PENETRATION ENHANCERS IN CURRENT PERSPECTIVE

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ABSTRACT

The advent of transdermal approach led to overcoming drawbacks of conventional dosage forms where skin being the only barrier to delivery of drugs through transdermal route. The role of penetration enhancers thus becomes commendable as they reversibly alter permeation characteristics of skin assisting transdermal devices in transporting drugs across skin. Sulfoxides, azones, pyrorroidones, alcohols and alkanols, glycols, surfactants, and terpenes are the commonly used penetration enhancers. This review is aimed at comprehensively describing effect of various penetration enhancers on drug permeation across skin through transdermal route which have been used in recent studies and reporting thepenetration enhancer that best improves the drug flux.

Keyword: Penetration enhancers, transdermal, permeation, skin

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1. Introduction

Transdermal drug delivery system has gained more interest of researchers as well as public owing to its advantages over traditional dosage forms (tablets and capsules) like, avoidance of presystemic metabolism, sustained release of drugs from transdermal device, minimum adverse effects, patient compliance, etc.(1) But skin is considered to be the barrier which hampers direct entry of drugs from transdermal device.(2) So, needless to say it becomes essential to alter skin permeation characteristics reversibly by use of penetration enhancers to allow passage of drugs across it without causing much damage like irritation.(3,4) Thus, it is imperative to study structure of skin and transport mechanism of drugs through skin before explaining penetration enhancers and its current state of the art. The review will provide effect of various penetration enhancers on drug permeability as studied in some recent studies have been reported in this article.

2. Structure of skin

Skin tissue of human body acts as a barrier against invading infections and restricts entry of drug molecules across it.(5) These properties of skin should be considered while designing transdermal patch with possibility of permeation of small drugs only with small daily dose.(6) Following are layers of skin:
2.1 Stratum corneum
This layer is outermost layer composed of a nucleated corneocytes arranged in layer of lipids. It is keratinized layer. The lipid layer frames barrier layer hydrophobic extracellular layer and underlying hydrophilic cells.(7)

2.2 Viable epidermis
It is that layer which underlies beneath stratum corneum and above dermis. It is constituted up of stratum granulosum and stratum basal layers. The cells from stratum basale continuously divide, and move to the surface after keratinization.(8)

2.3 Dermis
It is innermost layer of skin. Actually, it forms mesh like structure made up of connective tissues like collagen, elastic tissue, nerve endings, hair follicles and sebaceous glands. It performs function of protection of underlying and at the same time maintaining homeostasis. It is hydrophilic layer. It consists of 90% water. Blood vessels present here which travel through epidermis take substances with them.(9)

3. Possible mechanisms of drug permeation through skin

3.1 Drug permeation into stratum corneum
The movement of drugs into stratum corneum occurs based upon the partitioning behavior where partitioning of lipophilic molecules is favored. (10)

3.2 Movement of drugs through stratum corneum
The possible pathways to pass through stratum corneum are:
- Intercellular (paracellular) pathway
- Transcellular (intracellular) pathway
- Transappendageal (shunt) pathway(11)

4. Penetration enhancers
These are substances which may partition into stratum corneum and alter its composition in order to reversibly decrease barrier of permeability to drugs without damaging cells significantly.(12) The use of these compounds is aimed at improving permeation of drugs. Laurocapram or azone is considered first compound to be dedicately developed as penetration enhancer.(13)

Table 1 gives comprehensive idea about most suitable transdermal penetration enhancer for obtaining maximum flux of drug in various studies by researchers.

4.1 Mechanism of action penetration enhancers
They act via one of the following way:
- Disruption of lipidic structure of skin
- Interacting with intercellular proteins
- Enhancing partitioning of drug molecule or solvent into stratum corneum.(14)
<table>
<thead>
<tr>
<th>Model drug used for study</th>
<th>Penetration enhancers employed in study</th>
<th>Penetration enhancers with which maximum flux of drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td>d-limonene and oleic acid</td>
<td>d-Limonene 15% v/v</td>
<td>(15)</td>
</tr>
<tr>
<td>Galantamine</td>
<td>d-limonene, terpineol, borneol, oleyl alcohol, labrafacipohile, caproyl 90, propandiol, laurolglycol FCC\textsuperscript{TM}, docyloleate, octyldecanol, oleyl alcohol+oleic acid, d-limonene+oleic acid (all penetration enhancers in concentration of 5% w/w each )</td>
<td>d-limonene+oleic acid</td>
<td>(16)</td>
</tr>
<tr>
<td>Silver nitrate nanoparticles</td>
<td>4% tween, 20% propylene glycol, 20% polyethylene glycol, 4% sodium lauryl sulfate</td>
<td>4% sodium lauryl sulfate</td>
<td>(17)</td>
</tr>
<tr>
<td>Hydralazine Hydrochloride</td>
<td>10% Azone, isopropyl myristate (10,15 &amp; 20%), and 10% menthol</td>
<td>15% isopropyl myristate</td>
<td>(18)</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>tween80 (1, 2.5 &amp; 5%), N-methyl pyrrolidone (5,10 &amp; 20%), laurocapram (Azone\textsuperscript{(R)})(1, 2.5 &amp;5%), transcutol P (5,10 &amp; 20%), terpineol(2.5, 5 &amp; 10%), and cineole (1,2 &amp; 5%)</td>
<td>5% cineole</td>
<td>(19)</td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>capsaicin, dimethyl sulfoxide (DMSO), andN-methyl pyrrolidone (NMP), 1-8-cineole (all 50 mg each)</td>
<td>1-8-cineole</td>
<td>(20)</td>
</tr>
<tr>
<td>Tamoxifen citrate</td>
<td>5% dill oil, 5% coriander oil, 5% lemon oil</td>
<td>5% dill oil</td>
<td>(21)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>span-60 (0.5 mL), dimethyl sulfoxide (DMSO) (0.5 mL), glycerine(0.5 mL)</td>
<td>span-60 (0.5 mL)</td>
<td>(22)</td>
</tr>
<tr>
<td>Labetalol Hydrochloride</td>
<td>turpentine oil, dimethyl formamide (DMF), menthol, dimethyl sulfoxide (DMSO), pine oil, and 2-pyrrolidone</td>
<td>dimethyl sulphoxide (10% v/v)</td>
<td>(23)</td>
</tr>
<tr>
<td>Propofol</td>
<td>Propylene glycol (5,10,20,30 % w/w), isopropyl myristate (10,20,30,40 % w/w), macrogol (5,10,20,30 % w/w), menthol(2.5,5,7.5% w/w), d-limonene (5,10,15,20% w/w), oleic acid (2.5,5,7.5%</td>
<td>5% (w/w) menthol+10% (w/w) propylene glycol</td>
<td>(24)</td>
</tr>
<tr>
<td>Drug</td>
<td>Penetration Enhancers</td>
<td>Composition</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>dimethyl sulphoxide (DMSO), isopropyl myristate (IPM), sodium lauryl sulphate (SLS), tween 20, myristic acid, lauric acid, capric acid, tween 80, span 80, thyme oil, palmarosa oil, pe-titlgrain oil, basil oil, oleic acid</td>
<td>oleic acid</td>
<td>(25)</td>
</tr>
<tr>
<td>Bupranolol</td>
<td>2-pyrrolidone (2% w/v), 1-methyl-2-pyrrolidone (2% &amp; 5% w/v) and propylene glycol (10 &amp; 30%), menthol (2.5 &amp; 10% w/v)</td>
<td>Pyrrolidones and menthol</td>
<td>(26)</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>propylene glycol, polyethylene glycol 400, oleic acid, isopropyl myristate</td>
<td>oleic acid, propylene glycol</td>
<td>(27)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>oleic acid, propylene glycol, lemon oil and aloe vera (2 mL each)</td>
<td>oleic acid</td>
<td>(28)</td>
</tr>
<tr>
<td>Tizanidine hydrochloride</td>
<td>Span 20 and DMSO</td>
<td>Span 20 (15% w/w)</td>
<td>(29)</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>isopropyl myristate (IPM), dimethyl sulfoxide (DMSO), span20, Tween 20 and eucalyptus oil (10% w/w)</td>
<td>isopropyl myristate</td>
<td>(30)</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>Span-20 and d-limonene</td>
<td>d-limonene</td>
<td>(31)</td>
</tr>
<tr>
<td>Captopril</td>
<td>oleic acid, dimethyl sulfoxide (DMSO) and dimethyl formamide (0.25 mL each)</td>
<td>oleic acid</td>
<td>(32)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Geraniol, Isopropylmyristate (IPM), Lauricacid, Limonene, N-methylpyrrolidone, Oleic acid, Sodiumlaurylsulfate, transcutol P, tween 20 (1% w/w)</td>
<td>Isopropylmyristate (IPM) + limonene</td>
<td>(33)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Turpentine oil, eucalyptus oil, peppermint oil (15% each)</td>
<td>eucalyptus oil</td>
<td>(34)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>eucalyptus oil, transcutol P, DMSO, d-limonene (5% w/w)</td>
<td>eucalyptus oil</td>
<td>(35)</td>
</tr>
</tbody>
</table>
4.2 Concerns related to penetration enhancers

It is now established that penetration enhancers do improve permeation of drugs across skin but study of mechanism of action of many such compounds suggests that while improving penetrability of drugs via disruption of skin may cause toxicity. Amino acid based amphiphiles exhibit low toxicity and tolerable dermal irritation.(36,37) Penetration enhancers which alter lipids and destroy proteins in skin cause skin irritation whereas fatty acids, surfactants are compounds which improve permeability without much skin irritation.(38) It has been established in studies that there is not direct relation between potency and enhancer’s irritation.(39)

5. Conclusion and Future prospects

From the literature study, it becomes clear that penetration enhancers play a vital role in transdermal drug delivery. So, selection of an appropriate potent penetration enhancer is necessary to make a clinically and commercially successful transdermal patch.

All the recent explorations on transdermal patches reported in this review have yielded various different combinations of penetration enhancers which may provide best results in reported concentrations may serve as ready reference for the future researchers along with possibility of exploration of new enhancers which may be inexpensive so as to counter cost issues of transdermal patches and at the same time they should not pose problems to skin like skin irritation.

6. Bibliography


