Permeation Enhancers of Hormones Penetration through the Skin

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Hormones have attracted considerable interest in recent years due to their potential use in treatment of many diseases. Their ability to have a multidirectional effect leads to searching for new and increasingly effective drugs and therapies. Limitations in formulating drug forms containing hormones are mainly due to their low enzymatic stability, short half-life and limited bioavailability. One of the solutions may be to develop a hydrogel as a potential hormone carrier, for epidermal and transdermal application.

hydrogels hormone topical permeation enhancers

1. Fatty Acids and Surfactants

Fatty acids are often used to improve the transdermal delivery of hormones (estradiol, progesterone). Their action involves modification and disruption of the lipid matrix in the stratum corneum. It is suggested that they show higher efficiency for the absorption of lipophilic drugs. The beneficial features of fatty acids include the non-irritational effect on the skin, no toxicity, wide range of compatibility, high skin flux, reduced skin irritation and sensitization [1]. A synergistic effect of the system was found in propylene glycol-lauric acid w transdermal delivery of highly lipophilic drugs (antiestrogens AE 1/log p = 5.82 and AE 2/log p = 7.8) [2]. Oleic acid is effective at low concentrations (10%) [3]. In higher concentrations, it can act as a separate phase within the bilayer lipids, thus facilitating the permeation of hydrophilic permeants through the membrane [4].

Surfactants are usually added to solubilise lipophilic active ingredients. They enable permeation of drugs via a transdermal route [5]. At low concentrations, they act by solubilising lipids within the stratum corneum, disrupting the lipid and protein domains. They can penetrate through the lipid bilayer. The ability of surfactants to penetrate the stratum corneum depends on the partitioning behavior and solubility. They exhibit hydrophobic (oleic acid) and hydrophilic (sodium lauryl sulfate) properties. Their action causes skin irritation. Hydrophilic surfactants are generally less irritating and better tolerated than poloxamer, poloxamine and polysorbates [6]. It has been suggested that surfactants have a more lipid disorientating effect in the stratum corneum and create higher levels of cutaneous absorption than terpenes, alcohols and glycols [7].

Ann et al. [8] developed polyvinyl alcohol with polyisobutylene-based hydrogel formulation for testosterone (TS). They analysed the effect of selected excipients, i.e., dodecylamine, 1-(2 (Decylthio)ethyl)azacyclopentan-2-one (HPE101), oleic acid and lauric acid, on the rate of hormone permeation through the skin. In vivo studies were conducted in a rat model, applying the hydrogel on the dorsal skin. On the other hand, in vitro studies were carried

out with Keshara–Chien permeation cells, using a fragment of rat dorsal skin. The researchers confirmed the high efficacy of dodecylamine at a concentration of 3%. In in vivo studies, the area under the curve (AUC24hr) values calculated from the plasma concentration profiles of TS increased from 77.73 ng*h/mL to 407.29 ng*h/mL. In vitro, the permeation rate of TS in the presence of 3% dodecylamine increased 10-fold (0.54 μg/cm^2/h—without an absorption promoter, 4.92 μg/cm^2/h in the presence of 3% dodecylamine). The addition of 5% dodecylamine to the hydrogel reduced the TS permeation rate, probably due to an increase in the viscosity of the substrate.

Barreiro-Iglesias et al. [9] investigated the potential of carbopol/surfactant dispersion in the controlled release of estradiol. The efficacy of Carbopol® 934 was evaluated in the presence of Pluronic F-127, Tween 80, sodium dodecyl sulfate (SDS), and benzalkonium chloride (BkCl). Carbopol/surfactant aggregates increase the solubility of hydrophobic drugs. The researchers suggest that, by choosing surfactants with desirable properties, e.g., with appropriate HLB (Hydrophilic Lipophilic Balance), one may modulate the strength of hydrophobic interactions between carrier components and control the rate of API release (also in low viscosity medium). Estradiol release mainly seems to happen as a direct exchange between the carbopol/surfactant aggregates and the surfactant micelles of the receptor medium. The lack of organic solvent in the proposed formulations and the acidic pH potentially avoid the occurrence of adverse reactions after skin application.

Matsui et al. [10] evaluated the absorption of natural progesterone from alcoholic gel-based transdermal formulations in vitro and in vivo. They have studied the impact of hydrophilic surfactants (polyoxyethylene (7) oleylether (Oleth-7), polyoxyethylene (10) oleylether (Oleth-10), polyoxyethylene (20) oleylether (Oleth-20), polyoxyethylene (20) cetylether (Ceteth-20), polyoxyethylene (20) stearylether (Steareth-20) and polyoxyethylene (20) behenylether (Beheneth-20) and isopropyl myristate (IPM), benzyl alcohol (BA) or propylene glycol dicaprylate (PGDC) on the penetration of Prog through rat skin. The optimal carrier for Prog was an ethanolic gel containing Oleth-20 and PGDC. The formulation demonstrated high transdermal absorption in vitro and in vivo. Plasma concentration of progesterone after repeated-dose transdermal application was 13.9 ± 4.85 ng/mL ($p < 0.01$) after 48 h.

The subject of the study by Szcześniak et al. [11] was the analysis of the effect of selected absorption promoters (N,N-dimethylacetamide (DMA), propylene glycol-1,2, ethanol 760 g/L and Tween 20) contained in Carbopol 934 P on HC permeation. The researchers found that increasing the concentration of uptake promoters increased the amount of HC released. The value of the constant release rate increases in the presence of ethanol, Tween 20 and DMA.

2. Sulfoxides

Dimethylsulphoxide (DMSO) is a frequently used penetration enhancer as a ‘universal aprotic solvent’. Although it shows high efficiency in penetrating hydrophilic and lipophilic substances, it is problematic to use. In high concentrations (>60%), it can cause erythema and wheals of the stratum corneum and may denature some proteins [5]. Application of 90% DMSO to the skin of healthy volunteers caused erythema, scaling, contact urticaria, stinging and burning sensations and systemic symptoms [12]. Irreversible skin damage can also be caused by the

chemically related materials dimethylacetamide (DMAC) and dimethylformamide (DMF) [13]. In contrast, decylmethyl sulphoxide (DCMS) acts reversibly on human skin and is a potent enhancer for hydrophilic permeants [5].

A hydrogel based on hydroxypropyl methylcellulose (HPMC) containing ethanol (25% *w*/*w*) as a potential substrate for TS was proposed by Heo et al. [14]. The effectiveness of hydrogels modified with the addition of absorption promoters (propylene glycol, butylene glycol, diethanolamine, dimethyl sulfoxide/DMSO, N-methyl pyrrolidone/NMP) was studied in a rat model in vivo and in vitro using hairless mouse skin. The researchers achieved a significantly high TS plasma concentration profile using the developed hydrogel substrates. The combination of diethanolamine (2%) and NMP (6%) was the most effective among tested absorption promoters.

3. Alcohols, Glycols and Glycol Ethers

Alcohols are among the most commonly used sorption promoters. Ethanol increases the permeation of both polar and non-polar molecules. Depending on the concentration of the ethanol used in the donor solution/formulation and on the lipophilicity of drug/actives, different mechanisms of action are proposed. Ethanol at a concentration of 25% interacts with polar lipid groups causing fluidisation of the lipid bilayer. In contrast, ethanol at concentrations >50% causes conformational changes of α-keratin and partial extraction from the lipid bilayer matrix [15][16]. The permeation rate of ethanol through human skin is 1 mg/cm^2/h [17]. Alcohols are very good solvents and solubilisers. Unfortunately, they evaporate quickly and cause dryness of the skin [18]. Propylene glycols are effective cosolvents. Their action is based on improving drug partition properties and reducing drug-tissue binding by the solvation of α-keratin. In addition, they affect lipids in the stratum corneum [19][20]. It has been suggested that propylene glycol shows optimum activity in a system with oleic acid and in a propylene glycol-isopropyl alcohol (30:70% (*v*/*v*) system with essential oil [21].

Pabla et al. [22] proposed modifying the composition of commercially available transdermal hydroalcoholic gels containing 1% testosterone (Androgel®, Testim® and the generic form). They replaced part of the ethanol with isopropyl alcohol (IPA). The effectiveness of the modified hydrogel based on Carbopol Ultrez 10 was tested using in vitro release/permeation experiments versus Androgel®. The study confirmed that IPA does not increase the bioavailability of testosterone from hydroalcoholic gel preparations. This may be due to a potential interaction of TS–Carbopol Ultrez 10. The researchers suggest that IPA may enhance the release of TS from other types of Carbopol. The strongly dehydrating nature of ethanol causes rapid drying of the epidermis, making it difficult for API to penetrate the skin. The less volatile isopropyl alcohol prevents this process while maintaining an optimum ethanol concentration gradient for efficient hormone permeation. IPA also exhibits good cosolvent properties, without affecting the consistency or aesthetics of the finished formulation.

Antares Pharma has developed and patented Advanced Transdermal Delivery (ATD™) technology, which is based on a combination of solvents and compounds that enhance the permeation of API through the skin. The advantage of this technology is the possibility to optimise physicochemical parameters of the preparation (rheological properties, pH) and to modulate hormone permeation through the skin (selection of concentrations of active

substance and excipients, the thermodynamic activity of the molecule in the substrate). The most commonly used solvents in ATD™ technology are alcohols, glycols and glycol ethers. These compounds have a synergistic effect on delaying the crystallisation of the drug (while maintaining its molecular form), which enables the skin permeation of APIs (also lipophilic drugs) [23]. Olsson et al. [24] compared the rate of transdermal transport of testosterone from hydrogel 1% and 2% vs. Testogel. They performed the study on a Caucasian male model with reduced blood testosterone levels. A hydrogel (Carbopol 980) based on ATD™ was used as a TS carrier, which influenced faster testosterone absorption, according to first-order kinetics. The blood TS concentration profile was similar to the circadian one.

4. Esters

Sucrose esters are frequently used surfactant compounds. The properties of these compounds depend on fatty acid esterification and the nature of esterified fatty acid molecules in the sucrose [25]. Sucrose laurate increases the penetration of poorly water-soluble drugs [1]. Isopropyl myristate is a lipophilic molecule and can liquefy the lipids of the stratum corneum intercellular membrane [26].

Vermeire et al. [27], on the other hand, studied the efficacy of sucrose laurate (5%, 15% *w*/*w*) in the skin permeation of estradiol (ES). The study was performed in a male rabbit model and evaluated the absolute bioavailability of the hormone and the skin irritation after single and multiple applications. Two estradiol hydrogels based on hydroxypropyl methylcellulose, differing in laurate sucrose content, were developed and compared with the reference formulation Oestrogel. The base of the original formulation was carbopol 940 with ethanol (30%). It was found that sucrose laurate showed stability in the studied hydrogels during a four-month storage period (7 ± 2 °C). The preparation containing 15% sucrose laurate was characterised by higher bioavailability of ES after a single application. Oestrogel showed a higher efficacy when administered several times. The result of histological examination confirmed a significant increase in skinfold thickness after administration of the 15% sucrose laurate gel (indicating some skin irritation potential). Most surfactants hydrate the skin and an increase in hydration correlate with increased skin permeability. However, in this case, the increased skin penetration is due to sucrose laurate's ability to disrupt the ability of SC lipids, and consequently to dissolve and extract lipids.

A working group around Zidan [28] investigated the effect of isopropyl myristate (IPM) in hydroalcoholic carbopol gel on the permeation of testosterone through excised human cadaver skin. IPM could change the SC microstructure by fitting into the lipid lamellae because of its hydrophobic nature or could also liquefy the SC lipids because of its branched structure. The formulations tested contained IPM at concentrations of 0–3% *w*/*w*. The hydrogel formulation was supplemented with 73.5% (*w*/*w*) ethanol. A low concentration of ethanol influences increases drug diffusivity by interaction with SC. Moderate concentrations of ethanol increase both the diffusivity and solubility of drugs. Ethanol and IPM showed synergistic effects. The highest TS release was observed with IPM at a concentration of 2% *w*/*w*.

5. Terpenes

Terpenes enhance the permeation of lipophilic substances, hydrophilic substances and compounds in ionic form. Their advantages are reversible alteration in the stratum corneum, percutaneous absorption enhancement, low toxicity and low irritational effect [1]. When used in low concentrations (1–5%), they show high percutaneous enhancement abilities and low cutaneous irritancy [29]. Their effect depends on chemical structure and physicochemical properties, such as its lipophilicity, size and chirality, boiling point and energy of vaporisation and degree of unsaturation. Their mechanism of action involves temporary accumulation in the stratum corneum (and/or keratin) and disruption of the ordered intercellular lipid system of the stratum corneum [30]. Terpenes have been found to be skin safe and non-irritating. The optimal terpene enhancer is hydrophobic, it is liquid at room temperature, it contains an ester or aldehyde functional group and it is either a triterpene or a tetraterpene [31]. Terpenes show synergism of action with ethanol in the fluidisation of the intercellular lipids [32].

El-Kattan et al. [33] studied in vitro the rate of transdermal transport of Hydrocortisone (HC). The hormone carrier was HPMC gels containing terpenes with different values of lipophilicity log *p* = 1.06–5.36. The researchers found a positive correlation between the lipophilicity of the terpenes and the cumulative amount of hydrocortisone permeating through skin. Nerolidol, whose lipophilicity was the highest (log *p* = 5.36 ± 0.38), provided the greatest enhancement for HC flux (35.3-fold over control). Fenchone (log *p* = 2.13 ± 0.30) exhibited the lowest enhancement of HC flux (10.1-fold over control). The higher enhancement activity of hydrocarbon terpenes can be attributed to their higher thermodynamic activity in the hydrogel.

In another study [34], the researchers compared the rate of transdermal testosterone transport from hydrogels containing propylene glycol or limonene or oleic acid or transcutol or a combination of two permeation enhancers, respectively. They found that the highest amount of TS was released from hydrogel, which contains limonene and propylene glycol (in the concentration of 15%).

Monti et al. [35] to promote permeation of estradiol through the skin chose six oils: cajuput, cardamom, melissa, myrtle, niaouli and orange oil, all used at the 10% *w/w* concentration in propylene glycol (PG). Tests were performed in hairless mouse skin in vitro model. The results show that propylene glycol has a synergistic effect with the terpenes in the organogels increasing the penetration of the hormone. In addition, 1.0% NIA (main terpene components: 1,8-cineole, α-pinene, α-terpineol, D-limonene) significantly increased the estradiol transdermal flux. It has been suggested that essential oils may disrupt the ordered arrangement of lipids in the SC or increase the solubility of API diffusing into the stratum corneum [36][37].

6. Ureas and Lactam

Urea has an emollient and moisturising effect [38]. It lowers the stratum corneum barrier by changing its hydration. In concentrations of 10–50%, urea has a keratolytic effect (loosens keratin connections). It has the ability to the formation of hydrophilic diffusion channels within the epidermal barrier [5][38][39]. The disadvantage of urea is its ability to increase the water content of the stratum corneum (which acts as a humectant) and preserve its fluidity [1]. Laurocapram reduces the diffusional resistance of a substance into the stratum corneum and inserts it into the lipid

bilayer region [40]. It has been found that it can increase the permeation of hydrophilic compounds, hydrophobic compounds and peptides [41][42].

Bentley et al. [43] investigated the effect of a poloxamer 407 base containing lecithin or urea on the dermal penetration of hydrocortisone acetate (HCA, an analog of the natural glucocorticosteroid produced in the adrenal cortex). Tests were conducted in an in vitro model through hairless mouse skin. The transdermal transport of the hormone followed first-order kinetics. Diffusion and retention of HCA in the skin depended on the concentration of the absorption promoters used. Lecithin at a concentration of 8.0% (*w*/*w*) caused retention of seven times more than that of urea at a concentration of 12.0% (*w*/*w*). Lecithin affects the stratum corneum lipid matrix causing disruption of the intercellular lipid lamellar structure. HCA is a lipophilic drug and lecithin deposits the HCA in the skin layers. Urea increases the SC hydration and causes an exfoliative effect. The optimal formulation showed the characteristics desired by the researchers: maximum retention of HCA in the skin and its minimal systemic absorption.

Currently, there is no optimal dermatological preparation containing progesterone on the market because it is metabolised by 5-α-reductase in the skin [44]. However, ready-to-use hydrogel-based vaginal formulations of progesterone are available. Research is currently underway to develop a hydrogel preparation that will ensure the stability of Prog during its passage through the skin [45]. The subject of analysis by Valenta et al. [34] was the evaluation of the effect of permeation enhancers such as propylene glycol, urea and laurocapram on the percutaneous absorption of progesterone (Prog) from carbopol hydroalcoholic gels. The study was performed in vitro, in hairless rat skin or ears of female pigs model. The most effective promoter of absorption was 10% laurocapram.

7. Permeation Enhancement Technologies

In recent years, substances/mixtures of substances have been patented for their suitability in formulating hydrogels containing protein and peptide hormones. The pharmaceutical formulation Testim™ (testosterone), patented by Bentley Pharmaceuticals contains CPE-215® (cyclopentadecanolide). This substance supports the transport of proteins, peptides and low-molecular drugs across natural membranes into the bloodstream. SEPA® (1,3-dioxolanes) increases skin absorption by liquefying lipids in the outer layer of the skin. NexACT® (alkyl-2-[substituted amino]-alkanoate ester, alkanol alkanoate enables fast and efficient dermal absorption of APIs [23]. On the other hand, Ferring Pharmaceuticals Ltd. developed Testavan® using F.A.S.T. (Ferring's Advanced Skin Technology). The formulation includes ethanol, propyleneglycol and diethylenglycolmonoethylether, which increase the bioavailability of testosterone through the skin. In addition, the formulation is applied to the skin using a hands-free applicator, which reduces the risk of secondary transfer of testosterone to other parts of the body/person [46].

Another study [47] investigated the effect of albumin (Alb) added to glycerol hydrogel on the permeation of corticotropin (ACTH). It was found that, depending on the amount of albumin used, it can delay or increase the

hormone release process. The highest efficacy was obtained using Alb at a concentration of 15 mg/g in a 1:1 ratio to ACTH. Albumin can influence the increased transdermal absorption of ACTH.

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