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REVIEW

Effects of surfactants on antibacterial drugs – A brief review

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Abstract

More than 70% of new discovered/invented drugs are ones with either poor solubility, gastrointestinal absorption or both. These are the crucial issues that can affect the bioavailability of the drugs. Therefore, improving solubility of poor-soluble drugs is very important. One of the methods to solubilize them in biological fluids is using surfactants. Surfactants are an amphiphilic organic compound containing hydrophilic and lipophilic parts that allow it to reduce the surface tension between two opposite polar phases. Several popular methods used to determine critical micelle concentration which includes surface tension, conductivity and UV-vis spectroscopy. These surfactants play a number of roles in antibacterial compound synthesis including size reduction agent, stabilizer, solubilizer and drug-carrier. This review will also critically discuss on the roles of surfactants in antibacterial compound synthesis/production and their effects on the antibacterial activity of the drugs.

Keywords: Surfactants, pharmacological activity, critical micelle concentration (CMC)

INTRODUCTION

Surfactants, or surface active agents, are amphipathic organic compounds containing both hydrophilic head and lipophilic tail in the same molecule (Sekhon, 2013). The hydrophilic head interacts with water or polar molecules. Meanwhile, the hydrophobic tail which is made up of a long carbon chain favors hydrophobic interaction. In general, increasing the length of carbon chain or incorporation of branching carbon group in the alkyl group will increase the hydrophobicity of the surfactants. The combination of these two different components, hydrophilic head and hydrophobic tail, allows the surfactants to adsorb at the interface between the opposite phases; gas-liquid, solid-liquid and liquid-liquid (water-oil), thus allowing it to reduce the surface tension at the phase boundary (Muthuprasanna et al., 2009). The arrangement of surfactant molecules at water-air interface is shown in **Figure 1**. Novel surfactants such as biosurfactant, gemini (dimeric surfactant) and bolaamphiphile (surfactant with two hydrophilic head interconnected with hydrophobic chain) have been identified/developed to enhance the properties of the surfactants (Olorunsola and Adedokun, 2014; Fariya et al., 2015).

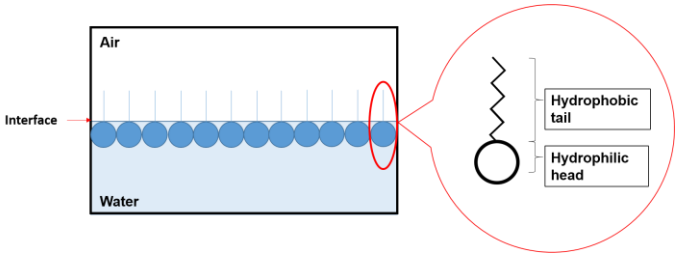

Fig.1: Molecular structure of surfactant and its arrangement at water-air interface.

The surfactants can act as an emulsifier, decontaminator, foaming, wetting, solubilizer and dispersion agents or stabilizers, depending on their polarity toward water (Olorunsola and Adedokun, 2014). They are indicated by hydrophilic-lipophilic balance values (HLB) and the values are usually in the range of 1-20, where the lower values prefer hydrophobic solvent while the higher values are more hydrophilic. These applications of surfactants are very important in almost every sector of modern industry including household/laundry detergents, pharmaceutical, biomedical, cosmetics and food applications (Khan and Shah, 2007). About 54% output of the total surfactants is utilized in household/laundry detergents application (Bhadoriya et al. 2013). For pharmaceutical applications specifically, the uses of the surfactant increase further as self-assembly vehicles for oral and transdermal drug delivery, as a plasticizer in semi–solid delivery systems and as agents to improve drug absorption and penetration (Sekhon, 2013).

Besides that, surfactants also have been used as antibacterial agent, for example, the ionic surfactants which have biocide property that can inhibit the growth of microbes. This property has been exploited in the cosmetic industry by making deodorant and antiperspirant (Flanagan and Singh, 2006). Masui et al. (2013) have patented the formulation of deodorant using antibacterial surfactants which include benzalkonium chloride (cationic surfactant) and N-lauryl β-aminopropionic acid (zwitterionic surfactant). Urgell and Seguer (2003) have also used cationic surfactant as antimicrobial enhancer in deodorant and oral care.

Also, surfactants have been used as an excipient for enhanced drug formulations which includes antibacterial drug. This antibacterial drug, also known as antibiotics, are bioactive compounds which exhibit ability to kill or inhibit the growth of bacteria. These drugs can be either found from natural sources or manufactured synthetically. High modification or variation of synthetic drug has led to decreasing use of natural antibiotics.

Solubility, dissolution rate and gastrointestinal permeability are crucial factors that control the rate and extent of drug absorption and its bioavailability (Khadka et al., 2014). Examples of poorly soluble compounds are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone (Savjani et al., 2012). Thus, these critical issues need to be solved immediately in order to enhance the bioavailability of the active compounds. According to the report by Khadka et al. (2014), almost 70% NCEs (new chemical

entities) developed or discovered for pharmaceutical applications have poor solubility in water. The approaches used to maintain high bioavailability of poor soluble drugs in aqueous solution include conventional method of particle size reduction and newer methods such as solid self-emulsifying drug delivery system (SEDDS) and polymeric micelles. Organic solvent can also be used as the medium for drug solubilization but it can bring side-effects in both short- and long-term usage.

This review will critically discuss the applications of surfactants on natural antibacterial drug and evaluate its effects on the solubility and bioavailability of natural products in the presence of surfactants.

CLASSIFICATION OF SURFACTANTS AND ITS ANTIBACTERIAL ACTIVITY

Surfactants can be classified into four groups according to charge of the hydrophilic head; anionic, cationic, zwitterion, and nonionic. Anionic and cationic surfactants are negatively and positively charged, respectively. Zwitterionic surfactants can either be negatively or positively charged based on the solution pH, while nonionic surfactants are neutrally charged.

Anionic surfactants

Anionic surfactants bear negatively-charged groups present at its hydrophilic head when it is in solution. The charged group can be carboxylate, sulfate, sulfonate, and phosphate ester. It is very effective in solubilizing proteins as it disrupts non-covalent bonds within and between proteins, thus denatures them (Johnson, 2013). These surfactants have moderate antibacterial activity against gram-positive bacteria, but none against gram-negative bacteria. Antibacterial activity of anionic surfactants was enhanced in the presence of low concentration of divalent cations against gram-positive bacteria (*Staphylococcus aureus*) and no effect on gram-negative bacteria (*Escherichia coli*), while another research reported that in combination with Lanthanum (III) chloride ($LaCl_3$), the antibacterial activity for both pathogens increase and its efficacy is comparable to cationic surfactants (Kastner, 1992).

Cationic surfactants

Cationic surfactants are molecules that are positively charged on its hydrophilic head. Among the classical cationic surfactants, quaternary ammonium compounds (QAC) are the most useful antiseptics and disinfectants. They have antibacterial activity against a wide range of pathogenic bacteria both gram-negative and gram-positive bacteria. Zhou et al. (2016) have reported that the antibacterial activity of the surfactant increases with the degree of oligomerization. The insight mechanism of antibacterial activity of cationic surfactant towards *E. coli* is divided into two phases. Firstly, the cationic head disrupts the integrity of the negatively charged outer membrane by electrostatic interaction. Then, the hydrophobic interaction between the hydrocarbon chains of the surfactant with the hydrophobic part of the inner membrane causes membrane disintegration, leading to the cytoplast leakage (Zhou et al., 2016). They are also effective as antifungal agents as the surfactants change the cell surface charge from negative to positive rather than bacterial lysis to cause cell death (Viera and Carmona-Ribeiro, 2006). So, they are mostly used as disinfectants and preservatives.

Amphoteric (zwitterion) surfactants

These surfactants have both positive and negative charge as its hydrophilic head. The positive charge is usually ammonium while the negative charge can be carboxylate, sulfate, sulfonate or phosphate. The presence of both anionic and cationic groups in the same molecule of surfactant allow it to be anionic, cationic, or non-ionic depending on the pH of the solution. The antibacterial activity of the zwitterion surfactants is lower than cationic surfactants. However, it offers a milder effect as compared to the other ionic surfactants due to its nonionic characteristics exhibited at the isoelectric point. Arvanitidou and Suriano (2004) have reported that amphoteric surfactants such as betaines, lowered and mitigated the irritability of the ionic surfactants and provide good foaming property for the formulation of antibacterial liquid dish cleaning formulation.

Nonionic surfactants

The nonionic surfactants are surfactants that have uncharged hydrophilic head. They can be classified as polyol esters (includes glycol, glycerol esters and sorbitan derivatives), polyoxyethylene esters, poloxamers. These nonionic surfactants are the most widely used type of surfactant compared to the ionic surfactants, while the most commonly used nonionic surfactants are ethers of fatty alcohols such as ethoxylated derivatives of sorbitan (referred as Tweens) (Sekhon, 2013). Nonionic surfactants have higher solubility/wetting properties than their corresponding ionic surfactants of the same alkyl chain length. This is due to the ability of both hydrophilic head and hydrophobic tail to adhere onto the hydrophobic surface.

Nonionic surfactants do not exert any antibacterial activity. Triton X-100 has no effect on the *S. aureus* and MRSA viability (Lee et al., 2015). Komatsuzawa et al. (1994) reported that this surfactant does not affect the bacteriolytic enzyme profile or the susceptibility of the bacterial cell wall to the bacteriolytic enzyme. It also did not promote binding of oxacillin to the penicillin-binding protein (PBP) 2A. Polysorbate 80 (Tween 80) was reported to possess antimicrobial activity against *Helicobacter pylori* (Figura et al., 2012) but has none against *Pseudomonas aeruginosa* and *E. coli* (Sabah et al., 2010; Rose et al., 1966).

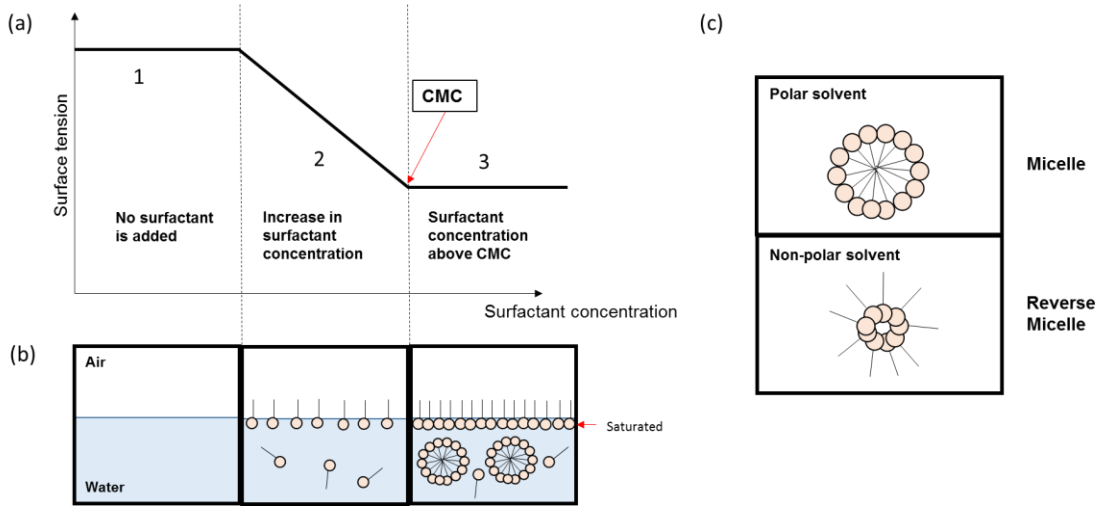

Figure 2: Micelle formation. (a) formation of micelle explained by the change in surface tension behavior as a function of surfactant concentration (b) the chronological order of micelle formation (c) micelle and reverse micelle structure in polar and non-polar solvent system, respectively.

CRITICAL MICELLE CONCENTRATION (CMC)

Critical micelle concentration (CMC) plays a significant role in many product formulations in various industries especially in formulating detergents. Micelle can be formed spontaneously in bulk liquid system when a surface between two phases is overridden with surfactant monomers.

Surface tension or interfacial tension (IFT) can be annotated as force per unit of length (mN/m). It is a result of unbalanced attractive forces between molecules at the surface, which cause surface energy and surface tension. For a system composed of two immiscible phases, the IFT is dependent on the attractive forces between the molecules in each liquid. The addition of surfactants greatly decreases the IFT as shown in **Figure 2 (a)**. When the surfactant molecules adsorb at the interface, they replace some of the water molecules at the interface. As the resulting surfactant-water interaction is weaker than the water-water molecule interaction, contraction force decreases, thus lowering the IFT.

When the interface is saturated/fully occupied with surfactant monomers, the surfactant monomers start to aggregate and form micelles in the bulk solution. This concentration is known as the critical micelle concentration (CMC). The formation of micelles from aggregation of surfactants is as illustrated in Figure 2 (b). The formation of micelles is due to mechanism of surfactants to reduce the exposure of their hydrophobic tail to the aqueous solution. When the CMC is reached, the concentration of surfactant remains at an approximately constant level, meaning that further addition of surfactant molecules will primarily entail increased formation of micelles, thus, there is no further effect of lowering the IFT.

Micelles have two forms depending on the solvent which can be micelles or reverse micelles. When polar solvent acts as the bulk liquid system, the surfactant monomers aggregate with the hydrophilic head interact with water molecule while the hydrophobic tails tend to be buried inside. On the other hand, if the solvent is nonpolar, reverse micelle forms as the hydrophilic head aggregated together while leaving the hydrophobic tails on the surface to interact with the organic solvent. These structures are demonstrated in Figure 2 (c).

The CMC can be affected by several factors which are:

1. Nature of hydrophilic and hydrophobic group

A general rule of thumb is that the CMC decreases by a factor of 2 per methylene group that is added to the tail for the ionic surfactants, and even stronger, by a factor of 3 for nonionic surfactants (Tadros, 2005). Increasing the alkyl chain length of the hydrophobic tail will strongly decrease the CMC. However, as the straight alkyl chain exceeds 16 carbons, the CMC no longer decrease rapidly and when the carbon atom exceeds 18, it may remain unchanged due to coiling of chain in water (Rosen and Kunjappu, 2012). Meanwhile, increase in hydrophilic character of the surfactant increases the CMC. Mahmood and Al-Koofee (2013) has reported using Tween series as the model surfactant where the increasing number of oxyethylene group on the hydrophilic part of the surfactant did increase the CMC. Meanwhile, increase in the length of carbon chain on the hydrophobic part lowered the CMC of the surfactant.

2. Addition of salt/electrolyte

Addition of salt/electrolyte decreases the CMC of the ionic surfactants. The electrolyte structure influences the CMC, where the synergistic hydrophobic interactions between the non-polar hydrocarbon chains of surfactant and alkyl chains of these salts favor the surfactant micellization. Thus, the increase in the length of alkyl chain of these salts strengthens these favorable interactions (Chauhan et al., 2014). The decrease in CMC values is noticeably higher when electrostatic interactions between two opposite charges of head group of surfactants and the salt as compared to electrostatic charges of the same charges.

3. Temperature

Increase in temperature reduces the CMC and surface tension until a certain temperature. After that, the CMC increases again with a further rise in temperature. Thus, the pattern displays a typical U-shaped behavior (Dai et al., 2014). As the temperature increases, some of the existing hydrogen bonds between surfactant and water would rupture due to thermal fluctuation, thus making the surfactant molecules more hydrophobic and decreasing the surface tension. Therefore, the dehydration effect would be somewhat more pronounced for longer chain length surfactants since the surfactant molecule binds considerably more water molecules (Mohajeri and Noudeh, 2011).

4. Type of counterion

The valency of the counterion in ionic surfactants has a significant effect on the CMC as increasing the valency of the counterion from 1 to 2 reduces the CMC by roughly a factor of 4 (Tadros, 2005). Micellar size increases for cationic surfactants follows this order, $Cl^- < Br^- < I^-$, while for anionic surfactants, they follow the alkaline metal group order which is $Na^+ < K^+ < Cs^+$. Ionic surfactants with organic counterions (e.g. maleates) have lower CMCs and higher aggregation numbers than those with inorganic counterions.

METHODS FOR DETERMINING CRITICAL MICELLE CONCENTRATION (CMC)

Determining the CMC of the surfactants is very crucial as it is the important indicator where it can effectively emulsify, solubilize and disperse. Increase in surfactant concentration leads to a steady increase/decrease in the physicochemical properties of the solution including surface tension, electrical conductivity, light scattering, osmotic pressure or density. But as the surfactant concentration exceeds the CMC, the trend comes to an abrupt change where the graph becomes almost constant or less change, as shown in **Figure 3** (Schramm et al., 2003; Khan and Shah, 2007). Thus, by exploiting this change in physicochemical properties, few methods to determine the CMC are discussed here.

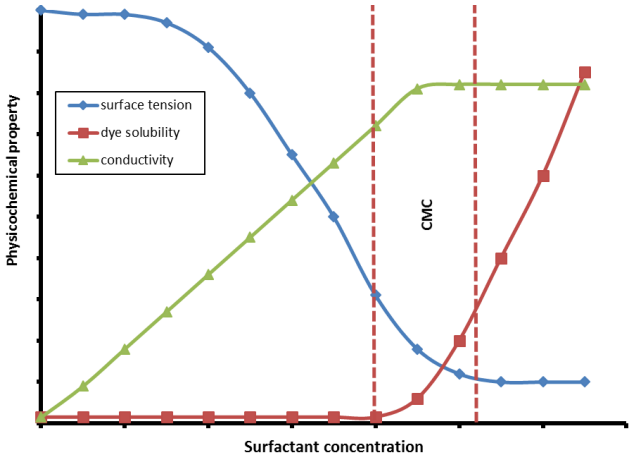

Figure 3: Determination of CMC based on physicochemical properties (surface tension, dye solubility, and conductivity) change against the concentration of surfactant (derived from Chakraborty et al., 2011; Tehrani-Bagha and Holmberg, 2013).

Surface tension

Surface tension measurement using tensiometer is one of the standard ways to determine the CMC, and can be carried out using several techniques including Du Noüy-Padday method, Du Noüy Ring Tensiometer, Wilhelmy Plate Tensiometer, and Bubble pressure Tensiometer (Olorunsola and Adedokun, 2014). The graph is plotted as surface tension against surfactant concentration and the CMC is determined when the surface tension becomes almost constant. The decreasing trend of the surface tension is attributed to the preferential adsorption of surfactant molecules. The surfactant monomers disrupt the degree of intermolecular hydrogen bonding among water molecules at the air/solution interphase. Thus, this lowers the interfacial tension. Beyond the complete interfacial saturation or CMC, however, the surfactants assemble to form micelles without perturbing the interfacial

rheology (Chakraborty et al., 2011). This method is applicable for all types of surfactant. However, this method is very sensitive to impurities in the solution.

Conductivity measurement

This method is effective in determining the CMC when using ionic surfactants rather than non-ionic surfactants due to its charge at the hydrophilic group. At low concentration where the surfactant is in monomer state, it behaves like strong electrolyte and dissociates completely in water. The ions contribute to the electrical transport of the solution as measured by the specific conductance (κ) or equivalent conductance (A). In the monomeric region, κ increases sharply with increasing concentration of surfactant. At and above micellization point, a certain fraction of the counterions condenses on the micellar interface inside the Stern layer as a result of Coloumbic (electrostatic) attraction. On counterion condensation, the net number of charges carriers reduce causing decrease in the rate of increment in κ with increasing surfactant concentration.

Dye solubilization spectroscopy

Dye solubilization is one of the methods to determine the CMC of surfactant by utilizing the insoluble property of some dyes in water or organic solvent. Below the CMC, the dye cannot solubilize in water while at or higher CMC, the dye starts to solubilize in water. (Tehrani-Bagha and Holmberg, 2013; Sobicch, 1992).

Prior to the CMC test, a calibration curve of the dye in a mixture of water and suitable solvent needs to be carried out across various concentrations of dye. Based on the plotted graph of dye, maximum absorbance against the concentration, dye molar extinction coefficient (ε) can be identified using the Beer-Lambert law. Next, the surfactant concentrations are varied from below to higher than CMC before added with an excess of finely powdered form of the dye. The suspension will later be stirred until it reaches its equilibrium at around 24-48 hours. The precipitate is removed using centrifugation or filtration and the absorption of dye solution is checked using UV-vis spectrophotometer and calculated for its concentration based on the determined ε.

The molar solubilization capacity or solubilization power (SP) of a surfactant is moles of solubilized dye per mole of micellized surfactant, can be referred to the equation below (Tehrani-Bagha and Holmberg, 2013).

$$SP = \frac{S_{total} - S_{wat}}{C_{surf} - CMC}$$

where:

S_{total} = molar solubility of the dye in aqueous system
S_{wat} = molar solubility of the dye in water
C_{surf} = molar concentration of the surfactant

ROLES OF SURFACTANT IN ANTIBACTERIAL COMPOUND FORMULATION

This section will specifically discuss on the roles of surfactants in antibacterial drug formulation that include being a particle size reducing agent, solubilizer, stabilizers, and carrier for drug delivery.

Particle size reducing agent

Nanosizing drug compound has gained much more interest due to its drastic changes in its physicochemical properties including crystallinity, solubility and bioactivity. One of the important factors in producing nanoparticles such as nanoemulsion, nanosuspension and nanoencapsulation is the selection of the surfactant. Li et al. (2016) have observed that Tween 80 gave smaller diameters of waxy corn starch nanoparticles as compared to sodium dodecyl sulfate and Span 80. The size of nanoparticles was bigger when added with Span 80 because of the weak adsorption of Span 80 onto the surface of nanoparticles due to its low HLB value. The same charges for both SDS and nanoparticles caused an electrostatic repulsion that made the size of nanoparticles bigger. Reducing the size of the poorly soluble active compound into a nanosize has increased its dissolution rate as the surface area in contact with solvent becomes higher (Khadka et al., 2014).

Solubilizer

One of the many important properties of the micelles that has particular significance in pharmaceutical industry is ability to act as solubilizer to increase the solubility of sparingly soluble bioactive compounds in water. The surfactants at CMC or above cause it to self-assembly to form micelle that allows the active compound or excipient to completely solubilize. The trend of increasing solubility as a function of increasing surfactant concentration above CMC indicates that the solubility is related to micellization. Tallury et al. (2007) have reported that the release rate of nystatin increased with the increasing proportion of surfactant to nystatin. They have also speculated that increasing amounts of surfactants in the copolymer system, increases the porosity facilitating the enhanced diffusion of drug molecules through the channels present in the matrix, leading to an increase in the rate of drug release.

Stabilizer agent

Reducing the particle size gives rise to a stability issue where the coalescence of the same phases of solid will likely be the issue. Coalescence is a phenomenon that occurs when substances prefer to interact with each other of the same kind in the solvent instead of interacting with the molecules of solvent to have lower kinetic energy, which means a more stable structure. The surfactant plays the role of stabilizer in order to maintain the active compound's micro-/nano- size. When the chemical/droplet is surrounded/trapped by ionic charge surfactant, the droplet charge can change to be either negatively or positively charged droplets. The same charges repel each other, thus slowing down the rate of coalescence (known as electrostatic stabilization) (Muthuprasanna et al., 2009). Stabilizing property is very important especially for pharmaceutical application. Instability of the insoluble active compound can lead to loss of bioavailability. Baicalein is a flavonoid that has potent antioxidant, anti-tumor, and anti-cancer synthesized into nanocrystal using homogenization and stabilized with the aid of a surfactant (Zhang et al., 2011).

Carrier for drug delivery

The use of surfactant that has specific target has allowed the drugs to be delivered to its specific target site. This method has minimized drug degradation and loss, increased drug bioavailability, fraction of drug accumulated in the required site and prevented side effect due to active compound attacking or harming unnecessary human cells (Torchilin, 2001). Scheeran et al. (2016) added anionic surfactant 77KS, as one of the excipients for doxorucibin-nanoparticle that gives its pH dependency behavior**.** The pKa of the carboxylic group of lysine increases from 2.2 to 5.4 which is about the same pH as the enhanced membrane lysis as it is included in the surfactant molecule. This increase could lead to changes in the protonation state of the surfactants in the late endosome pH range, and thus further increase binding to the membrane and enhance the hemolytic activity (Nogueira et al., 2011).

EFFECT OF SURFACTANTS ON THE ANTIBACTERIAL ACTIVITY OF ANTIBACTERIAL DRUG

Surfactants cannot be considered as inert excipients due to their capabilities of increasing, reducing or exerting no effect on the transfer of the materials to the target site (Lee et al., 2015). Thus, this section will evaluate the effectiveness of surfactant towards antimicrobial activity of antibacterial drugs.

Introduction of surfactants have a good effect as to enhance the antibacterial activity of bioactive compounds. Al-Thamir et al. (2010) have reported an increase of antibacterial effectiveness in a series of antibiotics including cloxacillin, cephalothin, cefotaxime, meropenem, and gentamicin against *P. aeruginosa* isolates at 5-6% concentration of Tween 80. But the bacteria were resistant against these antibiotics except meropenem at lower concentration (Al-Thamir et al., 2010). Enhancement of the antibacterial activity was attributed to the effect of Tween 80 on the membrane integrity of the bacteria that allowed better uptake of antibiotic molecules.

Besides that, Figura et al. (2012) have explored the antimicrobial activity of Tween 80 and its synergistic effect with other antibiotics

against *Helicobacter pylori* which is a microaerophilic gram-negative bacterium that can cause chronic gastritis and gastric ulcers. They identified that minimum bactericidal concentration (MBC) of Tween 80 ranged between 2.6 μg/mL to 32 μg/mL and it has a synergistic effect in conjunction with metronidazole and clarithromycin by decreasing their MBC by 4-fold and 20-1000 times, respectively. Hence, Tween 80 has shown to have antimicrobial activity against *H. pylori* but not with *P. aeruginosa*, and it enhances the antibacterial activity of the antibiotics.

For poor soluble active compounds, Lee et al. (2015) have reported an improvement on antibacterial activity of shikonin, a highly liposoluble naphthoquinone pigment isolated from the roots of *L. erythororhizon*, against MRSA when added with membrane-binding agents; Tris and Triton X-100. MRSA growth has decreased by 34% and 67%, respectively, as compared to the bacterial cultures treated with shikonin only.

The use of the curcumin has been restricted due to its low water solubility, poor oral bioavailability and rapid hydrolytic degradation in alkaline medium solution. The introduction of a mixed micellar system of Brij 96 and dodecylethyldimethylammonium bromide (DDAB) has improved the scavenging ability of curcumin by 2 to 3 times while providing better stability against alkaline degradation. Boruah et al. (2012) have reported the interaction between curcumin with chitosan is much higher in the presence of surfactant as the binding constant is ten times greater compared to its value in chitosan only. Combination of surfactants may improve the stability of the active compound and reduce the rate of degradation.

Surfactants also have been reported to have an adverse effect on the bioactive compound by inhibiting its bioavailability. Muthuprasanna et al. (2009) have reported that excess of surfactant above the CMC that is required to form micelles led to the rate of penetration of hexylresorcinol decreases nearly to zero.

Richardson et al. (2013) have reported that chitosan, bio-derived cationic polysaccharides has lost its antibacterial activity when SDS (anionic surfactant) is in excess as the zeta-potential became negative. This was due to the positive charge of the amine group of chitosan being filled with the negatively charged of the sulfate group from SDS. So, SDS neutralized the positive charges of chitosan that is the active site for the antibacterial activity. Besides that, the charges exerted by the compound are not affected when nonionic surfactant is used and the addition of a nonionic surfactant can enhance the colloidal stability of the chitosan. Hence, the physicochemical properties of the active compound also have to be considered as to select the suitable surfactants.

Scheeran et al. (2016) added anionic surfactant 77KS, a surfactant derived from Nα,Nε-dioctanoyl lysine with an inorganic lithium counterion, below its CMC in the nanoparticle formulation of doxorubicin. In its monomer state, the antitumoral activity of doxorubicin-nanoparticles was enhanced and given a pH-responsive behavior. Meanwhile, increase of surfactant concentration above CMC will cause flocculation.

CONCLUSION

Overall, surfactants play a very important role in good dispersion of poor soluble active compound in water. However, report on the loss of bioactivity of the active compound is little or none. In addition, the mechanism on how surfactant affects the antimicrobial activity of active componds or excipients is not well understood. Thus, further research needs to be carried out to identify this mechanism either using experimental, computational or both approaches.

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