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Mini review

Passive enhancement strategies in topical and transdermal drug delivery☆

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Abstract

The skin has an extremely good barrier function and to improve topical bioavailability it is usually necessary to employ enhancement strategies. Optimization of the applied formulation can improve release to the skin and the use of supersaturation achieves this objective. However, supersaturated states are inherently unstable. High solvent concentrations in the formulation may remove skin lipids reducing the barrier function of the stratum corneum. Alternatively formulation components can diffuse into the barrier function where they can have two distinct effects. They may intercalate into the structured lipids of the bilayer, decreasing their diffusional resistance. Alternatively they can modify the solubility parameter of the skin lipids; the diffusing drug may then have an enhanced solubility in the skin. If the two effects can be combined synergy is observed. Deeper permeation of solvent into the viable tissue may also result in increased drug concentrations in this layer of the epidermis. The viable layer is metabolically very active and perturbation of the enzyme systems responsible for the formation of the stratum corneum lipids can reduce the barrier function. Finally a diffusing drug will encounter the blood supply. If vasoactive drugs modulate the blood flow rate, absorption can be influenced.

Keywords: Skin penetration; Enhancers; Transdermal delivery

1. Introduction

Over the past decades there has been a general realization that the bioavailability of topically applied drugs is very low. For example, as long ago as 1967, Feldmann and Maibach (1967) assessed the bioavailability of hydrocortisone alcohol to be 1.7%. Since then there has been a renewed interest in using enhancement strategies with the general recognition that any chemical enhancer should possess certain characteristics. These are summarized in Table 1. It is unlikely that any enhancer will be found that has all of these properties and compromises will have to be made with appropriate benefit to risk calculations. Water is perhaps the ideal enhancer, since hydrated skin is gener-

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ally more permeable (Roberts and Walker, 1993). However, it is not applicable to all permeants.

Considering an idealized representation of the skin there are several different strategies that can be adopted to optimize dermal delivery. These are depicted in Fig. 1.

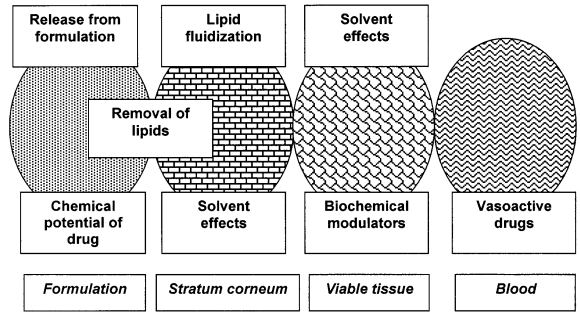

Fig. 1. A schematic representation of the skin and the way various enhancement strategies can be envisaged.

2. Formulation effects

The simple way in which the solubility and partition coefficient of the diffusing drug can impact on formulation strategies is often ignored but has been systematically studied in the 60s and 70s. An excellent review article by Katz and Poulsen (1971) should be referred to for further information.

The rate of delivery to the skin surface can be important, particularly in the case of transdermal systems. Where rate control is required, the diffusion through the polymeric matrix of the delivery system should be significantly slower than that through the stratum corneum. In general, diffusion through topical preparations, after they have been rubbed into the skin, does not control the absorption process. It is a common misconception that an increase in the applied concentration of a drug always results in an increase of drug flux. If the drug is presented as a suspension, the flux will be invariant with applied concentration. The driving force for diffusion through the skin is the chemical potential gradient. Twist and Zatz (1988) showed the significance of this in a diffusion study of parabens through a silicone membrane. The diffusant was presented to the membrane in a variety of solvents but in each of the solvents it was saturated. Due to the different solubilities in the solvents the concentration varied over two orders of magnitude. Despite this, the flux was the same for all 11 solvent systems tested. This is to be expected provided the solvent does not alter the properties of the membrane.

Table 1
Ideal characteristics of dermal permeation enhancers

Pharmacologically inert
Non toxic
Immediate in action
Reversible in action
Chemically and physically compatible
Cosmetically acceptable

In order to improve absorption it is possible to use supersaturated solutions which have chemical potentials greater than that of a saturated solution. They are, however, inherently unstable. It is possible that some changes in efficacy of transdermal systems after storage is due to their being supersaturated at manufacture with subsequent crystallization on extended storage. Changes in delivery rates have been observed for transdermal patches when the expiry date has been exceeded (Brain et al., 1993). Stabilization of supersaturated topical preparations can be achieved over limited periods using anti-nucleant polymers (Pellett et al., 1994) and enhanced absorption through skin achieved. There appears to be an almost linear increase in drug flux with degree of supersaturation.

In a further investigation, the absolute concentrations found in the different strata of the skin were also in direct proportion to the degree of saturation of piroxicam (Pellett et al., 1997). This is important since it is the ratio of the concentration of the drug at the site of action to that applied which needs to be as high as possible for optimal bioavailability.

Some solvents can remove lipids from the stratum corneum. The barrier function is reduced when the lipids are modified in this way, although the effect has been shown to be reversible. Some topical and transdermal products contain high

concentrations of solvents such as ethanol that may be capable of altering the lipid content of the skin (Bommannan et al., 1991). Little systematic studies have been conducted on the effect of lipid extraction.

3. Effects on the stratum corneum

An inspection of Fick's 1st law of diffusion shows that two major effects can be obtained if a formulation excipient permeates into the stratum corneum. It may intercalate into the structured lipids of the skin where it can disrupt the packing. The effect may render them more 'fluid' thereby increasing the diffusion coefficient of the permeant. This has been demonstrated using differential scanning calorimetry (DSC) and measuring the effect on phase transition temperature (Cornwell et al., 1996), ESR studies (Gay et al., 1989), FTIR (and Raman) investigations (Golden et al., 1986; Barry et al., 1992), and fluorescence spectroscopy (Garrison et al., 1994).

Recent structure activity relationships on Azone® and its analogues (Hadgraft et al., 1996) have indicated that hydrogen bonding between the polar head group in Azone may be important and that it probably interacts in a manner depicted in Fig. 2.

The molecular characteristic that typifies an enhancer which disrupts the skin lipids is a polar head group with a long alkyl chain (C_{10} to C_{14} appear optimal, Bouwstra et al., 1989). Compounds such as the non-ionic surfactants have such properties and Brij 36T has been shown to be an effective enhancer (Walters et al., 1988). Oleic acid also acts by disrupting the skin lipids but appears to form pools in the lipids rather than distribute homogeneously (Ongpipattanakul et al., 1991).

One of the problems of such structural features is that this type of molecule also tends to have irritant properties. When more is known about structure activity relationships for both enhancement and skin irritancy it should be possible to design molecules that have ideal properties.

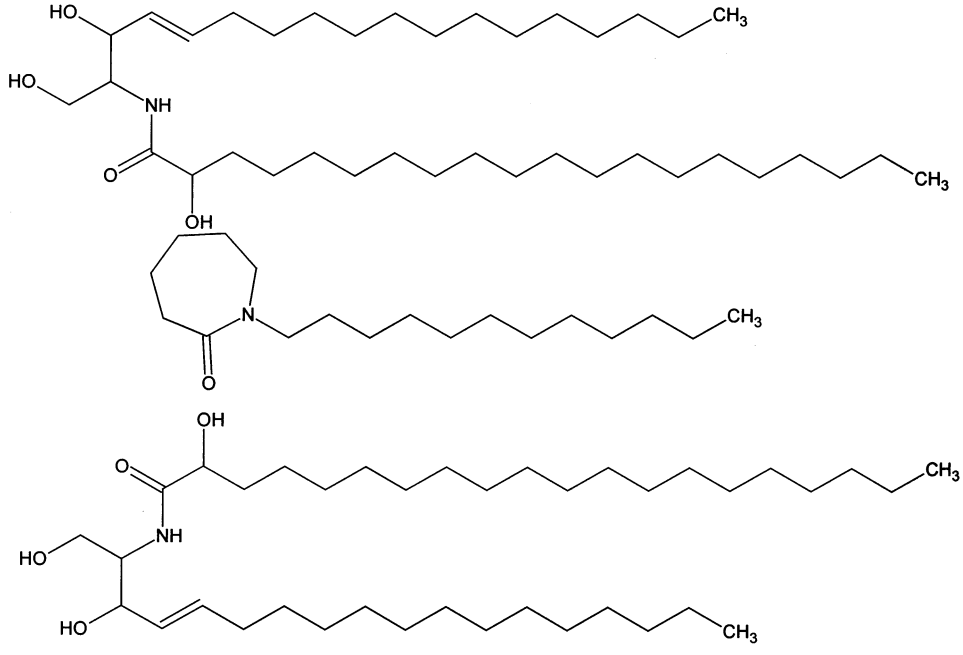

Fig. 2. A diagrammatic representation of the interaction between Azone® and ceramides.

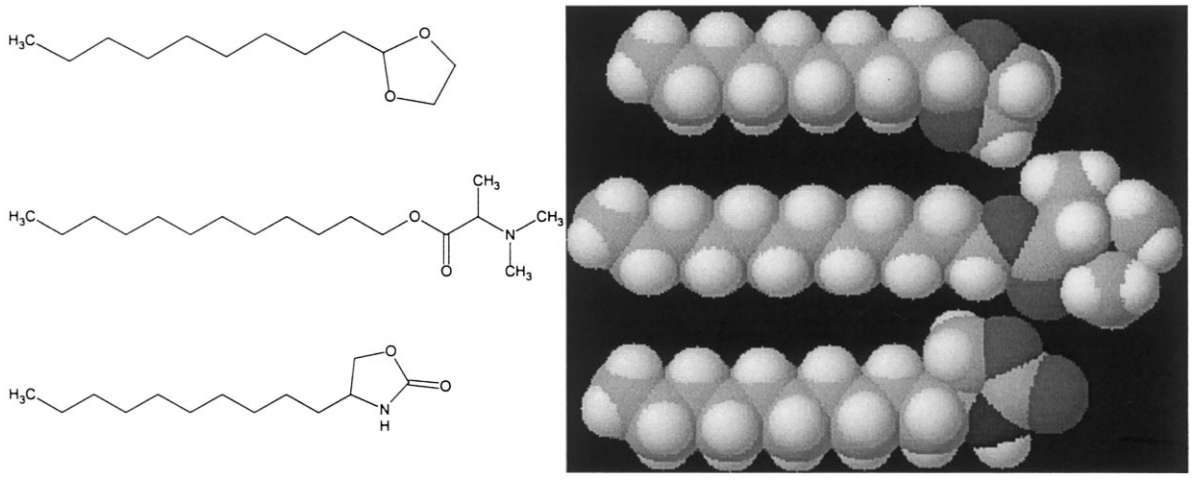

Fig. 3. Structures of commercial skin penetration enhancers, from top, of SEPA 009 (ex Macrochem); NexAct 88 (ex NexMed) and SR38 (ex Pharmetrix). The 3D images were energy minimized using ACD software (Toronto, Canada).

A number of commercial enhancers of this type have been developed and are depicted in Fig. 3. Structural similarities are obvious and it is thought that these compounds have minimal skin toxicity.

It is possible that some structures with similar molecular features will stabilize the skin lipids, reducing permeability (Hadgraft et al., 1996). Such compounds would have utility in formulations where systemic absorption needs to be minimized, e.g. UV filters, insect repellents.

The second way in which excipients can modify skin permeability is to shift the solubility parameter of the skin in the direction of that of the permeant. The solubility of the permeant in the outer layers of the skin will be increased and this, in turn, improves the flux. Simple solvent type molecules, such as propylene glycol, ethanol, Transcutol®, and *N*-methyl pyrollidone are thought to act in this way. For example, it is well known that propylene glycol permeates the skin, it therefore must be distributed in the stratum corneum (Potts et al., 1991). The inherent solubility parameter (δ) of the skin lipids is thought to be about 10 (Liron and Cohen, 1984). The presence of propylene glycol will increase this. Metronidazole (estimated $\delta = 13.5$) has an enhanced permeability if skin is pretreated with propylene glycol (Wotton et al., 1985).

It is interesting to note that Fick's laws of diffusion show that if enhancement strategies include both an effect on diffusion (D) and an effect on the solubility, a multiplicative result is expected. Synergy between these approaches has been shown for numerous systems including metronidazole (Azone plus propylene glycol, Wotton et al., 1985), prostaglandin (Azone plus Transcutol, Watkinson et al., 1991). The effect is also possible when supersaturation is combined with a 'lipid fluidizer', e.g. for flurbiprofen (increased degree of saturation plus oleic acid, Pellett et al., 1997).

It is often difficult to distinguish between the effects on D and solubility, however, a recent technique involving ATR-FTIR has allowed the deconvolution of the effects of Azone and Transcutol on the skin. In this instance the model permeant was cyanophenol and the results indicated the two discrete mechanisms for the two different enhancer types with Azone improving D by a factor of 3 and Transcutol having a similar effect on solubility in the stratum corneum (Harrison et al., 1996).

A number of formulation excipients have been incorporated into topical and transdermal systems that may be anticipated to act as permeation enhancers. Considering transdermal patches there are systems in which ethanol is present at high

concentrations. Other solvents include: propylene glycol, 1,3 butylene glycol, dipropylene glycol. Long alkyl chain (plus polar head group) excipients include isopropyl palmitate (and myristate), glyceryl mono-laurate (and oleate), methyl laurate, oleic acid.

4. Effects in the viable tissue

For very lipophilic permeants there could be a problem of poor solubility in the aqueous environment of the viable tissue. The presence of solvents such as propylene glycol in this region could be advantageous for permeability. However, there have been very few systematic studies to demonstrate the significance of solubility effects in the deeper tissues of the skin. This region is biochemically very active and enzyme systems present are responsible for controlling the synthesis of the lipids that maintain the barrier function of the stratum corneum. Use of fatty acid and cholesterol synthesis inhibitors have been shown to enhance the permeability of murine skin. A combination of the two inhibitors appears to provide a synergistic effect (Tsai et al., 1996). It is unclear how regulatory authorities will react to this biochemical approach to permeability modulation.

5. Blood supply

Vasoactive drugs will have an effect on the local removal of the permeant. However, it is generally thought that the process of elimination is efficient and that there is little that can be achieved in improving permeability using this mechanism. If vasoconstrictor drugs are used the removal rate will be impaired which may lead to enhanced local concentrations of the permeant in the viable epidermis and dermis.

6. Miscellaneous

There are reports that large molecular entities such as DNA can be absorbed into deeper layers of the skin using complexation with DOTAP. The resultant DNA lipid complex will have a size of several hundreds of nanometers and it is unclear what mechanism of penetration is involved. However, gene expression in murine epidermis, dermis and hair follicles indicates that the complex is capable of penetration (Alexander and Akhurst, 1995). Similar work in our laboratories has confirmed these findings. Similar sized entities (Transfersomes) have been reported to deliver insulin (and other large drugs) through rat and human skin in vivo (Cevc et al., 1998). In this instance it may be the hydration energy of the polar head groups of the highly deformable vesicles that is important.

7. Conclusions

The last decade has shown a huge growth in the application of sophisticated biophysical techniques to monitor skin permeability. The understanding of the mechanisms of absorption and enhancement has improved and the different determinants at a molecular level are beginning to be understood. This knowledge can be used in the design of better dermal and transdermal medicines and associated permeation enhancers. With these it should be possible to achieve bioavailabilities comparable to those expected as the norm in oral drug delivery. With this possibility developing safe and effective dermal and transdermal delivery systems should be far more successful.

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