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**Surfactant effects on lipid-based vesicles properties: a review**

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**Abstract**:

Designing a surfactant based vesicular system has held researcher interests to address the need for understanding the effect of different surfactant properties on the delivery system. This review mainly focused on analysing what have been carried out in literatures to explain the influence of surfactant properties on the behaviour of the vesicular systems, especially on their size, entrapment efficiency (EE), charge and stability. The surfactants effect on vesicles size is related to many parameters. Apparently, the size of the prepared vesicles decreases by increasing the surfactant concentration, its carbon chain length and number, the hydrophilicity of the surfactant head group, and the hydrophilic- lipophilic balance (HLB) value. However, the competition that could be raised between a surfactant and the lipid could lead to increase the vesicles size. On the other hand, the effect of surfactant on the vesicles entrapment efficiency not only depends on the surfactants properties but also on the encapsulated drug. The encapsulation of a lipophilic drug could be enhanced when surfactant with low HLB value is used while the surfactants with high HLB values enhance the encapsulation of hydrophilic drug. Generally, it was numerously reported that increasing surfactants carbon chain length, and using gel like surfactants or surfactants of high transition temperature (Tc) could lead to improve the entrapment efficiency. While using more liquid form surfactants or the ones that have unsaturated bonds in their carbon chain might increase the lipid membrane permeability of the vesicles and lead to drug leakage and consequently reduce its entrapment. The surfactant concentration have been argued to show several effects. Increasing the concentration sometimes improves the encapsulation efficiency due to increasing the number of formed vesicles, while in contrast other studies showed a reduced drug entrapment due to enhancing membrane permeability. Finally, that surfactant concentration seems to have an influence on the stability of the vesicular systems, it was reported that increasing the concentration could lead to increase the charge which in turn reduce vesicles aggregation and enhance the system stability.

**Keywords**: lipid based vesicles, Surfactant, Liposome, Transfersome, Hydrophilic- lipophilic balance, Entrapment efficiency, Zeta potential, and Stability.

# **Introduction**:

In recent years, the development of better delivery systems for drugs with some undesirable properties has gained much interest. Improving patient compliance is one of the main drivers for research through achieving a good therapeutic profile and reducing unwanted side effects. Substantial attempts have been carried out to alter pharmacokinetic and pharmacodynamics properties such as solubility, permeability, release profile and targeting. They are generally achieved by designing delivery systems such as the particulates, polymeric micro/nano spheres, and vesicular systems (1).Vesicular systems usually consist of amphipathic lipids which are self-assembled in aqueous media to form one or multi bilayers enclosing a hydrophilic core. They are employed as a carrier for both hydrophilic and lipophilic drugs. The hydrophilic drug will be encapsulated in the aqueous core or attached to the polar head of the lipid, whereas the hydrophobic drug will be placed between the bilayer since the lipid tails form a suitable lipophilic environment (1, 2) (Figure 1, A). Vesicular systems have many advantages such as increasing drug stability, efficacy, and targeting. In addition to reducing the toxicity and the exposure of the sensitive tissue to the encapsulated drug. However, they suffer from some disadvantages for instance drug leakage, high production costs, low stability of the system itself and poor encapsulation of hydrophilic drugs (3). Lipid based vesicular systems may be classified depending on many factors such as their constituents, size, and number of bilayers, all of which can affect the final vesicle properties in several ways (3). Table 1 summarises the main vesicular systems that are employed for drug delivery. Some vesicular systems such as transfersomes and niosomes may contain surfactants as well as lipids (table 1) and there are many claims that the presence of surfactants may improve properties such as the encapsulation efficiency and permeability of the vesicular system. However, the consequence of surfactant presence in the vesicle composition may vary as the properties of the surfactant itself changes. The aim of this review is to highlight the numerous studies that have been carried out to date and to summarise our current understanding of how surfactant properties influence the behaviour of vesicle drug delivery systems.

**Table 1** summary of the main lipid based vesicular systems, with their main constituents, and both their advantages and disadvantages.

|  |  |  |  |
| --- | --- | --- | --- |
| **Vesicular system** | **Main constituents** | **Distinctive properties** | **References** |
| **Liposomes**  **(Figure 1, B)** | * Natural or synthetic Phospholipids (neutral or charged). * Cholesterol. | * Sizes vary between 25-2500 nm * Suitable for both hydrophilic, lipophilic, small molecular weight and macromolecular drugs. * Reduced toxicity. * Targeted drug could be achieved.   **Disadvantages**   * Drug leakage. * Expensive. * Low stability. * Low encapsulation of hydrophilic drugs.   **Classified as**:   * Multilamellar vesicles (MLV): Onion structure, multiple bilayers enclosing many hydrophilic compartments. * Large unilamellar vesicles (LUV). * Small unilamellar vesicles (SUV). | (4, 5) |
| **Niosomes** | * Non-ionic surfactant (uncharged single-chain surfactant). * With/or without cholesterol. | * Microscopic lamellar vesicles. * More stable than liposome. * Osmotically active. * Suitable for loading drugs with wide range of solubility. * Relatively less expensive than liposome.   **Disadvantages**   * Aggregation. * Fusion. * Drug leaking. | (6, 7) |
| **Transfersomes /**  **Deformable or Ultra-deformable liposome**  **(figure 1, B)** | * Edge activator (surfactant). * Natural or synthetic Phospholipids (neutral or charged). | * High deformability. * Show very high encapsulation for lipophilic drugs. * More stability.   **Disadvantages**   * Difficulty of loading hydrophobic drug without compromising their deformability. * Expensive to formulate. * Chemically unstable as they are more prone to oxidation. | (8-10) |
| **Ethosomes/ Elastic vesicles** | * Ethanol (20-45%) as permeation enhancer. * Phospholipid. | * Increase cell membrane lipid fluidity due to the presence of ethanol. * Enhanced permeation profile, especially for dermal application. * Low risk profile or toxicity. * Relatively simple to manufacture.   **Disadvantages**   * Poor encapsulation/yield. * Possibility of vesicles disruption. | (11-15) |
| **Pro-vesicular system (Proliposomes/ proniosomes)** | * Water soluble porous carrier (solid particles). * In addition to the same ingredients of the liposome or niosome respectively. | * Mainly to overcome the disadvantages of liposome /niosome. * Free flowing dry form that enhance the stability. | (16) |
| **Other:**  **e.g. Herbosomes/ Sphingosomes/ Genosomes** | * Similar to liposomes, where lipid charge, type, or nature determine the type of the vesicles. | * Improved stability, e.g. herbosomes as they have phytochemical water soluble particles that form stronger bonds with phospholipids in comparison with liposomes. * Provide selective passive targeting, e.g. sphigosmoes as they contains sphingolipid which improves targeting. * Suitable for delivering specific substances such as gene, e.g. genosomes. | (1) |

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# **Surfactants:**

Surfactants, also referred to as surface-active agents or edge activators, are amphipathic molecules composed mainly from two main moieties; the polar hydrophilic part, which is attached to the non-polar hydrophobic or lipophilic part (17, 18). The lipophilic part is usually a straight or branched hydrocarbon chain (tail) consists of eight to eighteen carbon atoms (Figure 1, C and D) (19) . At low concentrations surfactants exist as monomers, and usually in aqueous medium they adsorb on the interfacial surfaces (solution- air interface) and consequently they displace some surface molecules and reduce the intermolecular forces, thus lowering the surface tension (20, 21). However, above a certain concentration (critical micelle concentration (CMC)) they aggregate and form micelles (Figure 1 E and F). The CMC depends on many factors but is mainly related to the nature of the surfactant. Surfactants form micelles due to the hydrophobic effect, and they could adopt several arrangements (22, 23). In aqueous medium, the hydrophilic heads face the aqueous surroundings and the hydrophobic tails directed towed the non-aqueous medium. However, in a non-polar medium, they work similarly but the micelles form in an opposite arrangements where the polar groups face each other and the tails project out towards the non-aqueous medium (Figure 1 E and F) (21).

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| --- |
| A)  Aqueous core  Hydrophilic drug  Lipophilic drug  Amphipathic drug  Bilayer membrane  (Lipid, surfactant)  Surfactant molecule  Lipid molecule  B) |
| ­­  E)  D)  C)  Hydrophilic (polar) head    F)  Hydrophobic (non- polar) tail |

**Figure 1.** A) Surfactant monomer with one tail, B) Surfactant monomer with two hydrocarbon tail, C) Micelle (surfactant assembly) in aqueous medium, D) Micelles in non-aqueous medium, E) comparison between conventional liposome on right half and transfersome (elastic liposome) left side, F) the dispersion of drug molecules within the lipid based vesicles.

## 2.1. Classification

Surfactants may be classified depending on either their molecular weight or their hydrophilic- lipophilic balance (HLB) (24) (Figure 2). Moreover, they are further categorised into several sub-groups based on properties such as the charge of the hydrophilic head group (24).

**Figure 2.** Illustrated diagram of surfactant classification based on molecular weight and hydrophilic lipophilic balance.

## 2.1.1. Classification based on Molecular weight

### A. Low molecular weight surfactants:

There are four main types of low molecular weight surfactants where the classification depends on the nature of the hydrophilic parts. **Anionic surfactants have negatively charged** hydrophilic parts. They are widely used due to their low cost. Generally, they could be carboxylates (CnH2n+1COO –x), sulphates (CnH2n+1 OSO3-X), sulphonates (CnH2n+1 SO3-x), or phosphates (CnH2n+1OPO (OH) O-x) with n= 8-18 (18, 24). **Cationic surfactants have positively charged** hydrophilic parts and often a natural fatty acid. Quaternary ammonium compounds are the most commonly used cationic surfactants such as alkyl dimethyl benzyl ammonium chloride (benzalkonium chloride), which is widely used as a preservative in pharmaceutical formulation or a bactericide (18, 25). **Amphoteric surfactants (zwitterionic)** contain both cationic and anionic groups and their behaviour is dictated by the pH of the medium in which they are dissolved. They act as anionic surfactants in alkaline pH due to their acquisition of a negative charge, while in acidic medium they gain a positive charge and behave like cations. They show good water solubility, improved stability, and better compatibility with other surfactants and within different mediums in comparison with the cationic and anionic surfactants. **Non-ionic surfactants** are characterised by the presence of uncharged hydrophilic groups that do not dissociate in aqueous solution such as alcohol, ether, ester or amide groups. They contain wide range of classes such as alcohol ethoxylate, sorbitan esters ethoxylate, and fatty acid ethoxylates. Additionally, there are multihydroxy products such as glycol esters, glycerol esters, glucosides and sucrose esters (18, 24, 25). Table 2 shows some of the most used non-ionic surfactants.

### B. Polymeric surfactants:

Polymeric surfactants have been developed in the last two decades and can be an assembly of one or several macromolecular structures that have hydrophilic and lipophilic character. They are now commonly used due to their wide application as stabilizers in emulsion and suspension formulation. Several modifications have been carried out on these surfactants to improve their properties and get molecules that are effective in several pH conditions, temperature, and media(18, 24). The number of the hydrophilic and lipophilic groups as well as their distribution along the carbon chain is considered a distinctive property of the polymeric surfactants. The high structural complexity of the polymeric surfactants results in several behavioural differences in comparison with low molecular weight surfactants (26). These polymeric surfactants are usually sub-categorised into two main classes which are polysoaps and macrosurfactants depending on the distribution of the hydrophilic and lipophilic moieties (27).

## 2.1.2. Classification depends on HLB

The hydrophilic-lipophilic balance classification system was first developed by Griffin in the last century and is a scale that represents the percentage of hydrophilic to lipophilic groups in surfactant molecules. HLB is subdivided into several range categories, each representing groups of surfactants with similar behaviour (18, 24). Surfactants with HLB values of 3-6 show more lipophilicity and they tend to form W/O emulsion, and micelles/vesicles that are more soluble in non-aqueous media. While HLB values of 8-18 represent O/W emulsifiers or solubilisers, which are more hydrophilic and water-soluble. However, surfactants with HLB values between 7-9 are considered wetting agents that may exhibit both properties. Sometimes it is possible to use two or more emulsifying agents (surfactants) at once to achieve the desired solubilisation effect. For example, mixing tween 80 (polysorbate) with a HLB value of 15 together with Span 80 (sorbitane monooleate), which has a HLB of 4.3 in different proportions will cover a range of HLB numbers and allow the best composition to be chosen in order to achieve the desired properties (18, 25). Therefore, the optimum use of the HLB value is to enable the selection of the surfactant composition.

**Table 2.** Chemical structures of the most commonly used surfactants.

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| --- | --- |
| Span 80 ([C24H44O6](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C24H44O6&sort=mw&sort_dir=asc)) | Span 60 ([C24H46O6](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C24H46O6&sort=mw&sort_dir=asc)) |
| Span 40 ([C22H42O6](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C22H42O6&sort=mw&sort_dir=asc)) | Span 65 ([C60H114O8](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C60H114O8&sort=mw&sort_dir=asc)) |
| Tween 80 ([C32H60O10](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C32H60O10&sort=mw&sort_dir=asc)) | Tween 60 ([C35H68O10](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C35H68O10&sort=mw&sort_dir=asc)) |
| Tween 20 ([C26H50O10](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C26H50O10&sort=mw&sort_dir=asc)) | Sodium deoxycholate ([C24H39NaO4](https://pubchem.ncbi.nlm.nih.gov/search/#collection=compounds&query_type=mf&query=C24H39NaO4&sort=mw&sort_dir=asc)) |

# **Surfactants in lipid- based vesicles:**

The uses of surfactants in lipid based vesicles has progressed over the last few decades (28). Some studies have focused on using surfactants from one group e.g. studying the non- ionic surfactants in case of niosomes (29), while others have considered the effects of using several surfactants with different characteristics on vesicle properties. Additionally, most studies have aimed to maximise the effect of the chosen surfactant in order to optimise the formation of the lipid vesicles and achieve the desired size, drug loading and physiochemical properties.

## 3.1. Surfactant effects on the size and polydispersity index (PDI):

The presence of surfactants in lipid-based vesicle systems has a noticeable effect on their size. In 2016, Singh et al studied the role of surfactant in the formulation of elastic liposomes for the transdermal delivery of the opioid analgesic tramadol. The effect of several surfactants was investigated such as span 80, tween 80, and sodium deoxycholate and liposome size was reported to be inversely related to surfactant concentration (30). It was suggested that the higher surfactant concentration covered the surfaces of the liposomes and prevented them from aggregation (30, 31). A small polydispersity index was also reported with the higher surfactant concentration and the consistent size distribution was thought to be an important factor in reducing interfacial tension and producing a homogeneous emulsion (32). The same three surfactants were used by Jain et al to prepare transfersomes and no significant differences in vesicle size was expected, as a result of the homogenization method (through polycarbonated membrane) used during the preparation of the formulations (10, 33). However, a reduction in vesicle size was noted when higher surfactant concentrations were used because >15% w/w of the surfactants was thought to form micellar structures rather than vesicles (10). A similar study of the influence of several surfactants on elastic liposome properties was carried out by Barbosa et al. (34). They investigated the incorporation of the non-ionic surfactants that have either one hydrophobic chain (such as octaethylene glycol laurate (PEG8L), polyoxyethylene glycol-4-laurate (PEG4L), and pentaethylene glycol monododecyl ether (C12E5)) or two hydrophobic chains (such as polyoxyethylene glycol-8-dilaurate (PEG8DL), and polyoxyethylene glycol-4-dilaurate (PEG4DL)). The study revealed similar results showing the higher surfactant concentration lead to the formation of smaller vesicles (34). Additionally, the presence of the surfactants with two hydrophobic chains resulted in a more homogeneous PDI in comparison to those with one carbon chain, which could be explained by their better capability to anchor within the lipid bilayer (34-36). However, not only does the number of the hydrophobic chains affect vesicle size, but also the length of the carbon chain of the surfactant. Duangjit et al. studied the effect of carbon chain length and content of the surfactant on meloxicam loaded liposomes (37). The size of the obtained liposomes decreased as the length of carbon chain of the surfactant increased from C4 to C16 (37). This was attributed to the rise of the surfactant hydrophobicity as its carbon chain length increase, which in turn led to improve the solubility of the surfactant molecules within the lipid bilayer (37, 38).

Moreover, a reduction in vesicle size was also reported to be influenced by the hydrophilicity of the head group of the surfactant, which was thought to be due to the shortness of the hydrophobic backbone in comparison to the hydrophilic head group, which was asparagine grafts in that case (37, 39). Similar results were achieved during niosomes loading with a β-carotene as model of lipophilic moiety, with the more hydrophilic surfactant ( higher HLB value) producing smaller vesicles (14). In contrast, the size of elastic transfersomes optimized for the transdermal delivery of pentoxifylline with several surfactants increased as the HLB of the surfactants increased. The surfactants were ranked as they formed larger transfersomes in the following order Span 80 < Span 20 < Tween 21 < Tween 20 (33). Similar ranking of several Spans on the niosomes size were obtained, since the size of the vesicles increased as the HLB progressively increased, Span 20 (HLB= 8.6) showed larger niosomes size, after that the size gradually decreased with Span 40 (HLB= 6.7), Span 60 (4.7) and Span 80 (HLB= 4.3) (40). This could be due the effect of the surface free energy which might decrease as the hydrophobicity increases (41).

Some researchers have investigated the effect of the lipid type on vesicle size. The inclusion of some lipids, for example, an anionic lipid such as dicetylphosphate (DCP) with Span 20- based niosomes reduced vesicle size. The reduction was explained by the increased the curvature of the bilayer caused by the electrostatic repulsion between the ionized head group of both the lipid (DCP) and the surfactant (42).

It has also been suggested that the lipid to surfactant ratio can effect on vesicle size. Using cholesterol at higher concentrations than usually specified was observed to increase niosomes size (43). Parallel results have been obtained by many studies, where the incorporation of cholesterol in niosomes or liposomes at higher concentration than the surfactant lead to increase the vesicle size. The increase in size was ascribed to the competition between cholesterol moieties and surfactant molecules during the arrangement of the lipid bilayer (42-45).

In summary, the inclusion of surfactants within lipid based vesicles has an obvious effect on vesicle size and many factors need to be considered when a surfactant is incorporated into the formulation. Parameters such as surfactant concentration, number of carbon chains, carbon chain length, and the hydrophilicity of the head groups have an inverse effect on vesicle size. While the competition of other moieties with the surfactant molecules during the arrangement of the lipid bilayer clearly showed an increase in lipid vesicle size.

## 3.2 Surfactant effects on entrapment efficiency:

Achieving a good encapsulation efficiency is considered to be the main goal during the developing of any vesicular delivery system. Many researches have tried to incorporate surfactants into lipid- based vesicles in order to improve the encapsulation of both hydrophobic and hydrophilic drugs as well as decreasing the liposomal drug leakage (14, 38, 39). Although many attempts have been carried out to investigate surfactants effects on improving the entrapment efficiency, there is still no definitive proof that specific surfactant properties could lead to certain entrapment. That is because many surfactant properties, such as the type and the concentration, could have an effect on the entrapment efficiency of a certain drug within a certain lipid composition (43). General trends could be observed from a set of surfactant properties on a hydrophilic drug entrapment, but that effect could be totally different when a hydrophobic drug is encapsulated.

### 3.2.1. Surfactant concentration

Many researchers have studied the effect of surfactant concentration on vesicle entrapment efficiency and it has been commonly reported that increased surfactant concentration decreases the entrapment efficiency. This effect has been explained by the possible formation of micelles when the surfactant concentration in the bilayer exceeds a critical lamellar/micellar transition temperature (10, 30, 31, 46). Furthermore, the permeability of the vesicles membrane might increase due to the arrangement of surfactant molecules within the lipid bilayer structure, which could introduce pores within the membrane and increase its fluidity. Overall this will prompt entrapped drug leakage (30, 47, 48). Additionally, it is thought that the optimum amount of surfactant depends on the packing density of the phospholipid used and the surfactant-phospholipid interaction. When the surfactant concentration increases and it is known to have a high tendency to interact with the lipid, this leads to a reduction in entrapment due to competition on the loading within the bilayer (44, 47, 49). For example, transfersomes were prepared and loaded with dexamethasone as a model lipophilic drug to evaluate sodium deoxycholate (SDC), Tween 80 and Span 80 as edge activators at five different lipid-surfactant ratios (95:5, 90:10, 85:15, 80:20, 75:25) (10). The study revealed that encapsulation efficiency decreased as the concentration of the surfactant increased. Transfersomes that were prepared with SDC showed the lowest encapsulation due to the competition between SDC and dexamethasone due to their similar steroidal structure (10). Similarly, Patel et al. studied the effect of surfactant concentration on the entrapment of a lipophilic drug (curcumin) in lipid based vesicles and demonstrated that higher surfactant concentration lowered the entrapment (47).

Conversely, other researchers have reported that increasing surfactant concentration will increase the number of vesicles formed, which consequently leads to a higher volume of the hydrophobic bilayer domain available to house a hydrophobic drug (40, 50, 51). The impact of surfactant concentration was similar when a low concentration was used to prepare Span based niosomes, a small number of niosomes was obtained, and it was recommended that a higher surfactant concentration would improve the drug entrapment (48).

### 3.2.2. Surfactant type

#### A. Surfactant structure (carbon chain length, saturation, hydrophilic head group) and transition temperature (Tc)

Generally it is suggested that by increasing the carbon chain length of the surfactant, the solubility of a lipophilic drug in the lipid bilayer should increase and consequently the entrapment efficiency will increase (52, 53). On the other hand, a point not to forget is that a surfactant with a long carbon chain might compete with a lipophilic drug as they assemble themselves within the lipid bilayer, and excluding the drug and thus reducing its entrapment (30). Similar results were observed when niosomes were formulated with different types of Span. All Span surfactants have similar head groups and only differ by their hydrophobic chain. Niosomes which were prepared with Span 60 showed the highest entrapment as it has the longest carbon chain (40, 48). In contrast, Span 80 resulted in the lowest entrapment efficiency, which was suggested to be related to the unsaturated double bond in its alkyl carbon chain. The presence of the double bond within the carbon chain might make it bend and thus would make the niosomes bilayer to be more permeable as the packing of the adjacent molecules would not be tight (40, 48). Comparable outcomes were observed by El-Laithy et al., when they prepared proniososomes by using several non-ionic surfactants such as Tween (80 and 20) , Span (80 and 20) and sugar esters (sucrose stearate, sucrose palmitate, sucrose myristate, and sucrose laurate) (50). Although the Tween based proniosomes showed the lowest entrapment efficiency, Tween 80 revealed better encapsulation due to its long carbon chain. Moreover, all sugar ester surfactants showed good encapsulation due to their long carbon chains in spite of their high HLB values (50, 54).

Additionally, it was proposed that not only the properties of tail but also those of the head group of the surfactant could also influence drug entrapment within vesicles (table 2). Previously, the physiochemical properties of Span 60/Tween 60 niosomes with ellagic acid as a drug were evaluated (55). The study revealed that entrapment efficiency increased with Tween 60 niosomes, possibly due the nature of the surfactant head group. The head group of Tween 60 (polyoxyethylene groups) is larger than the head group of Span 60, which in turn could help solubilize more ellagic acid (55). In addition, the formation of hydrogen bonds between the head group of Tween and the phenolic groups and lactone moiety of the ellagic acid is possible (55, 56).

Furthermore, the phase transition temperature (Tc) of the surfactant could be an important factor in explaining surfactant effects on entrapment efficiency of lipid-based vesicles. It was reported that the higher the surfactant transition temperature, the better their ability to form a more ordered gel structure and a less leaky bilayer, which could improve the entrapment efficiency (50, 53, 57). While surfactants with a lower Tc could be more liquid in form, leading to irregular structural formation and increased fluidity of the vesicles bilayer, that in turn reduces the drug entrapment (41, 48, 58, 59). For example, Gupta et al. proved that Span 80 gave the lowest entrapment as it has the lowest transition temperature (Tc= -12oC) in comparison to Span 60, 40, and 20 since their transition temperature are 53oC, 42oC and16oC respectively (40). These results were consistent with several other studies where the highest entrapment of drug was obtained from vesicles prepared from Span with the highest transition temperature (48, 60, 61).

#### B. Surfactant HLB value and surfactant physical state

Evaluating surfactant effects on vesicle entrapment efficiency not only depends on its chemical structure, but also requires an understanding of the influence of the hydrophilic-lipophilic balance (HLB). However, the effect of the surfactant HLB value on the entrapment still depends on the drug lipophilicity (10, 62). Reports suggest that the maximum entrapment of a lipophilic drug could be achieved by using a surfactant with a low HLB value (14, 43, 63). For example, Tween 60 was reported to give better encapsulation of β-carotene (model lipophilic drug) in comparison to Tween 20 since their HLB values are 14.9 and 16.7 respectively (14). Niosomes showed a lower tendency to entrap the lipophilic carvedilol as the HLB value of the surfactant used increased (43, 64). Chaudhary et al. obtained a higher encapsulation of curcumin from transfersomes prepared using Span 80 (HLB 4.3) as an edge activator compared with Tween 80 (HLB 15) (30). Similar findings were also achieved when dexamethasone loaded transfersomes were prepared, with both Span 85 and Span 80, with HLB values of 1.8 and 4.3 respectively, showing higher encapsulation than Tween 80 (HLB 15) and sodium deoxycholate (HLB 16) (10).

On the other hand, surfactants with high HLB values are thought to give better encapsulation of hydrophilic drugs (65, 66). This was proved by Shaji et al. when they prepared transfersomes loaded with piroxicam as sodium deoxycholate based transfersomes showed the highest encapsulation in comparison to Tween 80, Span 80 and Span 65 (65). Surprisingly contrasting results were obtained when the hydrophilic drug diclofenac sodium was loaded within transfersomes using different types of surfactant (62). The surfactants used were ranked according to their ability to give the highest encapsulation as: Span 85 > Span 80 > sodium cholate > sodium deoxycholate > Tween 80. Although Tween 80 did not show higher encapsulation than sodium cholate or sodium deoxycholate, Span based transfersomes showed the highest encapsulation efficiency in spite of their low HLB values (62).

Moreover, the physical state of the surfactant could have an effect on vesicles entrapment efficiency (42). Surfactants could be solids, such as sodium deoxycholate, gel form such as Span 60 and 40 or liquids such as Span 80. Gel-type surfactants are likely to produce less permeable vesicles than liquid surfactants. Several types of surfactant were used in the preparation of insulin-loaded niosomes and the presence of the gel-type surfactants such as Span 60 and Span 40 were found to improve drug entrapment whereas niosomes prepared using liquid surfactants such as Span 20 and Span 80 were thought to be more permeable and showed lower entrapment efficiency (42).

## 3.3. Surfactant effects on the charge and stability:

Measuring the electrostatic charge of lipid vesicles is important in order to evaluate their surface properties, as it might play a crucial role in their stability by either creating repulsive forces or causing aggregation (33, 65). The net charge on the vesicle surfaces was thought to be the combination of both the lipid and the surfactant charge. However, it was reported that the type of surfactant could greatly affect the zeta potential for example; between several types of surfactant based transfersomes, cholate based transfersomes exhibited the highest negative zeta potential value (65). Additionally, as the concentration of the surfactant increased, the net charge of the transfersomes increased as well (65). This high negative charge was advantageous as the research aimed to prepare transfersomes for transdermal drug delivery (33). Since it was thought to enhance the transfersomes permeability and stability due to the repulsive forces between the charge of the vesicles and skin surface (33, 49). On the other hand, the same research revealed that all Tween-based transfersomes showed positive charge, and the greater the hydrophilicity of the Tween (HLB value) the larger the positive charge on the vesicle surfaces (33). Similarly, many studies have reported that as the surfactant concentration increases, the vesicles hold a larger zeta potential. Generally, the high charge could improve the stability by reducing the aggregation due to the repulsion that could occur between vesicles when they bear similar charge on their surfaces (31, 32, 57, 67). Additionally, the surfactant transition temperature was also reported to have an effect on the vesicular system stability. It was thought that the surfactant with higher transition temperature could be useful to prepare more stable vesicles (40, 68, 69).

# **Conclusion:**

In summary, the article reviewed what have been reported in literatures about the influence of surfactant on the vesicular system properties. Parameters such as surfactant concentration, number of carbon chains, carbon chain length, the hydrophilicity of the head groups, the competition of other moieties with the surfactant molecules during the arrangement of the lipid bilayer and the HLB value of the surfactant clearly showed an effect on the vesicles properties such as size, charge and drug entrapment. The influence of these parameters varies as the composition of the vesicular system and the drug properties change.

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