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SURFACTANTS - THE ASTOUNDING NANOMATERIALS IN THE DRUG DELIVERY SYSTEM

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ABSTRACT

Nanotechnology can be defined as the technology which has allowed for the control, manipulation, and manufacture of materials in very small size range. Surfactants take on novel properties in micellization of biologically active substances that have low toxicity and high solubilization power towards poorly soluble pharmaceuticals to aid in large number of therapeutic protocols such as gene therapy, drug delivery, drug targeting. However, surfactants are used to reduce toxicity and side effects of drugs but this carrier systems impose various limitations like lack of target specificity, altered effects and diminished potency due to drug metabolism in the body, cytotoxicity of certain anti-carcinogenic pharmacological agents. Biocompatible surfactants with optimized physical, chemical and biological properties can serve to overcome the limitations faced in drug delivery systems by understanding the interactions of this nanomaterials with the biological environment, cell-surface receptors, drug releasing process and stability of the therapeutic agents. These newer generations of drug delivery systems have significant advantages over the other drug delivery systems. This article discusses the need for nanotechnology-based drug delivery systems, their advantages, applications, classification and limitations of such drug delivery.

KEYWORDS: Surfactant, nanomaterial, nanotechnology, nanoparticle, micellization, cytotoxicity.

1.1 INTRODUCTION

Pharmaceutical drugs and synthetic drugs gets rejected in their early stage of development and never points its way to the patient because of its poor water solubility or lipophobic

property which entail bioavailability problem.[1] Hence, the dissolution of different kinds of dosage form[2], is an important parameter to assure that the insoluble drugs are absorbed and available in the systemic circulation.[3]

In Pharmaceutical industry, water is used as a solvent and the compounds used have both the hydrophilic and hydrophobic regions respectively, the polar group will act as lyophilic (solvent pathy) while non polar group will act as lyophobic (solvent antipathy).[4] Both the groups resides in opposite directions in a manner that the ends are coupled in a bond forming an polar and asymmetric structure, these kinds of structure are referred as "parent structure" or "amphiphilic structure".[5] The dual characteristic of these kinds of compounds leads their accumulation at interfaces in a manner to remove the hydrophobic region from the aqueous environment with a consequent reduction interfaceal or surface tension between the liquids by forming a micellar structure at the interface.[6,7] This microheterogenous structures which contain the surfactant molecules are termed as micelle[8,9], and the amphiphilic compounds which contain both the hydrophilic, polar head and non-polar hydrocarbon tail (hydrophobic group) in the same molecule are termed as surfactant.[10,11] When the clusters of the surfactants overreach the critical micelle concentration (CMC) it increases the drug dissolution[12], solubilization[13], of slightly and sparingly soluble drug by micellar solubilization, wetting[14] and also improves the stability of the formulation[1], below CMC drug dissolution also takes place due to significant reduction in the interfacial tension between the excipients and the drug molecules.[15] Based upon the nature and number of groups on the surfactants, it may be called as lipophilic, hydrophilic or well balanced. The hydrophilic portion of the surfactant is contributed by the functional groups such as alcoholic(-OH), carboxylic acid (-COOH), sulphate ($-SO_4$), and quaternary ammonium (NH_4^+) etc. whereas alkyl chain contribute the lyophilic nature of the surfactant.[16]

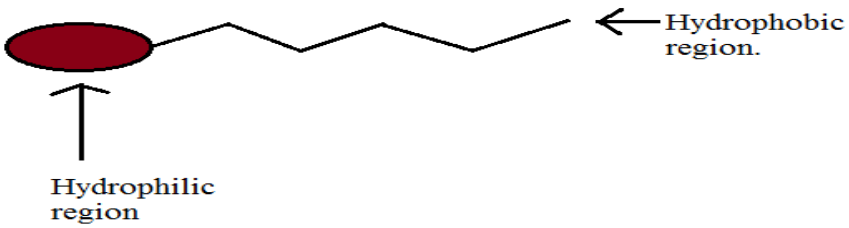

Figure :- Structure of a surfactant molecule.

The important properties of the surfactants are its propensity to form micelle. Knowing the pattern of orientation, distribution, location of the solublized drug in the micelle, which is useful to understand the kinetic aspect of the solubilization process. The locations of the drug undergoing solubilization in the micelle rely on the balance between the polar and nonpolar sites present in intermediate position within the surfactant molecules. The anisotropic distribution of the water molecule with the polar region of the drug leads to the solubilization of many insoluble drugs molecule in the water and the amount of the drug substance which can be solubilized by the surfactant is the function of polar-non polar property of the respective surfactant. The choice of the surfactant that to be use in the formulation should be such that it should be nontoxic, miscible with solvent (water), non-volatile, should be free from foul taste and odor and compatible with the drug molecule.[17] Surfactants are also used as excipients in the formulation of various drug delivery systems includes the conventional delivery system and also in the development aspect of colloidal drug delivery systems.[18] The incorporation of drugs in nanoemulsions, niosomes, nanoparticles and other nanostructures with the aid of various surfactants revolutionized the delivery and release technique of poorly miscible drugs.[19] In the field of pharmaceutical sciences, the surfactants are immensely used as de-emulsifiers and emulsifiers, solubilizers, micellars, wetting agents, detergents, defoaming or foaming agent etc.[35,36] Recently the development of surfactant enhanced to formulate various biomedials[37], and application of surfactant therapy shows a greater significant in gaseous exchange and blood oxygenation in newborn or premature diagnosed with RDS[38], with the less evidence of lung damage.[39]

Every now and then while studying about the surfactant in the development of the new drugs amazed us to find in detail how the surfactants have evolved as a revolutionary medium for the dissolution and delivery of drugs at different regions inside the body. This review article covers some of the important aspects about the classification of different types of surfactants and their advantages and disadvantages in the role of delivery and the dissolution of pharmaceutical drugs.

2.1. Classification and properties of surfactant in the drug delivery system

The head part of the surfactant determine its property[40], based upon the charge state of hydrophilic group[41], character and structure of hydrophilic group, water dissociation capacity, surfactants are categorized as cationic, anionic, amphoteric, nonionic surfactants.[42]

2.1.1 Anionic surfactant

This type of surfactant carries the negative charge on the head or hydrophilic part.[43]

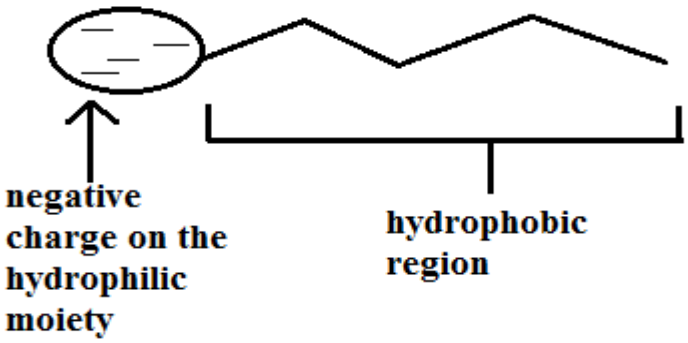

Figure:- Structure of an anionic surfactant.

Most of the surfactants under this category possess sulfate, phosphate, carboxylate polar group in merge with counter-ions such as Na and K (for water solubility) or Ca and Mg. This type of surfactant can be utilized as foaming agent, dispersants, emulsifiers and detergents etc.[2] In pharmaceutical prospective this type of surfactants can be utilized in preoperative skin cleanser and in medical shampoo.[44] Anionic surfactant possess unique morphological property which can deposit drug molecules by disruption of endosomal-lysosomal membrane[45], intracellular spaces.[46] It also has the preparedness to hold the drug with the polymer.[47] Different pore structure in anionic surfactant molecule influence control drug release[48] of poorly soluble drugs into the target site.[49]

2.1.2 Cationic surfactant

Cationic surfactants are amphiphiles which carries both the hydrophilic and hydrophilic part in the same molecule and carries the positive charge in the head region.[50] Another class of cationic surfactant use in drug delivery is classified as Gemini surfactant which posesses similar or different amiphiphilic molecules linked together at the polar head groups.[51]

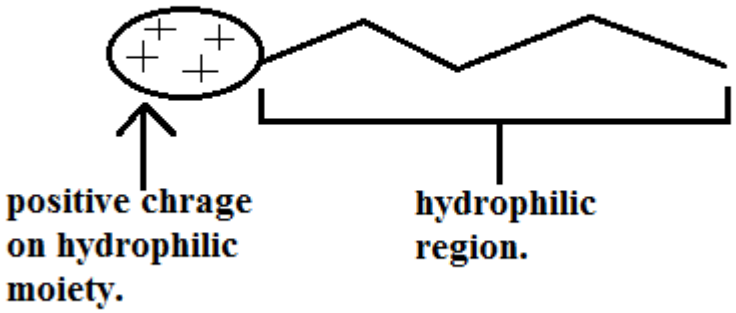

Figure:- Structure of a cationic surfactant.

The surface activity of cationic surfactant increases in the acidic medium but its activity decreases in the alkaline medium and tends to precipitate.[2] Cationic surfactant is used in the aqueous and non-aqueous system[52] which is mainly used in the determination of CMC[53] and has the capacity to lowers the interfacial tension of water.[54] Moreover it has great self assembling property to form different colloidal aggregates[55] and used in determination of API's.[56] The binding of drug with cationic surfactant reduces the recrystallization and increases the bioavailability of the drug molecule.[57] However, for amphiphilic nature it also assists to deliver the genes.[58] Cationic surfactant forms multilayer complexes with polyelectrolyte drugs to help in controlled and sustained release of the therapeutic agents.[59]

2.1.3 Zwitterionic surfactant

Surfactants under this category possess both the positive and negative ions that are known as amphiphiles.[2] Surfactant which contain two hydrophilic head region and two hydrophobic tail region in the same structure are classified as zwitterionic surfactants.[60]

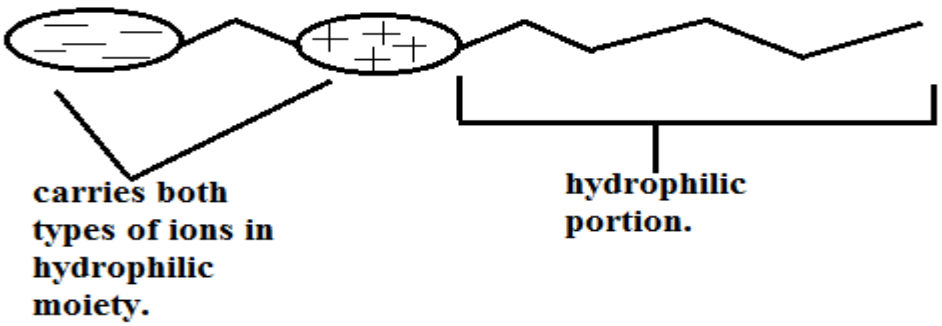

Figure:- Structure of an amphoteric/zwitterionic surfactant.

The nature of the head group, hydrophobic chain length and the nature of spacer moiety of zwitterionic surfactant influences the micellization of the drug[61], forms vesicles that aids to increases the stability[62], solubility.[63] It possess pH-dependent property[64], that prevents the coalescence of the drug molecules in dosage form.[65] These kinds of surfactant possess non-uniform pores on their structure which felicitates easy loading of drug molecules[66], for controlled and sustained release at the specific site of action.[67] Single chain zwitterionic surfactant is also used as biosensor, purification of protein membrane.[68]

2.1.4 Non-ionic surfactant

These type of surfactant contains polar head group and long fatty acid chain as its structure moiety and this type of surfactant largely contributes to the pharmaceutical prospective for biodegradable and biocompatible property.[69]

Nonionic surfactant are not only used in target drug delivery[70], but also in delivery of nucleic acid based drugs[71], for its strategy to improves the stability and role of the nanoparticles.[72] Moreover it can take up both the hydrophilic and hydrophobic drug by encapsulation and intercalation by its structural moiety[73], helps in sustained and controlled release and permeability of the drug [74], into the transdermal membrane[75] in different concentration of the surfactant.[76] Nonionic surfactant provides insulation to the nanocarrier limiting their elimination from the systematic circulation.[77,78]

2.1.5 Bio-surfactant

Natural class of surfactants containing both the hydrophilic and hydrophobic groups synthesized from the bacteria, fungi, yeast, plants(saponins) are classified as biosurfactant.[79,80] These type of surfactants finds its application because they are capable to increase the solubility of insoluble drugs[81], and has great bioavailability and low toxicity effect in the systematic circulation.[82,83]

Biosurfactants are used to aid in drug delivery system for its biodegradable property[84], and has a great permeability effect on the membranes.[85] However biosurfactant has got prominent adhering capacity with specific membranes which is why finds its application in targeted drug delivery[86] to target drugs in breast cancer and in gene therapy.[87]

3.1. Advantage of Using Surfactant in Modernize the Drug Delivery

Surfactant has got many advantageous action in modernize the drug delivery in which surfactant-polymer mixed drugs has greater colloidal stability when administered through microencapsulation[88], which increases the bioavailability and improves the dissolution of hydrophobic compounds.[89] In the study of biological drug process, surfactant layers are used as in-vivo model to obtain information of action and adsorption of drug molecule.[16,90] Surfactant – protein binding is a principle aspect in delivery of drugs that gives valuable information regarding the binding of drug with small molecules such as amino acids, lipids hormones[91], improving the therapeutic activity of the drug.[92,93] Surfactant-drug micelle has the ability to permeate into the cellular and nuclear components (DNA & RNA) of the cell and able to inhibit the DNA replication and RNA synthesis in the cancer and tumor cells.[94] Surfactant reduces the strong side effects of potent drugs by targeting directly to the specific sites and affected organs.[95]

4.1 Disadvantages of Surfactant in Drug Delivery

Surfactant can be termed as necessary evil, in spite of having numerous advantages there are many disadvantages of using surfactant as a carrier as it possess poor drug loading capacity in the miceller structure[121], the interaction of surfactant with the cell membrane or with liquid component, damages the functional protein of the cell.[96] Sometimes blood plasma invades the surfactant coated polymer as a foreign substance inside the body causing phagocytosis and leads to the expulsion of the drug from the body.[97,139] Sometimes surfactant causes leakage or fusion in encapsulated drug molecules.[98] Drug targeted at a specific site through surfactants (target drug delivery system) fails maintain the specified concentration of the drug in specific areas of the body.[99] Some surfactant at higher pH forms insoluble precipitate reducing the therapeutic effect of the drug molecule[100], sometimes they are unable to retain the active form of the drug which get destroyed by various physiological activity of the body before reaching to the target site.[130]

5.1. Dissolution of Drugs Molecules with the Aid of Surfactant

Surfactants are used in the modern drug delivery system for its high drug loading capacity[26], aids in storing and keeping the chemical entity in the active form for longer period of time[27], and enhances the penetration of drug through small capillaries and decreases its enzymatic degradation.[28] Studies suggested that the pharmacokinetics of the insoluble drug, when administered containing surfactant increased its dissolution.[29,13] But it is estimated that

majority of approved and underdeveloped pharmaceutical drugs are insoluble to the vehicle or carrier and possess poor solubility and less permeability to the biological membranes[101], leading to insufficient bioavailability.[102] Although various methods are conducted to improve the dissolution of poorly soluble drugs[103], one of which the use of various kinds of surfactant for the enhancement in dissolution of immiscible drugs is used from long ages.[104]

According to Biopharmaceutics Classification System (BCS) drugs which have high membrane permeability but low solubility and vice-versa[105] are major challenges faced by the researchers to buildout new drugs.[106] The initial steps needed for the drug dissolution involves the disintegration of the solid drug molecules from the dosage form and disaggregation of further disintegrated molecules and transfer of molecules into the solution form and further absorption by the biological membranes this whole sequence forms the dissolution of the drug from the dosage form.[16]

When surfactants are added they form a monomolecular film around the drug molecules[17], increases the effective surface area leading to the disintegration of the molecules[107], consequently reduces the interfacial tension due to wetting effect[108], which forms microenvironment around the particle converting in solution form[109], that improves in drug dissolution properties[110], which attributes in taking up the drug into the surfactant molecules[111], at different concentration[112], further inhibits the crystallization of the molecules and keeps it in a supersaturated state unless the absorption takes place[113], enhancing the permeability of less soluble drugs.[114] The in-vivo drug dissolution is also influenced due the presence of natural surfactants in the gastrointestinal fluid like bile salts[115], cholesterol, lecithin, and its esters[30], imparts emulsion and micelle formation and aids in dissolution of poorly soluble drugs[116] and enhances the bioavailability.[117] However to control the rate at which the drug leaves from the dosage form, the drug molecules are coated with surfactants to delay the immediate dissolution when it comes in contact with the body fluid so as to restrict the immediate release and expulsion of the drug from the body which leads to achieve the optimum therapeutic window.[138]

6. Surfactant: A Revolutioner in the Drug Delivery System

Drug delivery at the target site and controlled release of the drugs has gained much attention over few years[118], in which the surfactant plays a vital role in modernize the drug delivery for its ability to takeup the drugs in its hydrophilic and hydrophobic moiety for controlled delivery and sustain release with a consequent decrease in minimization and degradation of

the drug particles.[119] The goal of using surfactant as a carrier system is to upgrade the drug loading and release prospect with long bioavailability, reduce in toxicity and capable to pass through various physiological barriers inside the body.[120]

Surfactant at particular concentration forms micelle that contains hydrophilic head and hydrophobic inner core is capable of solubilization poorly soluble drugs. The incorporation of water insoluble or hydrophobic drug in the interior core takes place through driving force by physical entrapment and chemical covalent attachment[121], at a micelle concentration the Hydrogen bonding between the functional groups in the drug and with the surfactants molecules and the steric factors also leads to the incorporation of drug molecule in the inner core[122], the ability of the drug to self-aggregate in the micelle influences the drug loading capacity[123], which has increased in the drug delivery system as when the nanoparticles are coated with surfactants like (PEG), it reduces phagocytosis effect of macrophages[20,25], which shows a great promise in delivering the drug across several barriers of the body including the blood-brain-barrier(BBB) where the drug is bounded with the surfactant or carriers and targeted to the specific sites and organs which made possible to treat difficult diseases like brain tumor, brain cancer, lungs cancer[21], blocking the multiplication of tumor cells[22], surfactants are used to deliver drug in the intravascular sites like the leukemia cells, lymphocytes and many more.[23] Surfactants loaded with drugs targeted at different target sites forms films and felicitate the distribution of the drug and acts as a reservoir of drug around the specific sites.[24] Micro emulsions which are capable to enhance the solubility of both the hydrophilic and hydrophobic drug molecules[124], acts as a carrier to deliver drugs to different targeted organs in the body.[125] Majority of the drugs which are not able pass through the blood brain barrier due to larger molecular weight[126], this type of carrier system shows a great promise in delivering the drugs across BBB barrier[127], the cancer treatment is based on the principle of direct delivery of the cytotoxic drug at the infected site without damaging the healthy cells[128], which is accomplish by polymeric micelle to target the drug delivery directly at the tumor site.[129] Nanoparticles are also used in the delivery system[130], where wide range of surfactants are available for the production of nanostructure carrier for delivery and controlled release of hydrophilic and hydrophobic drugs.[131]

The therapeutic agents can only show its effect when the drugs are released from the carrier system, the release of the drug is also important because if the release is slow it will not achieve sufficient therapeutic effect whereas if the release is very fast it will not achieve the

targeting effect.[132] The bonding of the drug with the surfactant moiety must be sufficiently stable to retain the chemical integrity until the targeted site is reached where it undergoes proteolytic and acid mediated cleavage to release the drug.[133] Carrier systems which are responsive to the sudden change in the pH, temperature, concentration gradient and the enzymatic activity influences the drug release from the structural moiety.[134] The rate through which the drug will be released depends on the nature of the linkage between the drugs with the surfactant molecule, diffusion from hydrophobic core, stability and solubilization helps in achieving the controlled and sustained release of drugs for over a long period of time inside the body[135], by blending the drug with the membrane.[136] Nanoparticles are also used in the delivery system[137], where wide range of surfactants is available for the production of nanostructure carrier for delivery and controlled release of drugs.[138] Nanoparticles which are chemically stable, biocompatible, nonimmunogenic in nature also acts as a carrier for the delivery of both hydrophilic and lipophilic drug molecules that are incorporated in the aqueous core and the bilayer membranes of the particles that retards drug degradation and enables in achieving the delivery of drug at the target site.[118] Moreover, surfactant plays an important role in protecting the drugs when administered through nanoparticulate carriers, surfactant forms a layer of protective coat over the nanoparticles to increase longitivity, stability of nanoparticles, and felicitates to achieve the targeting effect[31] and also increases the size of nanoparticles.[32] Surfactants having large surface area helped to administered the microparticles or nanoparticles loaded with antigens which showed greater immune response than the conventional system.[33,34]

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