TECHNICAL REVIEW

SKIN BARRIER CHALLENGES IN DERMAL AND TRANSDERMAL DRUG DELIVERY SYSTEMS

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***ABSTRACT**: Transdermal drug delivery is an attractive and complicated field. There are various transdermal delivery systems already existing on the market. Nevertheless, the transdermal market is restricted to only some limited drugs that can penetrate through the deeper layer of skin and causes lower irritation. Some novel techniques can overcome skin barrier to enhance skin permeation of drugs and decrease skin irritations at the same time which can be used for hydrophilic and hydrophobic compounds and macromolecules delivery. Based on available results of clinical studies for transdermal drug delivery of so many therapeutic drugs, there is a wonderful chance for transdermal delivery of drugs in future.*

Key words: transdermal drug delivery, nano formulation, skin enhancer, Stratum corneum

INTRODUCTION

Advancements in new techniques are leading to so many medicines that can be administrated transdermally, such as general hydrophobic small molecule medicines, hydrophilic medicines and also macromolecules [1]. Transdermal drug delivery is an attractive model due to the noticeable advantages compared with all the other delivery routes. Transdermal delivery proposes simple painless administration for the patients. It prevents typical dosing administration and also plasma peaks related to oral administration and injections to sustain steady drug concentration as well as medicine with a short half-life could simply be delivered [2]. And this results in improved patient conformity, particularly whenever long-term medication is needed, such as chronic pain medication and also smoking cessation treatment [3]. Prevention of hepatic first-pass metabolic process as well as the GI tract for improperly bioavailable medicines is the other benefit of transdermal delivery [4]. Elimination of such first-pass impact enables the quantity of medicine taken to be less, and also risk-free in hepato-compromised patients from side effect [5]. Transdermal models are in general affordable in comparison with any other treatment options per month; patches are manufactured to deliver medications from one day to a week. Another benefit of transdermal delivery is that several dosing, on-demand or even variable-rate delivery of medicines is feasible with the modern programmable systems and provides more advantages to the ordinary patch dosage forms [6]. That is why transdermal products market is increasing.

There are basically two important pathways through which medicines are able to pass through the skin and enter the systemic blood circulation. The transcellular pathway is the most direct route that the drug can pass through the skin. Even though this is the quickest pathway, the medicines come across considerable resistance to permeation [6]. That is due to the fact that the medicines must pass the lipophilic membrane of every cell, consequently the hydrophilic cellular stuffs including keratin, thereafter the phospholipid bilayer of the cell once again [7]. Such sequence of procedures is continued several times to get out of the stratum corneum.

Intercellular route is the other more popular route through the skin. Medicines passing through the skin via this pathway must cross through tiny areas among skin cells, resulting in a more indirect pathway [8]. Even though the depth of the stratum corneum is basically around 20 µm, the specific diffusional route of nearly all molecules passing through the skin is 400 µm. The 20-times raised in the main route of permeating substances considerably decrease the rate of drug penetration. A third route to go through the Stratum corneum layer is by using tiny microchannels designed by a medical micro-needling tool [9]. The micro-needling strategy is in addition found as 'the vaccine of the coming future.

Advantages of transdermal administration

- It can ignore gastrointestinal medicine absorption troubles, the result of gastrointestinal pH, enzymatic action, and also medicine interactions with food stuff, as well as other orally taken medicines [10].
- They act as a better alternative to oral administration of medicine which may, if the pathway is inappropriate cause nausea and diarrhea [10].
- They prevent the first-pass influence , which is , the primary route of “s” medicine throughout the systemic and also portal circulation following gastrointestinal absorption , potentially eliminating the activation via digestive and liver enzymes [11].
- They are non-invasive, avoiding the problems of Parenteral therapy [12] .
- They can offer extensive treatment with a single administration , enhancing compliance over other dosage forms requiring more frequent dose administration [1].
- The drug effects having short half-life is expanded via the drug reservoir in the medicinal delivery system and its actual controlled release [13].
- Medicine treatment may be accomplished fast by removing it from the skin [14].
- However, transdermal drug delivery has some weaknesses that makes some limitations for transdermal delivery [15].

Disadvantages

- Only certain potent medicines are appropriate candidates for transdermal delivery due to the natural restrictions of the impermeability of the skin [16].
- The delivery system is unable to be applied for drugs needing high blood levels [16].
- Following transdermal delivery application might be costly [17].

Physical methods

The earliest common method to overcome the skin barrier physically is to use hypodermic needles [18]. Mostly it is the only promising technique of delivery for unstable compounds and the medicines which absorb weakly. Generally, solution of medicine is pressured under piston in direction toward tissue or bloodstream. This kind of medicine administration ends up with effective delivery of large compounds. However, it requires mechanical skin perforation utilizing a needle, which results in pain and trauma. Based on as Hamilton mentioned, phobia of needle is a medical situation that influences approximately 10% of the people [19]. This condition is a critical issue in the medical-related system that a person having needle phobia prefer to keep away from medical care. Several alternative physical skin techniques like jet injections, dermabrasion, laser, microneedles, iontophoresis, electroporation, ultrasound and mixtures of the earlier mentioned have been investigated [9, 20]. Such strategies focus on designing the delivery systems which are friendlier to users like sustained drug delivery systems.

Lipids and stratum corneum

The hierarchical configuration of lipid provides the barrier to skin for penetrating compounds. Three main pathways via which the compounds penetrate through the skin: transcellular, intercellular and appendaegeal pathway. [1]. The diffusion of this pathway prolongs the length of diffusion noticeably and enhances drug permeation significantly. The transcellular pathway is more direct way; nevertheless, drug substances have to cross both hydrophilic as well as lipophilic domains and come across serious penetration resistance. Lately, that penetration via appendaegeal pathway can be considered as an ideal route, which use just 0.1 % of the all skin area. Hair follicles as well as sweat glands and microlesions in the stratum corneum were recommended as vertical paths for skin penetration. So, it is really critical for transdermal drug delivery to improve newer permeation improving strategies to increase the number of drug substances that can be utilized in TDD. A variety of chemical, physical and biological substances permeation improving techniques have been designed. Such techniques consist of utilizing the chemical solvent, iontophoresis, electroporation, sonophoretic, microneedle application, skin shrinkage, heating and prodrug [2]. Out of all, combination of chemical solvent into the formulation is the easiest route without using extra physical tools [2a].

Such pores enable compounds applied to the skin to pass over and easily reach deeper layers of skin. This particular technique can extract interstitial fluid to determine glucose amounts in diabetic patients to be effective in augmenting transdermal flux of hydrophilic and hydrophobic substances [3]. Microneedles turned out to be one of the main enhancement strategies in the transdermal drug delivery area after improvements in microfabrication strategies were manufactured lately. Microneedles provide painless and efficient skin permeabilization [4]. Various designs of microneedle have been utilized in in vitro experiments. Solid microneedles are employed to pierce [5].

Jet injections consist of liquid or solid particles delivery influenced by high-pressure accelerators throughout the stratum corneum. The principle of drug delivering jets is reported for the first time in 1940 [3]. In spite of this, first attempts of using this technology translated into limited success. Technology advancements then facilitated the construction of more helpful tools driven by compressed helium. It confirmed great effect in insulin delivery for diabetic patients. This approach is like the hypodermic injection which enables hasty delivery of huge amounts of medicine, and has caused enhanced patient compliance [6]. Weaknesses of jet injections consist of a laser which is also able to be employed to thermally ablate parts of the stratum corneum creating pores [3].

Several strategies exist which utilize electric current as an approach to make the skin permeable. Iontophoresis is based on the constant electric current to run charged drug molecules over the skin by means of electrophoresis as well as electroosmosis [7]. Generally it is indicated that iontophoresis basically produces excess electrochemical driving power for drug transport across the skin, to increase skin permeability. Electroporation is the other strategy which relies on utilization of whether short (micro- to milli-second), or high-voltage electrical pulses to generate transient pores in the composition of the stratum corneum [3]. These pores assist the molecules to be transported through the stratum corneum without which it is impossible for the molecules to pass. It is reported that molecules can pass through the skin by electrophoretic diffusion and movement. Some small molecules like timolol as well as larger molecules like oligonucleutides based on in vitro results can prove the efficacy of electroporation. It is reported that synergistic effect can be obtained in combined enhancement strategies. Several combinations which have been investigated involve electroporation–iontophoresis, electroporation–ultrasound, and also microneedle–iontophoresis [8]. The main benefit of transdermal drug delivery is reducing the systemic adverse effects. Nevertheless, drug delivery via such routes can cause different kinds of side effects like skin irritations which need to be considered.

CHEMICAL METHODS

Chemical skin permeation products enable drug to permeate through the skin , by enhancing drug diffusion making it to participate into domains of stratum corneum [1]. Stratum corneum is heterogeneous constructed of keratin ‘bricks’ and intercellular consistent lipid ‘mortar’ properly organized in multilamellar strata. Based upon the characteristics of the medicine such domain can limit the rate of percutaneous permeation. Consequently, it is presumed that the enhanced permeation degree achieved with a provided special enhancer will change between hydrophilic and lipophilic drugs. Numerous strategies of technique are identified: raising fluidity of lipid bilayers in the structure of stratum corneum, intercellular lipids extraction, improved thermodynamic

effect of drug, stratum corneum hydration enhancement, and modification of proteinaceous corneocyte parts as well as others [9]. More in depth explanation of the types of action has been documented. Traditionally, permeation enhancers are classified into numerous groups according to their chemical construction in preference to the process of action [3]. It is partly because of the issues of identifying an initial or combined mode of mechanism required for most of them. Moreover, components from the similar group can make their effect throughout various strategies. Over 300 compounds have been revealed to have epidermal permeability enhancement potential and such number is still rising. Most identified enhancers can be classified as: alcohols (ethanol, pentanol, benzyl alcohol, lauryl alcohol, propylene glycols and glycerol), fatty acids (oleic acid, linoleic acid, valeric acid and lauric acid), amines (diethanolamine and triethanolamine), esters (isopropyl palmitate, isopropyl myristate and ethyl acetate), amides (1-dodecylazacycloheptane-2-one [Azone®], urea, dimethylacetamide, dimethylformamide and pyrrolidone derivatives), hydrocarbons (alkanes and squalene), surfactants (sodium laureate, cetyltrimethylammonium bromide, Brij®, Tween® and sodium cholate), terpenes (D-limonene, carvone and anise oil), sulfoxides (dimethyl sulfoxide) and phospholipids (lecithine). The significance of stratum corneum s hydration is not evaluated completely.

Transdermal drug delivery has been a challenging and attractive topic of the research. New strategies in modern technologies are concentrating on the numerous transdermal drugs consisting of hydrophobic and hydrophilic drugs [10]. Because of variety of benefits in transdermal drug delivery, it has been one of the most desirable routes of drug administration. Transdermal delivery systems (TDS) for the first time in 1970s were entered into the US drug market. The very basic form of transdermal drugs have been used a very long time ago where mustard seed were used as paste after mixing with water and applying to the skin. Such homemade dispersion after applying to the skin can form allyl isothiocyanate [3]. So many researches have been done after that and contributing to the advances in transdermal patches like nicotine. Prausnitz *et al.* have categorized TDSs into some groups. Based on such classification, the first group refers to small, uncharged and lipophilic compounds which are able to be delivered in the therapeutic range via passive diffusion [11]. Such groups consist of the TDS which currently are the most available transdermal drug on the market. However, the development in science and engineering lead to utilized chemical enhancers and other methods like iontophoresis and ultrasound to deliver the other drugs transdermally which was impossible to pass via passive diffusion. This property has been categorized as second group which disrupts the out layer of skin or stratum corneum reversibly to deliver the drug. Lidocaine as a charged compound is the most known example of such group [2a]. The third class of transdermal delivery system is still under research which focuses on targeting the stratum corneum to deliver macromolecules [2a].

Formulation Design

A system of transdermal drug delivery which consists of following constituents:

Physicochemical properties

1. The molecular weight of drug must be less than almost 800 Daltons [2a].
2. The drug should have hydrophilic and hydrophobic affinity in its chemical structure [12]. Extreme partitioning characteristic are not conducive to successful drug delivery via the skin.
3. The drug should have preferably low melting point [13].
4. The drug solution preferably must have pH in the range 4.2 to 5.6 to be in the range of skin pH to avoid damaging the skin [14].

Biological properties

1. The daily effective dose of drug must be some mg per day [15].
2. The half-life t½ of the transdermal medicine should not be long [15b].
3. The drug should not cause irritation or allergy [16].
4. Drugs that are degradable in the gastro intestinal (GI) tract or hepatic first-pass effect that inactivates them are proper candidates for transdermal drug delivery [17].

Polymer

Enhancements in transdermal drug delivery strategy have been fast resulting from the complexity of polymer science that enables polymers to incorporate in TDS. Various polymer compositions make it possible to have different release rate of TDS [18]. The proper polymer should have some properties such as:

1. The polymer should not be reactive chemically [19].
2. The polymer must be stable [20].
3. Physical properties, molecular weight and chemical characteristic of the polymer should enable the diffusion of the drug compound to be at proper rate [21].
4. The polymer must not be toxic. It should be compatible with skin [22].
5. The polymer should be easy to manufacture. It should enable it to incorporate with numerous amounts of active ingredients [23].

Penetration enhancer

A strategy generally studied is the utilizing of chemical penetration enhancers to enhance permeation of poorly skin penetrating compounds. On the other hand, physical forces like intophorosis and phonophoresis can be provided for special medicines [24]. Basically there are three strategies for the penetration improvement.

Chemical strategies based on Barry (1987) consist of:

(1) Lipophilic analogs to be synthesized [25].

(2) To make stratum corneum delipidized [26].

(3) To utilize permeation enhancers as co-administrator [27].

Formulation influence on skin irritation

It has been reported that the formulation utilized to deliver a compound can affect the form and level of skin irritation. For example, hydrogels absorb skin's moisture and cause irritation. Another research which compared the effectiveness and safety of a lotion containing co-administrated with polymeric microspheres showed that such co-administration decreased skin irritation in human beings without any change on its efficacy [28]. Based on such evidences, it was determined that controlled-release schemes can be beneficial in diminishing the irritation caused by applying topical drugs. Based on other reports liposomes have the potential to

diminish skin irritation [29]. The hypothesized mechanisms to reduce skin irritation influenced by liposomes consist of epidermis hydration and the sustained release of compounds, therefore toxic compounds concentrations in the skin will be avoided [30]. For instance, tretinoin co-administrated in liposome form demonstrated reduced skin irritation after applying to the patients [31]. Utilizing a hydrogel or a cream which contains liposome- or microsphere-entrapped compounds has the potential to reduce the skin sensitivity to irritation [32].

Role of drug features in skin irritation

Medicines that manifest moderate-to-severe result in animal irritation studies are generally excluded for further more applications in topical medicines. Thus it is not easy to estimate how much a drug is potent to show irritation effect without doing any test in cell and animal model. Certain studies have been accomplished to determine the characteristics of medicines that might be irritant [33]. Although there is a need to consider that skin treatment in pharmacological tests can cause irritation too [34].

Role of vehicle & devices in skin irritation

Researchers revealed that skin PH is in the variety of 5.4 to 5.9 and is critical to keep skin barrier attribution and resistance to infection and disease [35]. Moreover, skin has buffering ability to accommodate large changes in PH variety [36]. Despite, exterior factors like cleansing solutions, medicines and cosmetic products to the skin can increase pH of its surface and can in addition stimulate skin irritation.

Conclusion and Future perspective

Increasing the usage of novel methods to enhance skin permeation by using some macromolecules or other compounds are the interesting area for transdermal industry. Physical improvement techniques provide substantial enhancement delivery rate of therapeutic components through the skin.

Recently extensive studies and investigations have been undertaken on a variety of them and a new device-based TDS can soon be expected in the market. These new prodrugs may not only help to alleviate skin irritations but would also promote some drugs to reach the therapeutic levels. With the increasing availability of physical permeation enhancement methods and new breakthroughs in topical drug formulation, such as liposomes, microemulsions, nanoparticles and evaporating gels, we can expect a sizeable decrease in the incidence and significance of skin irritation. The recent breakthroughs in chemical permeation enhancer analogs show a significant improvement in limiting cutaneous irritation [37]. These remarkable findings provide great promise for the further development of safe chemical enhancers and a further study on this should be carried in the future.

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