic organic compound, was studied using specific conductance (x), viscosity (77), compressibility coefficient (), apparent molar volume (4), and apparent molar volume (4) to yield CMC values and thermo-acoustic parameters. They studied a process of interaction between the moieties in order to build a surfactant-assisted immobilized system with increased BHA inhibitory activity, which might be useful to pharmaceutical companies. They investigated the many forms of interactions between the moieties to develop a surfactant-assisted immobilized system with improved BHA inhibitory activity, which might be valuable to pharmaceutical businesses. In alcohol + water combinations, the basic effect and interaction of BHA on the SDS micellar system were investigated, taking into consideration the benefits of surfactant micelles as carriers. They studied the many forms of interactions between the moieties to design a surfactant-assisted immobilized system for improved BHA inhibitory activity, which might be valuable in the pharmaceutical and cosmetics sectors.

Cirin et al.[17] conducted a study that used conductance measurements to determine the critical micelle concentration (CMC) of sodium dodecyl sulfate mixed micelles with one of five nonionic surfactants (Triton X-100, Tween 20, Tween 60, Tween 80, or Tween 85). SDS-nonionic surfactants revealed considerable synergistic effects based on the calculated values of the b parameter. Nonionic surfactants with longer and more hydrophobic tails, on the other hand, have stronger interactions with SDS's hydrophobic sections, resulting in more synergism. In an SDS-Tween 80 binary system, the largest synergistic impact was seen. The antagonistic impact of the SDS-Tween 85 micellar system was most likely due to each of its three hydrophobic tails having a double bond (three C18 tails).

Camila Fonseca Bezerra et.al.[18] investigated Farnesol possessing antimicrobial action as well as the ability to suppress fungal morphology. Farnesol inclusion into liposomes considerably boosted this action. Fluconazole's activity was enhanced by the addition of liposomal farnesol. Candida infections provide a risk to humans. C. Albicans is the most common cause of candidiasis, particularly in immunocompromised people. The advent of resistant strains necessitated the development of novel treatment approaches. Liposomes as dosage forms are a viable alternative in medication development in this area. Given the evidence that sesquiterpene farnesol is a bioactive molecule with antifungal capabilities, this study assessed the efficacy of farnesol-containing liposomes against several Candida strains. Farnesol and its liposomal formulation were tested in vitro against Candida albicans, Candida tropicalis, and Candida krusei cells. The impact of combination treatment on the development of Candida strains was used to analyze the effects of fluconazole on antifungal resistance. Liposomes were characterized based on their vesicular size, polydisperse index, and zeta medium potential, as well as electron microscope study. Farnesol exhibited antifungal action, which may be related to the prevention of fungal dimorphism, particularly in Candida albicans. Farnesol inclusion into liposomes considerably improved its antifungal effectiveness against Candida albicans, Candida tropicalis, and Candida krusei. Furthermore, liposomal farnesol enhanced fluconazole's antifungal activity against Candida albicans and Candida tropicalis. Unconjugated farnesol, on the other hand, had antagonistic effects when combined with fluconazole.

Svetlana Blokhina and coworkers[19] studied the isothermal saturation technique is used to test the fluconazole solubility in buffer solutions of various acidity (pH 1.2, 2.0, and 7.4), 1-octanol, and hexane at temperatures ranging from 293.15 to 313.15 K. The solubility of the chemical in different solvents rises in the following order: hexane, buffer pH 7.4, buffer pH 2.0, 1-octanol, buffer pH 1.2, and does not exceed 0.2 moll1. The transpiration technique is used to determine the temperature dependence of fluconazole saturation pressure. The compound's sublimation enthalpy is 131.4 0.9 kJmol1. It is demonstrated that the sublimation enthalpy of fluconazole closely similar compounds may be calculated to use the HYBOT descriptors.

Varun Bhardwaj et al.[20] studied Butylated hydroxytoluene (BHT) as a bioactive lipophilic chemical molecule that is added to many foods to avoid rotting and is also used as an ingredient in many pharmaceutical goods. Major companies have employed sodium dodecyl sulfate (SDS). Using ethanol and ethanol-water combinations in various percent compositions, the effect of BHT on the micellar system was investigated.As a result, investigating the sorts of interactions that occur between BHT and developing a mechanism to assess its validity in food pharmaceutical formulations would be quite interesting. To further understand micellar characteristics, we combined experimentally collected and speed sound data with a simple and easily controlled technique to extract critical micelle concentration (CMC) values conductance. (x,) presence BHT variable molar adiabatic compression isentropic compression

Aumaid Uthman et al.[21] investigated the therapeutic medicines for the treatment of fungal infections as azole derivatives like fluconazole. Their mechanism of action, which involves altering the conversion of lanosterol to ergosterol, is well understood. The impact of fluconazole on the sulfur metabolism negative regulator gene (sconce) in Microsporum Canis is described in this paper. The ORF of the M. Canis scone c gene is 495 bp long, broken by four introns of 47–70 bp, according to analysis. Fluconazole increases the amount of scone c mRNA and protein expression in M. canis in suspension, as assessed by Northern and Western blot analysis, respectively. Upregulation of second was followed by suppression of the fungus's sulfur metabolism, resulting in a significant decrease in the incorporation of radioactively labeled sulphuric acid into fungal proteins.

This research shows that fluconazole affects various biological pathways in fungal cells in addition to ergosterol production.

Annie Wong-Beringer et al.[22] investigated systemic antifungal Therapy with New options and new challenges. Fungal infections have been increasing rapidly in the past few years. This is due to an increase in the population, which are invasive and amphoteric as well as azole, and fluconazole. Agents which were used in the druggist are limited Resistively as well as interactions with other drugs. The characteristics based on pharmacology & drugs caused are compared with new agents along with the providing of each agent's role.

Katharina Kainz et al.[22] studied annually over 1 million deaths occur due to fungal pathogens like Candida albicans, cryptococcosis neoformans & aspergillosis fumigation. These fungal pathogens target a huge population of patients with their immune systems compromised. Hence it became a necessity for modern medicine to be safe & effective as an antifungal therapeutic. Currently, only 3 classes of drugs are approved for the review article focusing on mycoses. The reviews matter with antifungal activity and cook upon the development of new antifungal agents. Charalambous Anthopoulos et al. investigated the fungal infections which are the extreme reasons for the motility as well as threatening to life. This is specifically for those people who have weak immune systems. The therapeutic solution for the treatment of fungal infections is quite less compared to bacterial ones. There are three classes of molecules presently used in the practices. But only 1 class of drug which is antifungal has developed in the last three decades. In this paper, there is a summarization of the needs which are not met for the antifungal therapy.

Taylor & Francis analyze[23] the Fluconazole properties & analytical Methods for its determination of ergosterol, an exclusive steroid of cell membrane of fungal cells that acts as a selective inhibitor by fluconazole. The drug is highly absorbed by the gastrointestinal tract & is easily spread out in the body via body fluids. Patients with prolonged treatment with a dosage of 400 mg per day show adverse side effects, nausea, headache, diarrhoea, and alopecia. In this article, the authors have discussed the pharmacological & physical-chemical properties of fluconazole & methods used in the

analysis of drug determination.

Charlier et al.[24] studied fluconazole for the management of invasive candidiasis in human candida species that are highly responsible for fungal infections. for the treatment & prevention of mucosal & invasive candidiasis fluconazole are fungistatic drug against yeast & is less active against moulds. Some notable species like candida krusei have become intrinsically resistant to fluconazole. The risk of azole resistance strains has led to questions about the first-line antifungal drugs.The article summarises the current position of fluconazole as the first-line treatment for candida species infections. It is also found that fluconazole may be used in the treatment of candidiasis in adult neutropenic patients among fluconazole, already the first-line drug for the non-neutropenic patients with candidemia.

MT Pasko et al.[25] reviewed the Fluconazole effects on antifungal bi - triazole exhibiting the novel properties of pharmacokinetics which contribute to its therapeutic activity the article focuses on pharmacokinetics properties & pharmacodynamics of the drugs it also discusses the therapeutic potential of the drug in superficial & system mycoses. The clinical targets of the drug are limited to a relatively small number of mycoses & the treatment is expected at its early stage of development optical doses & duration of treatment fluconazole produce rapid relief & eliminate the yeast in 90% of patients with oropharyngeal fluconazole is also a promising drug for the treatment of cryptococcal meningitis.

Reem Alswayeh et al.[26] investigated a Comparison between the physicochemical properties of two different concentrations of paracetamols (500mg and 650mg). Quality evaluation of medications throughout the process of production and distribution is very important, thus the quality of drugs is directly related to the effectiveness of drugs. We are comparing two PCM & acetaminophen (500-650 mg) quality control becomes an important criterion for the pharmaceutical sector, in addition to this, tablets must meet physical specifications & quality standards. The parameters we are for analysing quality standards are: - variations, thickness, friability, and hardness.

Sunil S. Jambhekar et al.[27] studied the drug dissolution test by physicochemical

properties. The dissolution test has evolved into a dependable replacement for bioavailability; it is widely used by FDA & pharmaceuticals industry at various stages of drug development from inspecting environments of the dosage form to spanning between the clinical & market formulation. Because of this increased dependence on dissolution testing & the FDA framed a different organization within an office of new drug quality to assess the biopharmaceutical. parts of drug products.

Deepika-Juveria et al.[28] studied the dissolution: significance of physicochemical properties and physiological conditions dissolution is an interaction by which a strong substance breaks up. As a key property of a solid, it is constrained by fondness between the solid and the fluid medium it composes. The proliferation interest in a drug dissolution can be basically, for the drugs that are generally very hydrophobic attributable to the way that the rate restrictions steps drug absorption process from the gastrointestinal tract is often the drug was from the solid dosage form.

Zhai Bing et al[29] studied the recent progress in Antifungal Drug development. Several fungal infections are very lethal to health this is specifically to those who are having weak immune systems. Some therapies are antifungal which are purposely improved but the results are not proper. This is because of a smaller number of clinically available classes. There are advancements in antifungal drugs which are in the stages of investigational and give new hope for antifungal therapy.

J. Clin. Med. et al.[30] studied immune suppression; diabetic patients have shown a higher tendency towards candida species infections. The treatment of fungal infections in diabetic patients can be complicated because of disease-related changes in the drug to pharmacokinetics & pharmacodynamics properties of antifungals. The Article comprises the challenges in treating the candida species & discusses applications of Pk/PD in choosing the appropriate antifungal dose.

Heping Wanga et al.[31] investigated the construction movement associations of amphiphilic penetration. In this study, enhancers including the length of the hydrophobic chains as well as the qualities of the polar head, O-acyl geraniol, and O-acyl Erol subordinates were created by combining geraniol/neroli

(cis-isomer of geraniol) with medication excipient acids. Flurbiprofen (FP), isosorbide dinitrate(ISDN), and donepezil (DNP), which were chosen based on their physicochemical features, were tested in vitro and in vivo in order to improve the percutaneous retention of three drugs as the model. Atomic reenactment, ATR-FTIR, CLSM, and histological perception were used to determine the enhancers' mode of action. That is what the results showed. The most notable upgrading capability for the three treatments was achieved by (E)- 3,7-dimethyl-2,6-octadien-1-yl tetra decanoate (GER-C14, trans-); moreover, the in vivo outcomes obtained were in excellent agreement with the in vitro data. The consequences of subatomic reenactment showed that GER-C14 and NER-C14 may embed into the middle of the lipid bilayer to frame a free stage, and atomic docking studies suggested that enhancers slacken the hydrogen connection among ceramides.The enhancers extricated lipids and affected the protein area, according to ATR-FTIR and histological analysis, disturbing the skin demonstrate.CLSM further revealed the significant effects of enhancers on lipids between layer corneum (SC) cells. Taking everything into account, GER-C14 had a superior entrance advancement impact, which expanded how we might interpret stereoisomeric infiltration enhancers.

Károly Mazák et al.[32] studied the arrangements of amphoteric mixtures that exist in anionic, non-charged, zwitterionic, and cationic structures. The significance of zwitterionic drugs is right now underrepresented in the writing. The corrosive base boundaries, lipophilicity, and solvency of such mixtures are examined to extend the sub-atomic level comprehension of their pharmacokinetic and pharmacodynamic conduct. Our new investigations show there are many medication particles, including thyroid chemicals and 5-hydroxytryptophan, the antecedent of the synapse serotonin, where the commitment of the zwitterionic microspecies to the general lipophilicity surpasses that of the non-charged one, which is of higher individual lipophilicity, yet happens in much lower focus. The second piece of the audit features the most significant zwitterionic compounds in treatment, gathered in remedial classes. The significance of the charge of the atoms is accentuated in their limiting to the objective particles.

Anita Saravana Kumar et.al[33] investigated the enzyme-intervened biotransformation

of pharmacological specialists is a pivotal advance in xenobiotic detoxification and medication demeanour. Thus, we explored the digestion and physicochemical properties of the main 200 most endorsed drugs (laid out) as well as medications supported by the US Food and Drug Administration (FDA) somewhere in the range of 2005 and 2016 (recently endorsed).

CHAPTER - 3

EXPERIMENTAL ANALYSIS

Experimental

3.1 Chemical and Reagents

3.1.1 Water - Water can dissolve more things than any other liquid, it is known as the "universal solvent."Water, a primary solvent in the study that is also used in instrument or equipment calibration, was produced by a double distillation method. Water is added in the surfactant SDS in 25ml with the addition of 2ml in the drug solvent and fluconazole drug in 100ml of water to check specific conductivity using a conductivity meter and Ostwald viscometer to check the viscosity of solvent at different temperatures.

3.1.2 Pharmaceutical Ingredients –

Meridian Pvt. Ltd. provided fluconazole (FLZ) as a free sample (Solan).FLZ is an antimicrobial drug used with surfactant Sodium dodecyl sulfate. Merck Chemicals supplied an anionic surfactant, sodium dodecyl sulfate (SDS) which was used as anionic surfactant with the drug fluconazole in the experiment to check the specific conductivity and viscosity at different temperatures.

3.2 Conductance Measurement:

3.2.1 Specific Conductance (SC) –

The specific conductance (SC) of well water is a measurement of its ability to carry an electrical current. These ions, which are formed by the breakdown of water compounds, will transmit a little amount of electrical current, and the physical phenomena of conductivity will rise as the quantity and quality of ions increase. These ions, which are formed when chemicals are broken down, conduct electricity when dissolved in water because they are negatively charged and shown in Fig 3.1.

3.2.2 Critical Micelles Concentration (CMC) - The critical micelle concentration (CMC) is the detergent concentration above which micelles form spontaneously. Because of high concentrations and the addition of detergents to form complexes with lipotropic proteins, the CMC is particularly significant in biology. Detergents merely partition into membranes below this line, without solubilizing membrane proteins. Ionic strength and temperature affect CMCs. In the case of ionic detergents, increasing the ionic strength of the solution reduces the CMC; however, in the case of non-ionic detergents, the temperature has no effect.

The CMC is unaffected by ionic strength; however, it will rise dramatically as the temperature rises.

Fig 3.1 Cyber scanCON-510 conductivity meter

3.2.3 Thermodynamics Studies

$\Delta H°m = -RT' (2-a) (d \ In \ Xcmc)/dt$

$\Delta S°m = (AH^{o}m - AG^{o}m)/T$

$\Delta G°m = RT (2-a) (In \ Xcmc)$

α denotes the degree of ionization of surfactant, ΔG°m is the standard Gibbs free energy change of micellization.ΔH°m is the standard Enthalpy for micellization, ΔS°m is the standard Entropy of micellization.

3.3 Viscosity Measurement

A viscometer (also known as a viscometer) is a device that measures a liquid's viscosity. The viscosity of liquids that change with the flow is measured with a rheometer. As a result, a viscometer is classified as a rheometer.

Only one type of flow may be measured using viscometers. In general, as an item travels through it, the fluid remains static, and the thing remains stationary while the fluid goes through it. The drag caused by the relative velocity of the fluid and a surface determines the viscosity. For laminar flow to occur, the Reynolds number of the flow conditions must be minimal enough.

3.3.1 Ostwald Viscometer

Glass capillary viscometers or Ostwald viscometers, after Wilhelm Ostwald, are other names for these devices. The suspended level viscometer, which uses a U-shaped glass tube placed vertically in a regulated temperature bath, is another option. One of the U's arms has a vertical piece of the precise narrow bore (the capillary). Above it, a light is positioned, and on the opposite arm, another light is located. The suction pulls liquid into the top bulb, which then flows down the capillary into the lower bulb. Two marks represent a known volume (one above and one below the top bulb). The time it takes for the liquid level to travel between these positions is linked to the kinematic viscosity. A fluid with known characteristics can be used for calibration. A conversion factor is included with most commercial units. The time it takes for the test liquid to pass through a capillary with a known diameter between two designated sites is calculated. The kinematic viscosity is calculated by multiplying the time taken by the factor of the viscometer and shown in Fig 3.2.

Fig 3.2 Ostwald Viscometer

General Calculations:

The temperature of water = TC

The density of water at this temperature = dw gm/lt

Time of flow of water = tw

The viscosity of water = new centipoises

(a) To calculate the density of the liquid (ds)

Weight of empty bottle = W 1

Weight of empty bottle = water = W2

Weight of empty bottle + solvent = W3

The density of the liquid (ds)= (Wt. of solvent/ Wt. of water) X Density of water.

(W3-WI/ W2-WI) x dw gm/cm

(b) To calculate the viscosity of the liquid

ns = (ds. ts/ DW.tw) x nw centipoise

CHAPTER - 4

RESULT AND DISCUSSIONS

Result and Discussion

4.1 Conductivity measurements

One of the simplest approaches for measuring the critical micelle concentration (CMC) of a surfactant is to test its conductivity. As a result, the CMC of SDS was calculated by plotting the specific conductance (x) against the concentration of SDS containing FLZ in hydro-ethanol solutions. CMC values were then utilized to determine the H°m, G°m, and S°m, which were then summarized in SDS using calculated FLZ.

Conductivity Studies and Determination of CMC

0.1g of SDS was dissolved in water to check the specific conductivity of an anionic surfactant at four different temperatures (25°C, 30°C, 35°C, and 40°C). The specific conductivity values were used to calculate the CMC which was obtained by plotting the graph between specific conductivity versus surfactant concentration as shown in Fig 4.1.

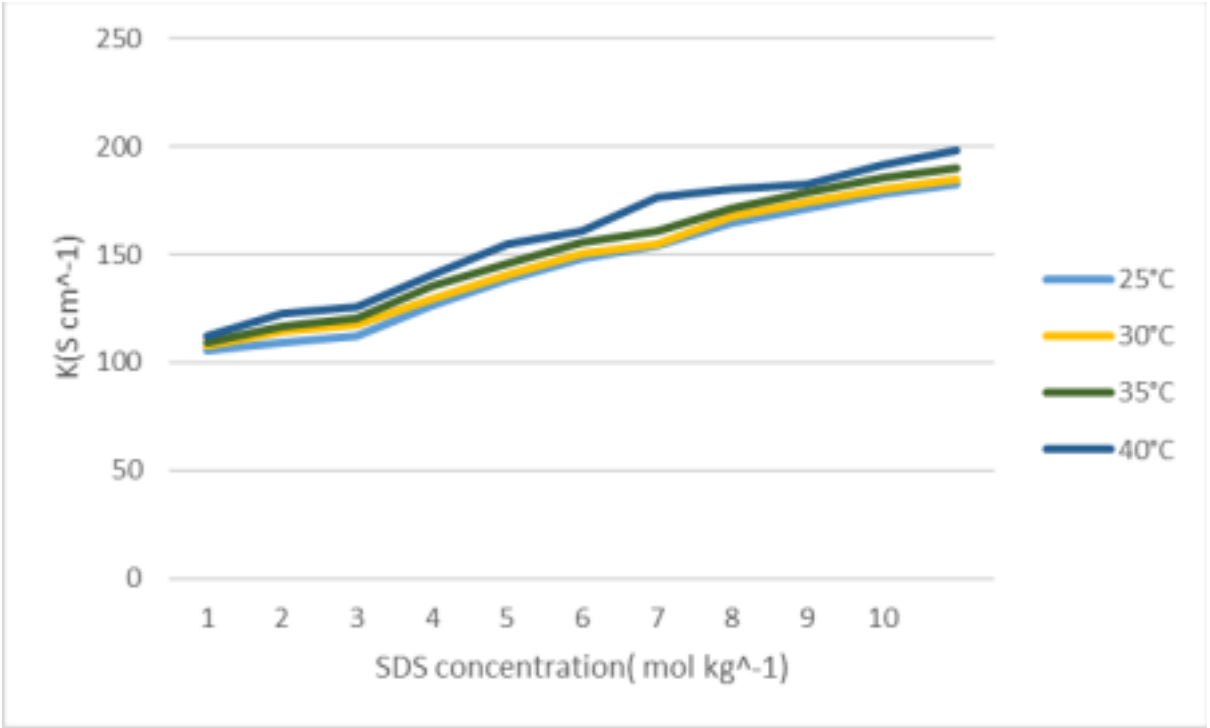

Fig 4.1.The plot of specific conductance versus SDS concentration at four different temperatures.

Fluconazole is an antimicrobial drug used with surfactant Sodium Dodecyl Sulfate (SDS). 0.1g of fluconazole was added to 100ml of water to make the main solution and 0.1g of SDS was added to 25ml of water to make a stock solution. In this experiment, we observed the critical micelles concentration(CMC) by plotting a graph between the specific conductance vs. surfactant concentration (SDS). the plot for specific conductance versus SDS concentration at four different temperatures is shown in Fig 4.2. Four different temperatures (25°C, 30°C, 35°C, and 40°C) are shown in fig 4.3-4.6. we observed the CMC and plot the graph between them differently shown in Fig 4.1.1.CMC values were then utilized to determine the H°m, G°m, and S°m, which were then summarized in SDS using calculated Fluconazole shown in tables 4.1- 4.4. And the plot of standard enthalpy versus SDS concentration is shown in Fig.4.7.

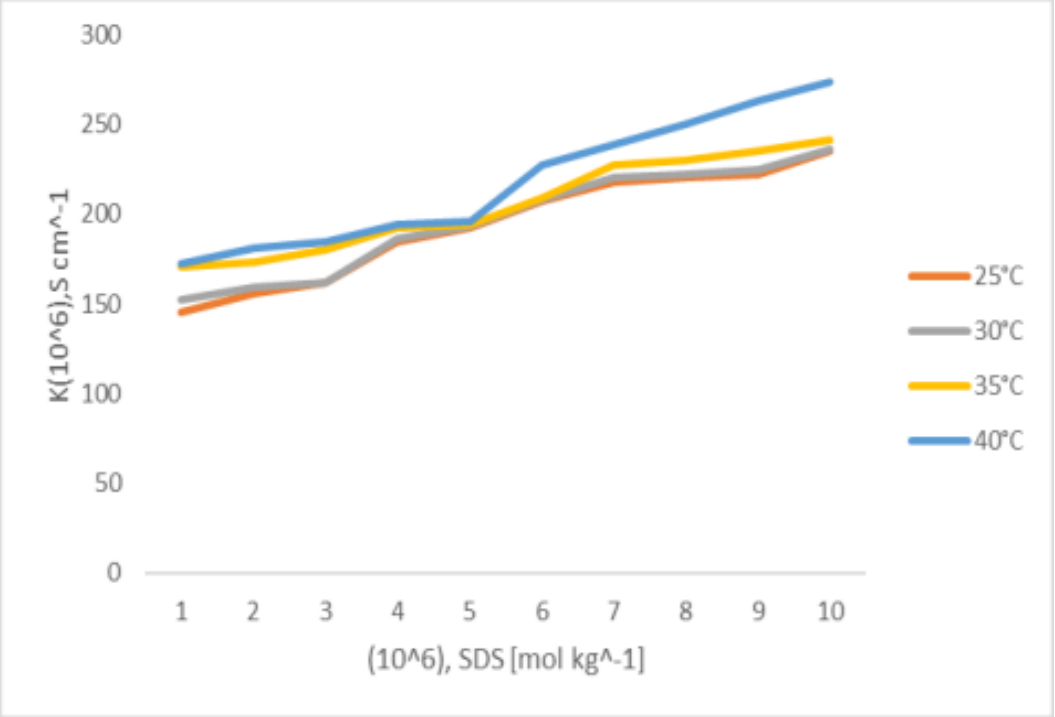

Fig 4.2. The plot of specific conductance of FLZ versus SDS concentration at four different temperatures.

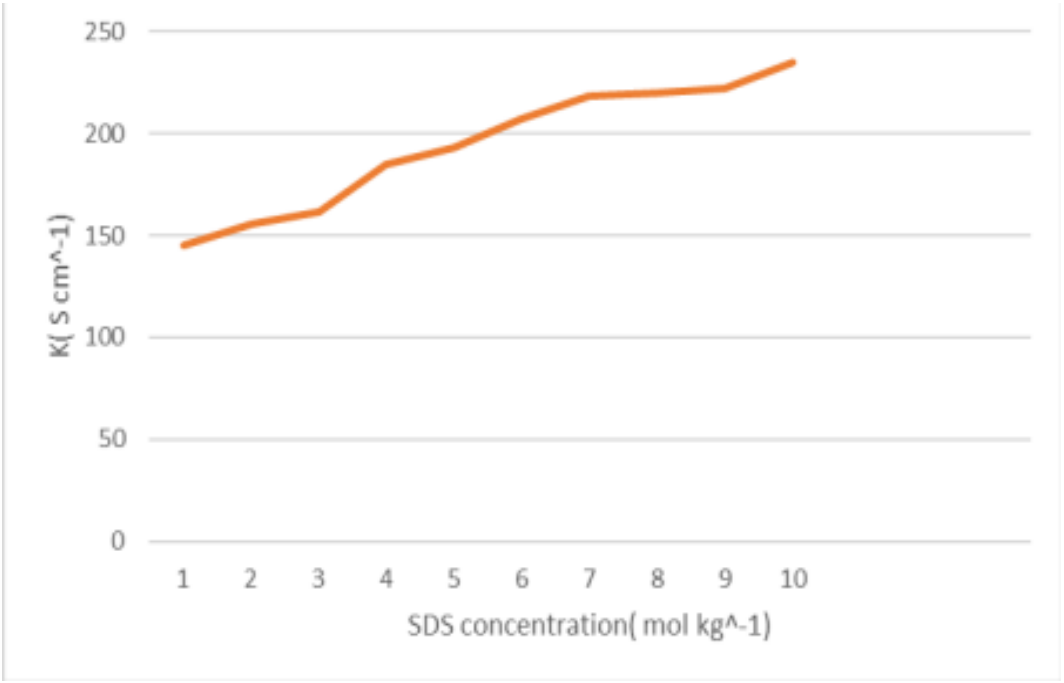

Fig 4.3. The plot of specific conductivity of FLZ versus SDS concentration at 25°C

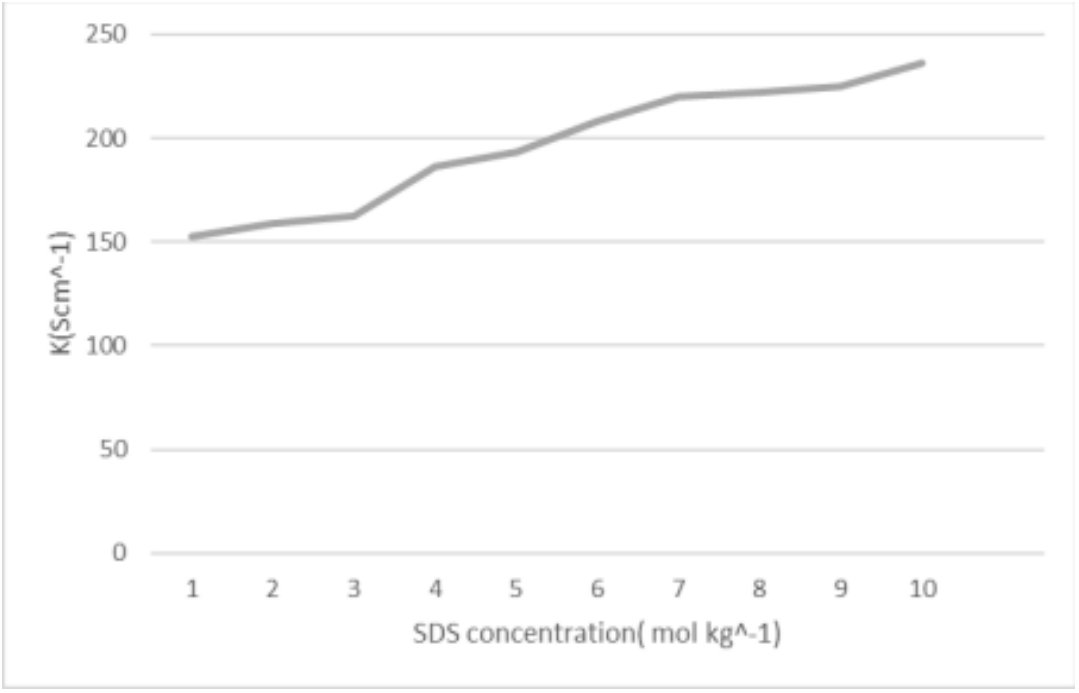

Fig 4.4. The plot of specific conductivity of FLZ versus SDS concentration at 30°C

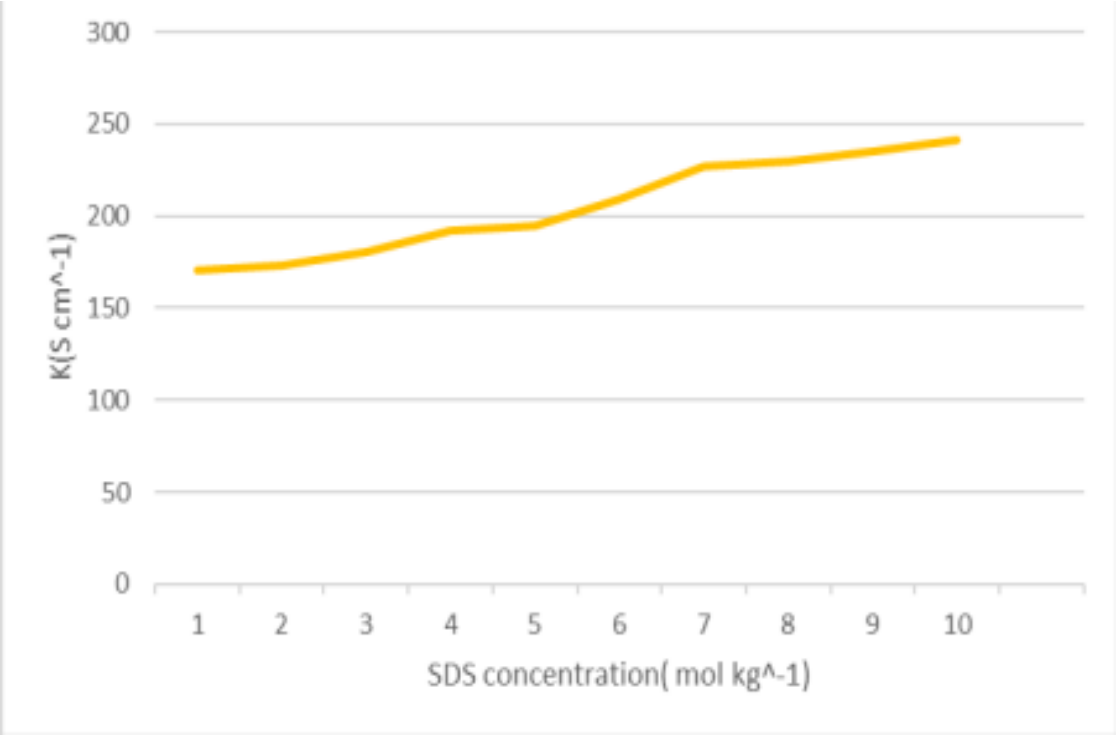

Fig 4.5. The plot of specific conductivity of FLZ versus SDS concentration at 35°C

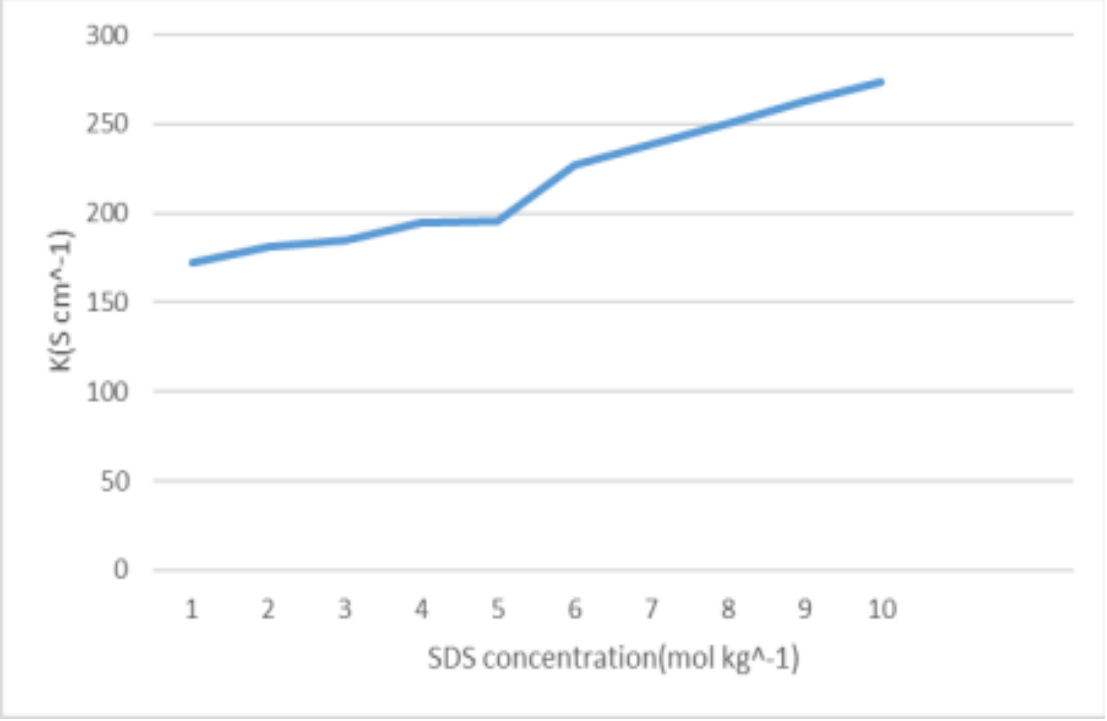

Fig 4.6. The plot of specific conductivity of FLZ versus SDS concentration at 40°C

Table 4.1. At 25°C, the value of ΔH°m, ΔG°m, and ΔS°m value of FLZ with SDS.

S.NO	Critical micelle concentration	ΔH°m (kj mol^{-1})	ΔG°m (kj mol^{-1})	ΔS°m (J mol^{-1}K^{-1})
1	0.00568	20.70	-21.61	142.0
2	0.00800	21.42	-21.65	141.9
3	0.00975	22.14	-21.72	142.2
4	0.01120	22.87	-21.88	142.7
5	0.01246	23.62	-21.19	143.8
6	0.01359	22.15	-21.81	144.6
7	0.01467	23.72	-22.74	145.8
8	0.01555	22.76	-22.04	146.3
9	0.01642	21.37	-22.35	147.8
10	0.01722	22.81	-22.05	142.6

Table 4.2.At 30°C, the value of ΔH°m, ΔG°m, ΔS°m value of FLZ with SDS.

S.NO	Critical micelle concenteration (CMC)	ΔH°m ((kj mol-1)	ΔG°m (kj mol-1)	ΔS°m (kj mol-1)
1	0.00568	20.75	-21.63	142.2
2	0.00800	21.46	-21.67	142.2
3	0.00975	22.18	-21.73	142.5
4	0.01120	22.91	-21.90	142.9
5	0.01246	23.66	-21.22	143.8
6	0.01359	22.20	-21.77	144.5
7	0.01467	23.75	-21.75	145.9
8	0.01555	22.81	-22.04	146.5
9	0.01642	21.40	-22.37	147.9
10	0.01722	22.87	-22.07	142.9

Table 4.3.At 35°C, the value of ΔH°m, ΔG°m, ΔS°m value of FLZ with SDS.

S.NO	Critical micelle Concentration (CMC)	ΔH°m (kj mol-1)	ΔG°m (kj mol-1)	ΔS°m (kj mol-1)
1	0.00568	20.77	-21.65	142.5
2	0.00800	21.50	-21.69	142.4
3	0.00975	22.20	-21.76	142.6
4	0.01120	22.93	-21.93	143.1
5	0.01246	23.68	-21.25	143.7
6	0.01359	22.24	-21.78	144.8
7	0.01467	23.79	-21.77	146.1
8	0.01555	22.85	-22.07	146.6
9	0.01642	21.46	-22.39	148.1
10	0.01722	22.89	-22.09	143.0

Table 4.4.At 40°C, the value of ΔH°m, ΔG°m, ΔS°m value of FLZ with SDS.

S.NO	Critical micelle concentration (CMC)	ΔH°m (kj mol-¹)	ΔG°m (kj mol-¹)	ΔS°m (kj mol-¹)
1	0.00568	20.80	-21.69	142.7
2	0.00800	21.53	-21.71	142.6
3	0.00975	22.25	-21.79	142.9
4	0.01120	22.97	-21.95	143.5
5	0.01246	23.70	-21.28	143.9
6	0.01359	22.27	-21.79	144.5
7	0.01467	23.81	-21.80	146.7
8	0.01555	22.87	-22.10	146.9
9	0.01642	21.49	-22.43	148.3
10	0.01722	22.91	-22.11	143.5

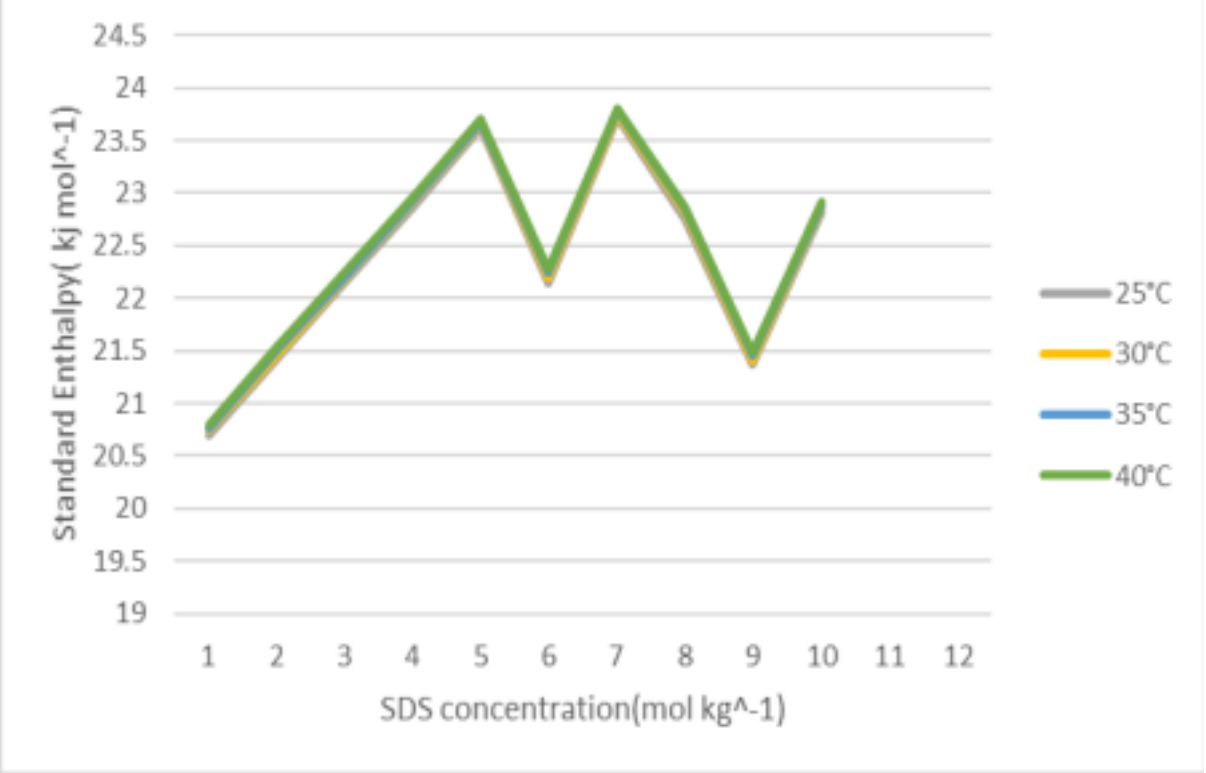

Fig 4.7. The plot of standard enthaply versus SDS concentration at four different temperatures

4.2 Viscosity Measurement

In this experiment , we determine the viscosity of fluconazole with addition of SDS(sodium dodecyl sulfate) at four different temperatures (25°C, 30°C, 35°C, and 40°C). Firstly, we prepare a solution of fluconazole by taking 0.1gm of FLZ in 100ml of water. Second, we prepare the stock solution by taking 0.1gm of sodium dodecyl sulfate(SDS) in 25ml of water and then the addition of 2ml of SDS in a viscometer and observing the time of flow(s) and density, and viscosity is shown in Table 4.5 to 4.8.The plot for viscosity versus SDS concentration is shown in Fig 4.8.

Table 4.5. At 25°C, the viscosity of water is 0.89cp and density of water is 997gm/l, and the time of flow of water is 14:08s.

S.No	SDS Concentration	Time of flow (s)	Density (gm/l)	Viscosity in centipoise (cp)
1	0.81	59:08	1.70	6.08
2	1.12	55:39	1.74	5.85
3	1.35	50:52	1.80	5.49
4	1.55	51:42	1.82	5.67
5	1.72	47:28	1.85	5.27
6	1.94	56:21	1.95	6.61
7	1.99	58:12	1.98	6.94

Table 4.6. At 30°C, the viscosity of water is 0.79cp and density of water is 995gm/l, and the time of flow of water is 15:22s.

S.No	SDS Concentration (ml)	Time of flow (s)	Density (gm/l)	Viscosity in centipoise (cp)
1	0.81	52:49	1.71	5.86
2	1.12	51:28	1.76	5.92
3	1.35	54:34	1.79	5.07
4	1.55	50:42	1.81	4.76
5	1.72	55:14	1.85	5.34
6	1.94	56:29	1.9	5.57
7	1.99	58:24	1.94	5.89

Table 4.7. At 35°C, the viscosity of water is 0.71cp and density of water is 994gm/l, and the time of flow of water is 16:28s.

S.No	SDS Concentration (ml)	Time of flow (s)	Density (gm/l)	Viscosity in centipoise (cp)
1	0.81	50:26	1.71	3.72
2	1.12	55:39	1.75	3.25
3	1.35	52:42	1.77	4.35
4	1.55	58:31	1.81	4.64
5	1.72	56:19	1.85	4.53
6	1.94	52:29	1.9	4.35
7	1.99	51:52	1.94	4.46

Table 4.8.At 40°C, the viscosity of water is 0.65cp and density of water is 992gm/l, and the time of flow of water is 16:28s.

S.No	SDS Concentration (ml)	Time of flow (s)	Density (gm/l)	Viscosity in centipoise (cp)
1	0.81	58:26	1.7	4.55
2	1.12	50:52	1.74	4.05
3	1.35	51:42	1.78	4.27
4	1.55	56:21	1.81	4.67
5	1.72	58:12	1.86	4.97
6	1.94	52:28	1.89	4.52
7	1.99	50:26	1.94	4.48

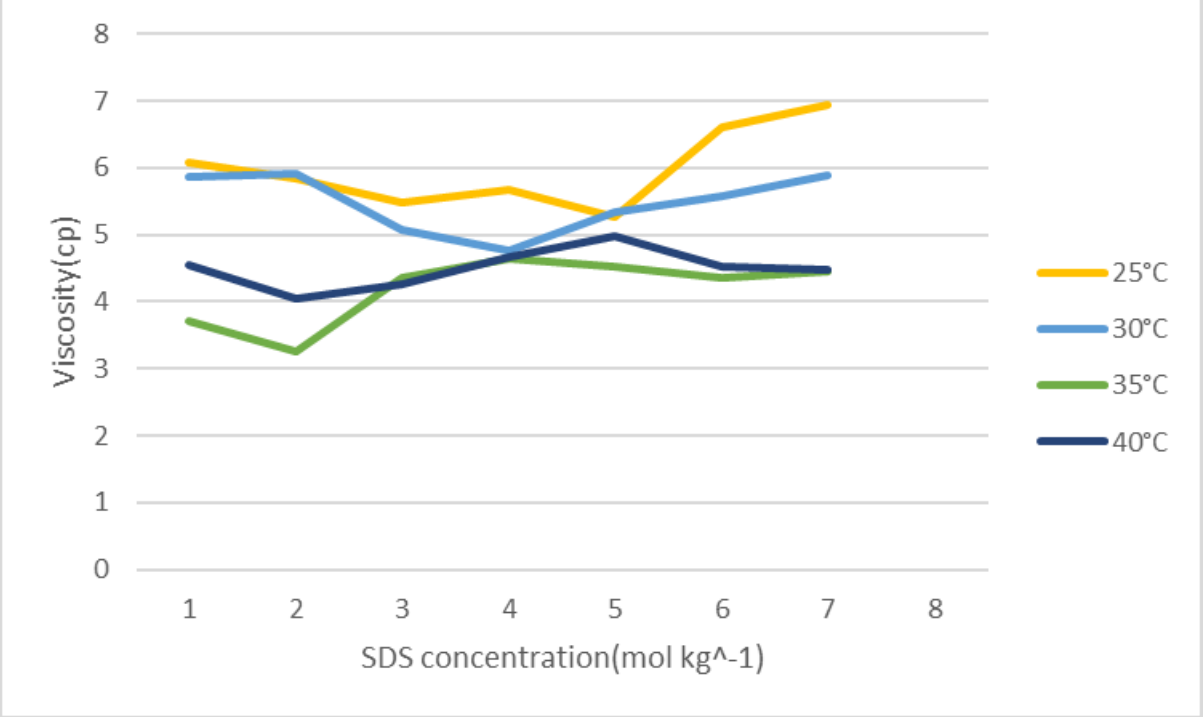

Fig 4.8.The plot of viscosity versus SDS concentration at four different temperatures

CHAPTER - 5

CONCLUSION

Conclusion

The thermodynamic parameters of surfactant SDS has been calculated in presence of the antifungal drug fluconazole. The presence of fluconazole delays micellization as CMC values are less as compared to standard CMC of SDS. Micellization is also influenced by solute-solvent interactions which are well observed by different thermodynamic parameters The standard entropy $\Delta S°m$ were discovered to be positive indicating all entropy-driven processes while standard Gibbs free energy $\Delta G°m$ and standard enthalpy $\Delta H°m$ are negative and positive respectively. The positive value of $\Delta H°m$ indicates an endothermic reaction whereas $\Delta G°m$ confirms the spontaneity of a reaction. Furthermore, increasing values of density and viscosity also supports the observation of conductance measurement. So, measuring all these physicochemical parameters which are included in pre-formulation studies can be helpful for increasing the efficacy and stability of new drug formulations. These studies can be related to various drug ingredients and provide new ideas about suitable modifications to show better performance by formulation.

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