A CONCISE OUTLINE ON INNOVATIVE PERMEATION ENHANCERS IN TRANSDERMAL DRUG DELIVERY APPROACH

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ABSTRACT

The transdermal drug administration system represents a potent substitute for administering medications orally and is also designed to offer a substitute for hypodermic injections. Presently, three generations of penetration enhancer to permeate through skin are available. 1st generation embraces chemical approaches and pertain to augment the efficacy of the drug transferred across the integral skin, 2nd generation encompasses physical permeation technologies and 3rd generation consists of microneedle and needleless penetration enhancers. There is renewed interest in transdermal drug delivery. This review focuses on some existing novel approaches and the additive upshot of techniques for increasing the permeation of drugs via skin penetration. By using the right methods, drug carriers, or certain chemical agents, it is important to cause the stratum corneum to change physically or biomolecularly.

Keywords: Transdermal, skin, barrier, penetration enhancers, penetration enhancing techniques, generations.

INTRODUCTION

"TRANSDERM-SCOP" was the earliest transdermal patch of an antiemetic medicament, containing scopolamine, which was endorsed by the FDA in 1979. As of now, transdermal medication conveyance is a standout amongst the most encouraging strategies for medication application. The transdermal route offers a few favorable circumstances over customary delivery system, for example, infusions and tablets besides, escaping first-pass digestion. Percutaneous retention includes the entry of medication from surface of the skin to stratum corneum (SC) affected by a fixation slope and its ensuing transport from the SC to the epidermis, dermis and systemic circulation. Further, the skin carries a distinct barrier to puncturing of particles. The SC gives the best protection from entrance and also rate-limiting advance to percutaneous ingestion. Permeation enhancers (PEs) encourage the assimilation of penetrant across the skin by briefly enhancing skin permeation. These materials should, ideally be non-irritating, non-toxic, pharmacologically inert, compatible with medication as well as excipients and possess excellent dissolving qualities. A single PE cannot have all the required properties. This review article endeavors to characterize PE and explain system activity; this will assist in deciding appropriate enhancer(s) intended for transdermal delivery of medications. The review discusses about a couple of vital saturation enhancers utilized in transdermal medication delivery. The transdermal route offers a non-invasive option in contrast to parenteral, subcutaneous, and intramuscular infusions and is appropriate for patients with motion sickness or nausea, etc. But there are some limitations in the transdermal route as it causes erythema, tingling and local edema. Moreover, high M.W. drugs (>500Da) are usually difficult to penetrate through SC, while drugs possessing low or higher partition coefficient fail to achieve systemic dissemination. The drug should possess certain attractive physicochemical characteristics for infiltration through SC and the quantity essential for restorative is over 10 mg day⁻¹, else the transdermal delivery will be exceptionally troublesome, even if certainly feasible. The different sites of the skin have variation in absorption efficiency, adherence difficulty in certain types of skin like excessive oily skin and challenges in time duration for which a patch can be applied on any area due to change in permeability (usually not more than 7 to 10 days). The review of various penetration enhancers used in transdermal patch formulation presents how the subject is approached for the development of suitable formulations.

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Table I summarizes the diverse penetration enhancers used in the development of transdermal formulation[^1][^35].

**CHEMICAL ENHANCERS**

Chemical penetration enhancers are the 1st generation of penetration enhancers; their purpose is to use methods that maximize medication solubility in the skin or disturb membrane structures to reversibly alter the stratum corneum’s barrier properties. Drugs can enter the body through different skin-penetration pathways: non-polar, polar, and non-polar/polar[^6]. Causing protein conformational exchange or solvent swelling, changing the rigidity of lipid structure, and fluidizing the crystalline channel are essential for changing polar pathway; increasing the diffusion rate results in changes in non-polar pathway[^46][^57].

**Water, alcohol, glycerol and glycerides**

Water serves as the most frequently employed penetration enhancer; permeation of other hydrophilic and lipophilic permeants is increased via hydration of the stratum corneum. About 15-25 % of the dry weight of human stratum corneum is made up of water. Improved skin hydration may also cause stratum corneum’s dense structure to expand and eventually open, which would augment penetration. However, increased hydration may not always be the cause of the growth in permeation[^40][^43]. Ethanol enhances diversity of loose sulfhydryl groups of keratins within the stratum corneum protein and functions as a penetration enhancer by removing significant lipid contents from stratum corneum[^1]. Normally, ethanol pretreatment of skin will improve permeability of wide range of drugs with varying lipophilicity[^48]. Triethanolamine salicylate from a hydrophilic emulsified base and ketoprofen from gel-spray will permeate readily in presence of ethanol[^59]. Additionally, efficient permeation promoters include short-chain glycerides, for instance, tricaprylin and ethanol are combined to create a solvent derivative[^60]. Papaverine was better distributed across the skins of hairless rats when glyceryl monocaprylate was used[^61][^62]. Papaverine hydrochloride was able to penetrate the skin more readily due to Sefsol® 318’s medium chain glycerides improving the fluidity of stratum corneum’s lipoidal membrane[^36][^62].

**Urea, sulfoxide and similar compounds, and azones**

Urea encourages transdermal penetration by hydrating the stratum corneum together with utilizing the development of hydrophilic diffusion modes inside the barrier. When combined with a polar moiety and an extended chain alkyl ester group, cyclic urea permeation enhancers are non-toxic as well as biodegradable[^63][^64]. Dimethyl sulfoxide (DMSO) can enhance absorption of drug substances by interacting with lipidic contents of stratum corneum and changing the shape of intercellular keratin from α-helical to β-sheet[^43][^65]. Azones disrupt lipid bilayers, cause lipid solubilization and accelerate fluidization of lipids, all of which contribute to an increase in permeability of diverse drugs, for instance methadone, indomethacin, propranolol hydrochloride and 5-fluorouracil[^66][^67].

**Oxazolidinones, terpenes, terpenoids, vital oils and surfactants**

According to several studies, oxazolidinones localise the transport of various active components in the skin’s layers, including retinoic acid and diclofenac sodium[^67][^68]. Eucalyptol dramatically increases the flow of lipophilic (indomethacin) and hydrophilic (urea) compounds. Terpenes have been used therapeutically for a variety of reasons, including carminative, antispasmodic, aromatic and other properties, but some studies have suggested that they may also increase percutaneous absorption[^66]. Ketoprofen’s percutaneous penetration through two complexes including d-limonene as well as oleic acid was studied. d-Limonene had a higher rate of percutaneous absorption, but it also led to more skin injury. The increased concentration of d-limonene (20%) in the case of verapamil hydrochloride becomes effective in greatly improving its permeability. A 2 % concentration of the long chain sesquiterpene nerolidol increased enoxaparin sodium permeability by twofold. Using samples of human skin, researchers examined properties of another unsaturated sesquiterpene, α-bisabolol, for improving penetration of model drugs i.e., 5-FU and triamcinolone acetonide[^67][^70]. Surfactants are amazing transport enhancers due to their ability to denature keratin and solubilize/extract lipids. Non-ionic surfactants are frequently perceived as safe, however anionic and cationic surfactants can damage human skin. Surfactants studied include nonoxynol surfactants as non-ionic, cetyltrimethylammonium bromide as cationic, sodium lauryl sulphate as anionic, and dodecyl betaine as zwitterion[^42-43][^67][^69][^71].

**Miscellaneous**

Phosphatidyl glycerol derived compounds amplified bifonazole deposition in the skin along with tenoxicam percutaneous permeation, while phosphatidyl choline variants increased erythromycin percutaneous permeation[^64]. Indomethacin has been studied by employing six derivative products of phosphatidyl glycerol i.e. PGE (from egg yolk), PGS (from soyabean),...
Table I: Review of various penetration enhancers in transdermal patch formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>Penetration enhancer</th>
<th>Plasticiser</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cissus quadrangularis</em> extract</td>
<td>(HPMC E -15)</td>
<td>DMSO</td>
<td>Dibutyl phthalate11</td>
</tr>
<tr>
<td>Anti-anxiety drug</td>
<td>Eudragit® RS100, (HPMC E15)</td>
<td>--</td>
<td>Dibutyl phthalate12</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>Duro-Tak®, Polyisobutylene,</td>
<td>--</td>
<td>Mineral oil13</td>
</tr>
<tr>
<td>Fenoterol hydrobromide</td>
<td>Duro-Tak, Scotchpak™</td>
<td>Azone</td>
<td>Propylene glycol14</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Scotchpack™</td>
<td>--</td>
<td>Ethyl dibutyl phthalate glycerine15</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>CA/PVP</td>
<td>Azone</td>
<td>Fiber mats16</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>HPMC, PVA, PVP, Eudragit® RL-100</td>
<td>DMSO</td>
<td>Propylene glycol17</td>
</tr>
<tr>
<td>Diltiazem hydrochloride</td>
<td>Eudragit® RL 100: Damar Batu gum</td>
<td>DMSO</td>
<td>Damar Batu gum18</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>HPMC and PVPK 30</td>
<td>Isopropyl myristate</td>
<td>PEG, PG19</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Duro-Tak® 87-4098, ScotchPak®</td>
<td>Isopropyl myristate</td>
<td>Oleic acid20</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Ethyl vinyl acetate, Eudragit®</td>
<td>--</td>
<td>Carbon dioxide at 450 psi21</td>
</tr>
<tr>
<td>Lidocaine hydrochloride</td>
<td>Poly (sodium methacrylate, methylmethacrylate)</td>
<td>Azone, Propylene glycol, Isopropyl myristate</td>
<td>PEG 400, glycerine, sorbitol, sodium chloride22</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Duro-Tak®</td>
<td>Azone</td>
<td>Propylene glycol, Isopropyl myristate23</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Acrylic adhesive (87-900A) Polyoxyethylene cetyl ether</td>
<td>Propylene glycol monolaurate, isopropyl myristate</td>
<td>Co Tran™24</td>
</tr>
<tr>
<td>S-Amolidipine</td>
<td>Duro-Tak® 87-2677, 87-4098,87-9301</td>
<td>Isopropyl myristate, l-menthol</td>
<td>PEG-40025</td>
</tr>
<tr>
<td>Ketotifen fumarate</td>
<td>HPMC, Ethyl cellulose</td>
<td>Dimethyl sulfoxide</td>
<td>Di-butyl phthalate in chloroform and menthol26</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Duro-Tak® 87-2677, 87-2852, 87-4098</td>
<td>Isopropyl myristate, l-menthol</td>
<td>Polyethylene glycol 40027</td>
</tr>
<tr>
<td>Gestrodene &amp; ethinylestradiol</td>
<td>Eudragit® RL100, Eudragit® RS 100, Eudragit® E 100</td>
<td>Isopropyl myristate</td>
<td>Polyethylene glycol -40028</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>HPMC, PVP, Eudragit® RS100</td>
<td>Dimethyl sulfoxide</td>
<td>Polyethylene glycol29</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>Water insoluble but permeable polymer</td>
<td>--</td>
<td>Sugar fatty acid ester30</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Duro-Tak® Scotch Pak® 1022</td>
<td>Isopropyl myristate</td>
<td>PEG -400, propylene glycol (PG), glycerine triacetate31</td>
</tr>
<tr>
<td>Isosorbide dinitrate &amp; bisoprolol</td>
<td>Acrylic resin composition</td>
<td>Azone, Tween 80</td>
<td>Glycerol32</td>
</tr>
<tr>
<td>Pinacidil</td>
<td>Eudragit® RL 100, PVP</td>
<td>Dimethyl sulphoxide</td>
<td>Polyethylene glycol33</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Eudragit® RL 100, PVP</td>
<td>PEG-400, Tween 60</td>
<td>Propylene glycol34</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Eudragit® E, Eudragit® RL Scotch Pak™</td>
<td>--</td>
<td>PG35</td>
</tr>
</tbody>
</table>
dimyristylphosphatidyl glycerol (DMPG), dipalmitylphosphatidylglycerol (DPPG), distearylphosphatidyl glycerol (DSPG) and dioleylphosphatidyl glycerol (DOPG). In addition to this, five derivative products of phosphatidylcholine i.e., PCE (from egg yolk), PCS (from soya-bean), dinoleoyl PC (DLPC), dioleyl PC (DOPC) and hydrogenated PC (HPC), together with derivatives of phosphatidyl ethanolamine have also been explored for indomethacin\textsuperscript{54, 72}.

A related composition of clonazepam using methyl-\(\beta\) -cyclodextrin accelerated the drug’s release contour through Carbopol hydrogel across cellulose nitrate membrane, and an inclusion complex of piroxicam made with \(\beta\) -cyclodextrin amplified drug flux cases throughout the shaved mouse skin\textsuperscript{72-73}. Permeation of hydrocortisone from its suspension was increased by applying N-dodecyl-1-amino acid methyl ester and N-pentyl-N-acetyl prolinate to excised hairless mouse skin 1 h before drug treatment. \(N\)-pentyl-\(N\)-acetyl prolinate is significantly safer at low dosages and boosts flux of benzoic acid through the human cadaver skin. Theophylline’s transdermal permeation in both oily as well as aqueous conditions was improved by the omega amino acid esters octyl-6-aminohexanoate and decyl-6-aminohexanoate, respectively\textsuperscript{49, 74}. Acid phosphatase, phospholipase A2 and triacylglycerol hydrolase (TGH) were three epidermal enzymes that also increased the flux of both mannitol and benzoic acid. Papain pre-treatment of the skin led to reversible changes in the stratum corneum’s protein structure that increased the penetration of proteins of diverse molecular weights, with the effect failing with larger molecular weight. Despite the limited efficacy of individual chemical enhancers, combinations of enhancers present new prospects in transdermal formulations\textsuperscript{49, 75}.

**PHYSICAL ENHANCERS**

These techniques involve the usage of more recent devices which might be designed to avoid skin barrier for immediately delivering the drug to the dermis by piercing pores and skin mostly under supervision. Iontophoresis, electroporation, ultrasound, microporation, radiofrequency and microneedles are the few techniques of the physical approach as described in Fig. 1\textsuperscript{56, 59, 76-77}. 

![Fig. 1: Various physical techniques describing penetration through skin\textsuperscript{56, 59, 76-77}](image-url)
Iontophoresis

Iontophoresis is a second-generation electrically assisted technique to supply precise medicine dosage via skin along with control of its desired therapeutic plasma level. Iontophoresis complements transdermal drug delivery by using ion electric discipline interplay, the flow of electric current and electrophoresis. The ionization of the medication is managed by using pH, density, molecular weight, the concentration of drug, physiology and and wavelength. Pilocarpine transport is an FDA-approved application of iontophoresis to treat hyperhidrosis by triggering sweating related to cystic fibrosis diagnostic test.

Electroporation

The introduction of bigger macromolecules, including insulin, heparin, DNA, oligonucleotides and microparticles, has also been accomplished using a combination of electroporation and chemical enhancement technique. Electroporation is the development of aqueous pores within the lipid bilayer with the use of short electrical pulses that range in voltage from 100 to 1000 V cm⁻¹. For charged molecules, flux increases up to 10,000-fold have been observed. The number of medications that can be applied transdermally increases when electroporation is employed alone or in conjunction with other enhancing procedures.

Sonophoresis / phonophoresis

In sonophoresis, a second-generation permeation enhancer, drug molecules are moved through the skin while being affected by ultrasound, which causes gaseous cavities to form inside the intercellular lipid and causes disruption of the skin. Low-frequency or electricity ultrasound is used for lithotripsy, liposuction, cataract emulsification, dental descaling, ultrasonic scalpels (18-100 kHz) and cancer treatment. High-frequency or diagnostic ultrasound is used in medical facility imaging (3-10MHz); medium-frequency or healing ultrasound is used in bodily remedy (0.7-3.0 MHz); and low-frequency or electricity ultrasound is used in body remedy (18-100 kHz). Also used are shock waves that are not ultrasonic, with stress amplitudes between 300 and 1,000 bar and short duration. Additionally, 1-10 s have been used to improve transdermal medication delivery.

Microneedles

When microfabricated technology allowed for manufacturing of solid microneedles for skin pretreatment to promote skin permeability, third generation penetration enhancers for microneedles entered the spotlight. Currently, transdermal administration is accomplished via arrays of minuscule needles. These microneedle arrays can improve permeability by orderliness for small medicines, big macromolecules, and nanoparticles by creating a conduit for drug transport across the stratum corneum after being inserted into the skin. Proteins and DNA are included in the microneedle-based vaccine delivery system to target Langerhans cells. Silicon needles with a diameter of a few microns are used in microfabricated microneedles technology. This technology enables the delivery of medicinal substances like insulin into the skin. The swellable silk fibroin microneedle for TDDS exhibits minimal distortion and controllable swelling characteristic and can easily puncture porcine skin resulting in strong transdermal drug kinetics and finally accumulating release ratio as compared to non-swelling hydrogel microneedles.

Needleless injection

The third-generation permeation enhancers, known as liquid jet injections, use a high-speed jet to pierce the skin then administer medication exclusive of the usage of a needle or throbbing sensation. The basic way to create pressure is by utilizing either a gas (helium, carbon dioxide or nitrogen). Disposal Cartridge Jet Injectors (DCJIs) and Multi-Use Nozzle Jet Injectors (MUNJIs) are the two primary classes of liquid jet injectors. A needle is put just a few millimeters into skin, and a micro-infusion pump housed inside a sizable “patch” adhered to the skin rashes medication solution into the skin at controlled rates. This method has been used to administer morphine to human test participants. Intra-Ject®, ImplaJect®, mechanical perturbation, jet syringe, Macro Flux™, Crossject, magnetophoresis, mechanical perturbation, and laser ablation are a few of the needle-free injectors currently in use.

FUTURE ASPECTS AND THE SYNERGISTIC IMPACT OF ENHANCERS

Although each of the above-discuss permeation-enhancement techniques has been proved to improve transdermal medication delivery, their combination is frequently still more efficient. Combining several boosters can lessen required “dose” of every single enhancer in addition to enhancing transdermal transport in a potentially synergistic way. Despite the benefits that come from combinations, most commercial efforts have focused on single enhancers, mainly because it is difficult to combine different technologies. Many different compounds, such as polyethylene glycol, linoleic acid, isopropyl myristate and sodium lauryl sulphate have been used to show how chemicals and
ultrasound work in harmony. The goal of this synergy is to boost the enhancer’s penetration and dispersion in the stratum corneum because of ultrasound. It has also been shown that ultrasound and ionophores work together synergistically to administer heparin trans-dermally. The substances which are thought to either widen or stabilize pores include urea, polysaccharides (heparin and dextran) and sodium thiosulfate. Iontophoresis and electroporation have been shown to work together for transdermal distribution of drugs.

Chemical enhancers have only limited success; chemical enhancer combinations offer fresh options for transdermal preparations. Transdermal medication delivery is once again receiving attention because of improvements in physical permeation enhancement technologies including microfabrication.

CONCLUSION

The transdermal patch has developed into a trusted technology over the past 20 years which provides many important clinical advantages over alternative dosing modalities. Large drug molecules were difficult to distribute through the skin in the past. To date, numerous chemical and physical techniques have been employed to improve the effectiveness of material transfer over intact skin. Transdermal medication delivery is now again gaining popularity because of improvements in physical permeation augmentation technologies.

REFERENCES