



**A REVIEW ON SURFACTANTS AS EDGE ACTIVATORS IN
ULTRADEFORMABLE VESICLES FOR ENHANCED SKIN DELIVERY.**

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ABSTRACT

Edge activators are bilayer softening component, such as biocompatible surfactant in to which an amphiphilic drug is added to increase lipid bilayer flexibility and permeability. Many drugs having severe gastro-intestinal toxicity can be successfully delivered transdermally, but threshold barrier that is stratum corneum is the main limitation. An approach for enhancing the drug flux through the skin is by the chemical interaction of surfactant and solubilisation of the lipid in stratum corneum and enhances the penetration of many drugs. This article insights the mechanism of interaction of edge activators (surfactant) with lipid bilayer, influence of edge activators on vesicular morphology, entrapment efficiency, zeta potential, drug release, deformability, skin permeation and skin deposition. This article also reviews measurement of permeation capacity of surfactants, the application of deformable vesicles containing edge activators in transdermal delivery of various biological.

KEYWORDS: Ultra deformable vesicles, Edge activators, Skin impedance, Skin permeation



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INTRODUCTION

While focusing to research field in drug delivery around one-third of biologicals find its successful delivery through transdermal route. The entry of the rest is restricted by the heavy lipid stratum corneal barrier and therefore the flux rate can be increased by using penetration enhancers. Permeation enhancers either get complexed with lipid bilayer or solubilise the lipid barrier in stratum corneum. Surfactant proportionally increases the fluidity of the membrane and enhances the penetration through the skin. Surfactants are amphipathic molecule that consist of a nonpolar hydrophobic portion usually a straight or branched hydro carbon or fluorocarbon chain containing 8-18 carbon atoms, which is attached to hydrophilic portion. The hydrophilic portion can be ionic, non-ionic, or zwitter-ionic. Vesicular system found its benefit in transdermal delivery of many biologicals that had undergone high rate of first pass metabolism. Mainly the physical properties of vesicles and its composition contribute to the permeation properties of the delivery system. The main component of the vesicular system is the phospholipid bilayer, having the similar lipid composition as that of the skin. Edge activators are mainly incorporated in the lipid bilayer. An edge activator is often a single chain surfactant that destabilizes the lipid bilayer of the vesicles and increases the deformability of the bilayer by lowering its interfacial tension. The first deformable vesicles with edge activators was developed by *Cevc et al* and hence named as transferosomes. In 1998 deformable vesicles consisting mainly of non-ionic surfactants were introduced. The most interesting debated question is that will the deformable vesicles act as carriers or penetration enhancers? The

microscopic images of the fluorescent labelled studies shows that the vesicle containing non – ionic surfactant rapidly enters the deeper layers of the stratum corneum and could reach layers almost as deeper layers of stratum corneum –viable epidermal junction. Mechanisms that have been proposed for the improved skin delivery of deformable vesicle include:

- Vesicle can act as drug carrier systems, whereby intact vesicles enter the stratum corneum, carrying vesicle-bound drug molecule into skin, under the influence of naturally occurring *in vivo* transcutaneous hydration gradient¹.
- Vesicle can act as penetration enhancers, whereby vesicle bilayer enter the stratum corneum and subsequently modify its intercellular lipids, hence, raising its fluidity.
- Phospholipids have a high affinity for biological membranes, thus, the mixing of vesicle –phospholipid bilayer with the intercellular lipid layer of skin may also contribute to permeability enhancement of deformable vesicles².

Interaction of edge activators with lipid bilayer:

Before commenting on the interaction of edge activators on the lipid bilayer, it is more important to study the affinity of surfactant towards lipids and water. HLB gives the surfactant affinity for water and lipid. HLB of tween 80, span 80 are 4.3, 15 respectively. The molar ratio of surfactant to lipid should be determined for considering the distribution of surfactant between lipid and aqueous components of vesicle. In order to find out the molar ratio (Re) of surfactant, distribution coefficient K should be calculated³.

$$Re = \frac{\text{total surfactant concentration}}{\text{Total lipid} + 1 / \text{distribution coefficient}}$$

Surfactant concentrates and interacts with skin by reducing the interfacial tension. They can bind with the cell / cell membrane and can change the porosity/permeability characteristic

of cell membrane⁴. Surfactant can penetrate to the deeper corneal regions of the skin by diffusion. After diffusion the surfactant starts denaturation of the protein and finally the

stratum corneum swells⁵. The surfactant concentration can be increased up to CMC⁶. The surfactants, anionic/cationic can interact with the protein by ionic bonds⁷, while non-ionic surfactants bind via hydrophobic interaction¹¹.

Criteria for selecting surfactants as permeation enhancer

Surfactants use their unique property of reducing the interfacial tension, for enhancing the skin permeation. The permeation capacity of surfactant depends solely on its affinity to bind with the polar or non-polar portion of the lipid bilayer. Effect of surfactant whether desirable or irritation, depend on the type of surfactant, concentration applied and duration of application¹⁰. The activity of surfactant is determined by the alkyl and ethylene oxide chain in the entire structure. Alkyl chain in a surfactant contributes to its hydrophobic, nonpolar part and ethylene oxide chain is polar hydrophilic end of surfactant⁸. The surfactant with relatively shorter alkyl chain forms vesicle⁹. As the carbon chain length of surfactant is lowered, entrapment efficiency may become higher. Sureewan Duanjit et al reported that the enhancers containing the ethylene oxide chain length of 2-5, HLB value of 7-9 and an alkyl chain length of C16 -C18 were effective flux promoters of meloxicam¹². Solubility of lipophilic drug in a bilayer can be increased by increasing the alkyl chain length. An increase in ethylene oxide chain can contribute to its enhanced flux^{6, 10}. In piroxicam, as the polyethylene length of non-ionic surfactant increases the absorption also increased but achieves saturation¹⁰. The HLB of surfactant can be related to alkyl chain length. HLB of sodium oleate, tween 80, span 80 were 18, 15, and 4.3 respectively. HLB value has a direct relationship with the entrapment efficiency of vesicle¹⁵. HLB of surfactant relates its polarity in order to bind with the skin¹¹. The HLB value 4.3 indicates more lipophilic nature than surfactants having higher HLB value 15, thus can encapsulate lipophilic drug more efficiently. Critical micellar concentration (CMC) plays an important role in the micellation of surfactant containing vesicle. The formation of micelles is driven by the decrease of free energy in the system because

of the removal of hydrophobic fragments from the aqueous environment and re-establishing of hydrogen bond network in water. Additional energy gain results from formation of Van der Waals bonds between hydrophobic blocks in the core of the formed micelles¹⁴. It has been reported that presence of polysorbate 80 at a concentration close to surfactant CMC might increase the polarity of absorbing membrane, disrupt the stagnant diffusion layer surrounding membrane¹³. The use of certain special amphiphilic surfactants results in micellar building blocks can also extend the blood half-life of biologicals upon intravenous administration. Micelles having a size range of 5-100 nm penetrate into the body compartments with leaky vasculature liketumors and infracts by the enhanced permeation and retention (EPR) effect, a form of passive targeting¹⁴.

IMPACT OF EDGE ACTIVATORS IN VESICULAR DRUG DELIVERY

Vesicular drug delivery systems are gaining importance recently owing to act as a means for sustained release of drug. These systems have several other advantages: they can encapsulate both hydrophilic and lipophilic moieties, prolong half-life of drug by increasing duration of systemic circulation due to encapsulation, ability to target organs for drug delivery, biodegradability, better permeability and lack of toxicity. Edge activator is often a single chain surfactant that destabilises the lipid bilayer of vesicles and increases the deformability of bilayer by lowering the interfacial tension. The deformable vesicles are a novel type of liquid state vesicle¹⁶.

Effect of Phosphatidyl choline: Edge activator ratio on entrapment efficiency (PC: EA)

Proportion of edge activator concentration can be varied from 5-25% of phosphatidyl choline shows a variable effect in entrapment efficiency. An increase of 0-5% of edge activator produce increased entrapment efficiency. Further increase in edge activator concentration not only increases entrapment efficiency, but also a significant growth in vesicular size that is, up to 15% increase results in pore formation in lipid bilayer.

Predominance of mixed micelle can be observed if concentration of edge activator exceeds 15 %. Smaller size and rigidity of mixed micelle causes relatively lower drug entrapment¹⁷.

Effect of edge activators on the entrapment efficiency

The influence of edge activator on entrapment efficiency solely depends on HLB value of that surfactant. Lower HLB value of surfactant shows lipophilic nature. Surfactants of bile salts origin like sodium cholate and sodium deoxycholate also showed not much variation in the HLB values (16.7) and in their entrapment efficiencies. HLB value of surfactants affects entrapment efficiency, such as HLB value of 14 to 17 is not suitable for niosomes but HLB value of 8.6 has highest entrapment efficiency and entrapment efficiency decreases with decrease in HLB value from 8.6 to 1.7¹⁸. The carbon chain length of edge activators also contributes to the entrapment efficiency. The lower the carbon chain length of the surfactants, the higher the entrapment efficiency. The increase in the carbon chain length of the surfactant increased the lipophilicity and the solubility of lipophilic drug in the bilayer¹². As the transition temperature of surfactants increase it leads to increase in the entrapment efficiency and decrease in the permeability. Spans with highest phase transition temperature provide the highest entrapment for the drug. The drug leaching from the vesicles can be reduced due to high phase transition temperature and low permeability¹⁹.

Effect of edge activators on deformability

Being less bulky tween 80 showed higher deformation when compared to steroid like bulkier groups of spans. The less deformation indicates hydrophobicity. Hydrophilic hole formation can also be reduced and decreases the membrane fluidity. Bulkier ester surfactants being less flexible, less deformable.

Effect of edge activators on In vitro drug release

The low edge activator concentration results in lower drug release as the lipid membrane were more ordered and less leaky. At high edge

activator concentrations, vesicles lack their vesicular structure and forms rigid mixed micelles results in lower drug release. Mixed-micelles are less sensitive to osmotic gradient when compared to transfersomes. Undeformable mixed micelles also accumulate on the top of stratum corneum. Tween 80 has a large volume of hydrophilic head group consisting of several polyethylene chains. This structure could impede penetration into tails of the lipid bilayer on the stratum corneum. Generally the drug adsorbed on the vesicular surface will be released rapidly after that entrapped drug will show a sustained release profile. Deformable vesicle shows highest drug release and entrapment caused by particular edge activator and typical drug used²⁰.

Effect of edge activators on the size analysis

There exist a relationship with vesicle size and HLB. The use of surfactant with increased hydrophobicity results in decreased surface energy leading to the formation of vesicle with smaller size²¹. While considering hydrophilic surfactants their aqueous solubility do not allow them to get into a compact vesicular structure, resulting into an aggregated coalesced lamellar nature¹⁹. But in case of elastic vesicles, the selection of surfactant to get smaller size vesicle may be irrelevant, as they are ultra-deformable.

Effect of edge activators on zeta potential

Many non-ionic surfactants like tween 80 exhibit a low negative zeta potential, leading to repulsion between the bilayers. The reason behind this low zeta potential value may be due to the chemical structure. The disadvantage is that there is a significant increase in the size of vesicles²².

Effect of edge activators on stability of vesicle

Hydrophobic surfactants, sorbian esters 85, yield vesicles with ordered bilayers, having more stability than non-ordered ones²⁰. The amount of drug retained in the vesicle can be studied and evaluated after 2-3 months. Stability can also be evaluated by vesicular size. There is a significant increase vesicular

diameter on storage, due to the hydrophobic cohesion tendency of smaller vesicles²³.

MEASUREMENT OF PERMEATION CAPACITY OF SURFACTANTS

It is generally accepted that reduction in skin barrier properties occurs only after surfactants have penetrated /permeated into the skin barrier. Overall, the action of edge activators on the keratin and lipids thus results in looser or more permeable structures which are presumably responsible for the observed increase in flux. Thus, barrier properties of SC, which are related to the composition, and complex structural arrangement of its lipids is decreased after treatment with those formulations containing suitable edge activators subsequently leading to an increase in stratum corneal permeability. Thus a change in permeability and fluidity can be very well understood by measuring skin impedance, analysing DSC and from FT-IR of skin.

CALCULATING SKIN IMPEDANCE

Mitragotri developed the methods for calculating skin impedance for skin care biomedicals and pharmaceutical applications²⁴. Skin permeability can be directly measured by skin electrical impedance. Skin permeability relates skin integrity, skin barrier damage etc²⁴. When exposed to different chemicals the perturbations produced in skin can be expressed by measuring changes in skin impedance. In perturbed skin, electrical impedance is expected to decrease and transport rate of ions flowing through the skin is higher^{24, 25, 26}. Several factors like viscosity, temperature, and pH contributes to the altered impedance of skin.

Effect of viscosity on impedance

Guojin Lu and David J. Moore found that addition of 10% glycerine as viscosity enhancer to SDS surfactant solution reduces surfactant-induced skin barrier perturbation, as they cause obstruction to the aqueous porous pathway of the Stratum corneum. The addition of glycerine reduces the ability of SDS micelles to penetrate the SC resulting in an overall increase in skin impedance²⁷.

Effect of temperature on skin impedance

The skin perturbation by surfactants is more significant at higher temperature. This trend is expected as higher temperature accelerates the penetration of surfactant molecules into the SC, as well as enhancing the removal and organizational disruption of SC lipids, resulting in greater barrier disruption at higher temperature²⁸.

Effect of pH of surfactants on impedance

In the presence of surfactants the hydration and swelling of stratum corneum takes place. Possible mechanisms of pH effect would promote surfactant ions binding to, and penetrating into, the skin thereby damaging to the skin barrier. It has been known that the pH of stratum corneum is acidic 4.5-5.²⁹ The attraction and penetration of basic surfactant solution is more favourable. The increase in pH of surfactant from 4.4 to alkaline will show an increase in barrier damage³⁰. Under basic pH anionic surfactant binds primarily by hydrophobic functional groups to hydrophobic lipid sites on skin to minimise the repulsion of negative charges³¹. Totally, an alkaline pH alone induces irreversible lipid phase change in stratum corneum. The change of impedance to a lower value indicates the increased penetration of ions through the skin barrier, as the barrier is disturbed by physical or chemical stress.

DSC ANALYSIS OF SKIN

Differential scanning calorimetry is an invaluable tool for a detailed thermodynamic characterisation of macromolecule and their interactions with skin¹⁵. Brandys *et al* in 1989 evaluated the change in thermal properties of SC with the aid of DSC³². The change into lower transition temperature suggests an increase in the gross fluidity of the SC lipids, that is a transition from ripple to gel phase, expressed as, ΔH value is observed when a small amount of drug, which is placed at the level of hydrophobic core of bilayer due to high lipophilicity of these molecules. The greater the drug molar fraction in the bilayer structure, lower the ΔH values. A shift of DPPC lipid transition to a lower temperature was observed particularly in the case of hydrocortisone¹⁵. This is consistent with the general view that the

mechanism of action of the surfactant is attributed to the alteration of the lipid organization and an increase in lipid lamellae disorder in the SC. Sureewan Duanjit *et al.*, studied the effect of surfactant in lowering the lipid transition temperature of meloxicam loaded transfersomes thereby increasing the fluidity of SC¹². A. Azeem *et al.*, formulated proniosomes containing span 40 surfactant and soya lecithin showed a decrease in protein endotherm to lower melting points suggesting keratin denaturation and possible intracellular permeation mechanism in addition to the extraction of lipid bilayers³³.

FTIR ANALYSIS

The FTIR provides information about the molecular and conformational changes in SC lipids and proteins. Many of the IR spectra bands of SC can be attributed to lipid or protein molecular vibrations. The molecular vibrations of lipids and proteins are related to various peaks in the IR spectrum of the SC. Sureewan Duanjit *et al.* developed a transfersomal delivery of meloxicam that showed an absorbance broadening for both the C–H (CH₂) asymmetric stretching peak near 2920 cm⁻¹ and the C–H (CH₂) symmetric stretching peak near 2850 cm⁻¹. The height and area of these two bands are proportional to the amount of the lipids present¹².

APPLICATION OF EDGE ACTIVATORS IN THE DELIVERY OF VARIOUS BIOLOGICALS

A Kim *et al.*, complexed negatively charged plasmid DNA with cationic lipids, and positively charged surfactants are used in formulating one of the promising non-viral gene delivery system. Ultra deformable liposomes containing sodium cholate and sodium deoxy cholate showed a positive zeta potential, which might leads to a firm binding with negatively charged DNA and showed substantial transdermal absorption. This proves the choice of edge activators in the transdermal delivery of plasmid DNA via ultra-deformable liposomes²². Huang Y *et al.*, pegylated synthetic surfactant vesicle for cellular delivery of oligonucleotides, composed of DC-chol, PEG2000-SSPE and span. Advantages include neutral zeta potential with a particle

size of 300nm, prevent binding of serum protein. The loaded nuclear acid drug exhibited increased resistance to serum nuclease. The PEGylated niosomes showed a higher efficiency of oligonucleotide cellular uptake in serum. Therefore, in terms of their stable physiochemical properties in storage and physiological environment, as well as low-cost and widely available materials, PEGylated cationic niosomes are promising drug delivery systems for improved oligonucleotide potency in vivo^{34, 35}. Carriers for drug targeting: Biswal *et al.*, reviewed non-ionic surfactants (Niosomes) vesicles and their drug delivery potential.³⁵ The ether type surfactants with single alkyl chain as hydrophobic tail is more toxic than corresponding dialkylether chain^{21, 36}. The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter as ester-linked surfactant undergoes degradation by esterase to triglycerides and fatty acid in vivo²¹. The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosomes. Span series surfactants having HLB number between 4 and 8 can form vesicles. Critical packing parameters of surfactants can predict geometry of vesicle, whether bilayer, spherical, or inverted.

CONCLUSION

All the studies performed with the surfactant-based deformable vesicles indicate an intact partitioning into the stratum corneum but very limited partitioning into the viable epidermis. Specific types and concentrations of edge activators are required for providing the maximum deformability to vesicle membranes. Validation and the use of skin electric impedance to predict the impact of a surfactant-based formulation will have on skin barrier, including skin irritation and damage. Surfactant plays a vital role either in pharma and non pharma field. An exhaustive study of its role and mechanism towards medical field would reveal a wide range of its potential in therapeutic usage. Narrowing the research on each and every surfactant would certainly benefit the field of medical science.

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