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STUDY OF PHARMACEUTICAL DRUGS ENCAPSULATION WITHIN SURFACTANT MICELLES BY MOLECULAR COMPUTATIONS

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ABSTRACT:
The surfactant micellar structures possess an unique ability to entrap hydrophobic molecules in their interior. The entrapment occurs due to the favorable interactions of hydrophobic molecules with the hydrophobic core of the micelle. Such ability of surfactant micelles make them potentially useful in pharmaceutical and biotechnology applications. Here, we have utilized computational molecular simulations to understand the binding capacity of a sodium dodecyl sulfate surfactant micelle for capturing pharmaceutical drugs such as aspirin. We have observed that the empty micelle capture aspirin molecules from the surrounding water molecules due to the hydrophobic forces between the micelle and aspirin molecules.
KEYWORDS: surfactant micelles, pharmaceutical drugs encapsulation, molecular investigation

INTRODUCTION:

The surfactant molecules are amphiphilic in nature, means they contain both the polar and non-polar groups in their head and tail structure respectively. The surfactant molecules possess two crucial features, which make them outstanding for their application in many significant areas such as petroleum recovery and processing, medical and healthcare, personal care products, cleaning agents, etc. [1, 3, 4] The first important feature is called as interface, which is the boundary formed between two different phases of matter. When surfactants are adsorbed at the interface, they show the significant reduction in surface tension. The addition of even a minute amount of surfactant changes the interfacial free energy of the system significantly [5].

The second important feature of the surfactants is self-assembly process [5, 7]. The individual surfactant molecules play a major role in several applications, although certain important applications are only possible by forming colloidal clusters called 'micelle' (Figure 1) [3, 6]. When the sufficient amount of surfactants are added into solvent, the formation of ordered micellar assembly takes place as a result of local molecular interactions between the individual surfactant molecules, which is termed as self-assembly. The micellar formation occurs mainly due to the non-covalent interactions between the surfactants without the help of any external force [8]. Such assembly formation takes place only when surfactant concentration take over the the critical micelle concentration (CMC) [2, 9]. When surfactant concentration reaches above the CMC, the hydrophobic surfactant chains join together to form an interior core, which is surrounded by hydrophilic groups present in contact with the aqueous solution [10]. In an organic solvent, the same surfactants form a reverse micelle, where the hydrophilic core gets formed [11, 12].

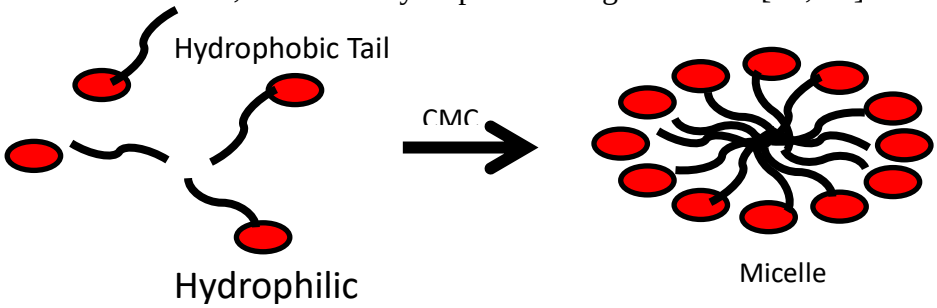

Figure 1. Surfactants micelle formation in aqueous solution at critical micelle concentration from individual surfactants molecules, whose hydrophobic tails are shown in black color and hydrophilic heads are shown in red color.

As micelle possesses a well-defined nano-sized compartment inside, they are considered as an important drug delivery vehicle and a molecular transporter [13]. The non-polar oil-like core of the micelle can easily entrap pharmaceutical drug molecules inside. Micelles formed using surfactants have extremely high solubility considering the poorly soluble pharmaceutical drugs trapped within them [14, 15]. Such drug molecules can be delivered at the targeted systems within the body that can have several important advantages. Firstly, the drug molecules will not be degraded due to the protective encapsulating corona of the micelle [14]. This will help to maintain the desired biological activity of the drugs that is needed to carry out its appropriate function within the body. Secondly, the drugs will not be lost or reach to the undesired regions within the body, which will greatly help to reduce their unwanted side effects [14].

The self-assembled surfactant micelles are good substitute for lamellar and micro emulsion based drug delivery vehicles [15].The use of surfactants micelles extends the biomedical applications because of their solubility and targeted drug delivery [14,18,20,21]. Many drug delivery objects are crashed before they reach to targeted area or they reached in very small quantity; most of the drugs absorb in lungs, kidneys, plasma and other body parts unneccerely and harm them. These problems happens with the passive drug delivery systems because it is not working on the focused body parts directly in treatments of cancers like chemotherapy but also it acts on other good cells and damages healthy tissues. The ideal drug delivery vehicle should have some qualities like acting on infected cell, should not damage good tissues with unhealthy one, run for long residence time in blood stream, and should be biodegradable [16].

Maintaining the stability of micelle is an important aspect in drug delivery. While injecting micelles as a drug delivery vehicle; they go through lot of environmental changes throughout the surroundings such as disclosure of pH, salts, different cells and vesicles in the body. The micelle should be intact in structure when used in drug formulation [17]. For the micelle, two types of stabilities are important; the first one is the thermodynamic stability and second one is the kinetic stability. The equilibrium in the system is decided by thermodynamic stability [10, 17]. The kinetic stability decides the changes in the micellar system with respect to time [19]. It is important to stay micelle safe before reaching the targeted area. The different factors affect the stability of micelles are Critical micelle concentration (CMC), the polarity and non-polarity in surfactants, the strength of non-covalent interactions between the drugs, polymer and solvent.

The hydrophobicity of polymers is also the important factor which affects the values of critical micelle concentration. The length of hydrophobic block can be increased because of hydrophobicity of polymer. The hydrophilicity of copolymers also increased the values of critical micelles concentration. The various kinds of interactions are there between polymers such as ionic forces or hydrophobic and electrostatic interaction, stereocomplexation, hydrogen bonding. These interactions play very important role in mutual conversion between micelles and free polymer chains and are important for the stability of polymeric micelles during their application pharmaceutical drug delivery.

COMPUTATIONAL PROCEDURE:

GROMACS (GROningen Machine for Chemical Simulations) molecular simulation package is used to carry out molecular dynamics simulations [22]. GROMACS is a multipurpose computational chemistry package that can be used to analyze a wide range of molecular systems, especially for analyzing the physical behavior of the systems under consideration [24]. The initial input systems needed before running actual molecular dynamics simulations are built using AmberTools suite [25]. AmberTools package (antechamber) is utilized to apply generalized amber force field parameters and partial charges to surfactants and pharmaceutical drug molecules [26]. TIP3P water model is be used to treat explicit water conditions. Packmol package is utilized to combine all the molecules initially and to further form a pre-arranged micellar structure [23]. Initially, energy minimization is performed on the entire system, which is further equilibrated. In the end, the complete molecular dynamics final runs were carried out at constant temperature and pressure (NPT) conditions for a nanosecond time period. The simulations temperature and pressure are maintained at 300K and 1 bar respectively. Anderson thermostat and Berendsen barostat are respectively utilized for maintaining the constant temperature and pressure of the simulated system. The cut-off distances for the evaluation of expensive non-covalent interactions are applied appropriately.

RESULTS AND DISCUSSION:

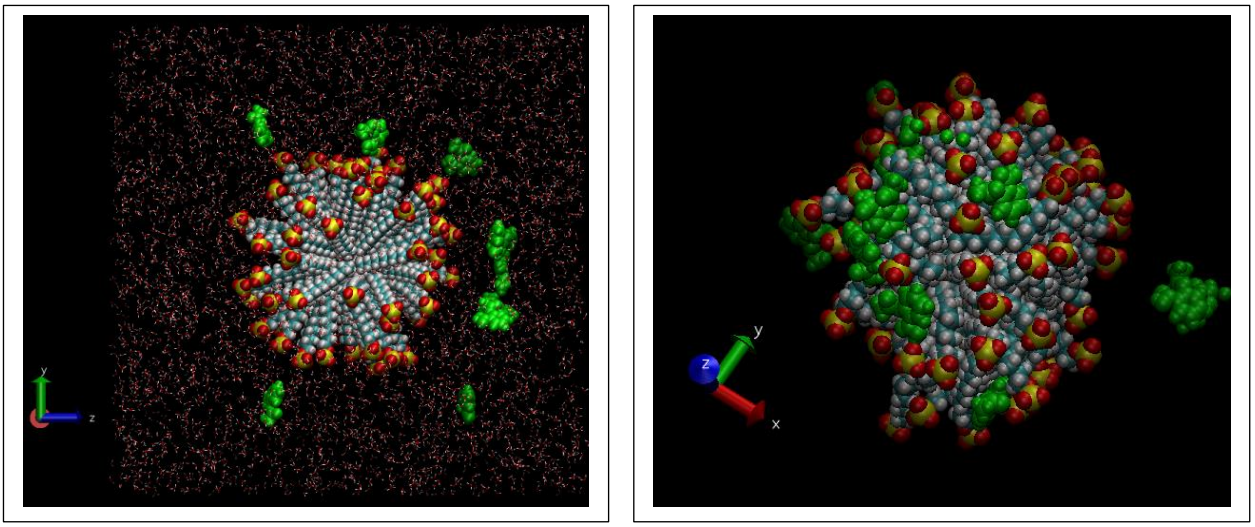

Figure 2(a). Initial step of MD simulation Figure 2(b). Final step of MD simulation

Here, we have utilized molecular dynamics simulations to understand the binding capacity of a sodium dodecyl sulfate surfactant micelle for capturing pharmaceutical drugs such as aspirin. To perform the simulations, initially we built a sodium dodecyl sulfate micelle with the help of packmol software, which consists of 60 surfactant molecules. The simulation system consisted of a sodium dodecyl sulfate micelle and 10 aspirin molecules solvated in 5000 water molecules. The hydrocarbon tails of surfactants are indicated by blue/white color and the hydrophilic heads are indicated by red/yellow color. The water molecules are indicated by small red/white lines and the aspirin molecules are indicated by green color (Figure 2(a)). To check the loading capacity of surfactants micelle we have added the aspirin molecules to the system and ran the simulation for the period of 1 nanosecond (ns). After 1 ns time period, we found favorable encapsulation of aspirin molecules by micelle. For clarity in vision we hide the water molecules in figure 2(b). We can clearly see that out of 10 aspirin molecules, 6 got permanently entrapped inside the SDS micelle due to the hydrophobic effect. It can be concluded that as the aspirin molecules are non-polar and water molecules are polar in nature, the aspirin molecules hide themselves away from water and get captured inside the hydrophobic interior of the micelle. We can still observe the remaining aspirin molecules staying out of the micelle in figure 2(b). If we will increase the running time of simulation, possibly more aspirin molecules will get entrapped inside the micelle.

CONCLUSIONS:

In this work, we have investigated the pharmaceutical drug loading capacity of the sodium dodecyl sulfate micelle using molecular dynamics simulations. In around 1 nanosecond simulation time period, the micelle has permanently entrapped 6 out of 10 aspirin molecules solvated in 5000 water molecules. Here, the aspirin molecules avoided the contact with the aqueous solution due to their hydrophobic nature. As the micellar core is also hydrophobic, aspirin molecules got favorably captured inside the core of the micelle. Our results demonstrate that the surfactant micelles are highly capable of entrapping non-polar drugs inside and show their potential to be useful in the pharmaceutical industry as drug delivery vehicles.

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