Enhanced Delivery Of Transdermal Drugs Through Human Skin With Novel Carriers

Behzad Ehdaie *

Department of Pharmaceutics, College of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ABSTRACT

Enhancement of drug delivery through human skin is important in modern therapy. The transdermal of drug delivery has gained great interest of pharmaceutical research, as it circumvents number of problems associated with drug administration. The major barrier in transdermal delivery of drug is the skin intrinsic barrier, the stratum corneum, the outermost envelop of the skin that offers the principal hurdle for diffusion of hydrophilic ionizable bioactives. Various new technologies have been developed for the transdermal delivery of some important drugs. Physical and chemical means of crossing the lipophilic stratum corneum, the outermost layer of the skin, are being explored. Some nanocarriers like nanospheres, nanoparticlaes, nanocapsules, lipid nanocarriers, polymers etc., are utilized to facilitate drug through the transdermal barrier. This review associated with nanocarriers, transdermal delivery, toxicology of nanocarriers, interaction and transportation of nanocarriers through skin and deals with the skin structure.
KEY WORDS: Nanocarriers, Skin Physiology, Transdermal Delivery, Toxicology.

1- INTRODUCTION

Novel carrier system used for delivery of drugs having low penetration through the biological membrane mainly skin [1]. Also transdarmal delivery provides methods of increased safety, greater convenience, drug administration, including enhanced efficacy, and improved patient compliance. Over an extended period of time delivering the drug's flow into the bloodstream, transedarmal systems avoid the peak and valley effect of oral injectable therapy. The therapeutically equivalent for the transdermal delivery of certain compounds would be significantly less than the corresponding oral dosage by means of avoiding the first pass metabolism through the gastrointestinal tract [1, 2].

2- Transdermal Drug Delivery

Delivery via the transdermal route is an interesting option in this respect because a transdermal route is convenient and safe which offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, utility of short half-life drugs, minimizing undesirable side effects, improving physiological and pharmacological response, inter-and intra-patient variations, avoiding the fluctuation in drug levels, and most importantly, it provides patients convenience[3]. Some of the greatest disadvantages to transdermal drug delivery are possibility that a local irritation at the site of application and Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation, there are different permeation rates depending on age, site of application and individuals, and also skin diseases can influence it [4].

Transdermal occlusive patches is the current transdermal delivery system which capable to deliver drugs in cases that side effects associated with high peak plasma concentrations or poor compliance oral administration is limited by poor bioavailability, due to the need of frequent administration [5].Occlusive condition is created without the use of adhesive bandages, thereby eliminating sensitivity reactions caused by contact with and removal of the adhesive material [4]. Figure 1 is represented the pathway postulated for the substance's absorption under normal conditions which called transcellular, intercellular and transappendageal [3].The penetration of the drug by both transcellular and intercellular pathways, as well as its interchange between these pathways, is considered.
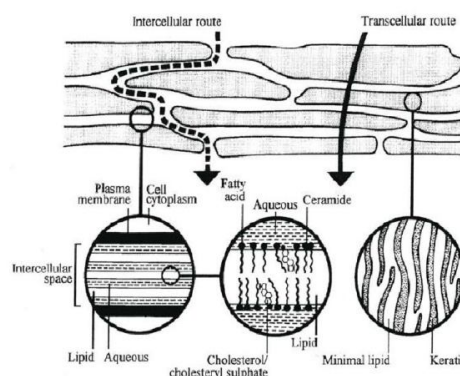

Figure1- Simplified diagram of stratum corneum and two microroutes of drug penetration.

*Corresponding Author: Behzad Ehdaie, Department of Pharmaceutics, College of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. E-mail: ehdaiebehzad@yahoo.com

If the transcellular pathway is predominant, the diffusion involves several partitioning steps into the lipo and hydrophilic domains of the coenocytes and the lipid layers before reaching the viable epidermis [6].The drug for transdermal delivery should be pharmacologically potent and has physicochemical characteristics. The permeation through the skin will be depending on the ionization degree of the drug at physiological and formulation pH, influencing as well its solubility and partition behavior [7].A novel drug carrier system which is composed of lipid ,surfactant and water for enhanced transdermal delivery. A suitable transdermal delivery system will not only provide an adequate drug release from the formulation, but also allow considerable amounts of drug to overcome the skin barrier. And also ensure that the drug will not be inactivated on the skin's surface .By the way ensure a non-irritancy of the skin [8].

3- Physical method to overcome the epidermal barrier

3.1- Electroporation

The transport of charged molecules across human skin can be dramatically enhanced by application of high-strength, pulsed electric fields. This phenomenon is theoretically characterized here in terms of the electroporation of lipid bilayers within the stratum corneum above the transbilayer voltage for which electropores have been observed in single bilayer membranes [9]. Accounting for the size, shape and charge of the transporting molecules, predictions of transdermal molecular flux are made in two electric field conditions. At small field strengths (100 V), representative of standard skin iontophoresis, charged molecules are modeled as transporting through the pre-existing shunt routes of the skin[10]. At electric field strengths sufficiently large (> 100 V) to electroporate lipid bilayers, a transcorneocyte pathway is accessible to charged molecules, with transbilayer transport occurring through electropores within the lipid bilayers. Experimental data of transdermal molecular flux compared favorably with the respective theoretical predictions in the small and large electric field strength limits. Predictions of the skin's electrical resistance are also found to be consistent with experimental data at small and large electric field strengths. In both limits, electrophoretic transport is shown to be predominantly convective (i.e., dominated by electric-field drift); however, a unique form of transport enhancement involving convective dispersion may be significant during skin electroporation[11].

3.2- Iontophoresis

Iontophoresis is one of the physical approach in enhancement of transdermal permeation. This utilizes electric current as a driving force for permeation of ionic and nonionic medications. The basic principle of

Iontophoresis is like charges repels each other and opposite charges attracts[12]. Transdermal iontophoretic drug delivery provides constant blood level, avoids first pass metabolism, increased patient compliance and dose dumping never occurs.The protein, peptides and other macromolecules drug entities emerging from biotechnology research have provided their own special challenges in terms of delivery technology[13]. However, the advancement in enhancement techniques like Iontophoresis which reversibly alter the barrier properties of skin can improve the penetration of such drugs. Iontophoresis seems to be an ideal candidate to sort out the limitations associated with the delivery of ionic drugs. In this review, efforts have been made to summarize all the aspects of iontophoretic delivery including history, types, various factors affecting the drug delivery and applications [14].

3.3- Sonophoresis

To disrupt the lipid packing in the SC creating aqueous pores which improve the drug delivery uses low frequency ultrasonic energy [14, 15].

3.4- Micro-needles

Microneedle, a microstructured transdermal system, consists of an array of microstructured projections coated with a drug or vaccine that is applied to the skin to provide intradermal delivery of active agents, which otherwise would not cross the stratum corneum[16]. Microneedles are somewhat like traditional needles, but are fabricated on the micro scale.

4. Chemical method to overcome the epidermal barrier

To prevent the trans epidermal water loss from the tissue, which occur by increasing the SC's hydration state by occlusion and a high water content in the formulation.
Patches and ointments are given as examples, but tissue over-hydration is not a general rule for penetration enhancement. DMSO or urea as Enhancers disrupts the lipid organization, terpenes, fatty acids, dimethylsulphoxide (DMSO) and alcohols. Compounds able to alter the protein organization, such as DMSO or urea. The enhancement effect of Modifying the thermodynamic activity of the drug can also act indirectly in the formulation at the moment of the application, e.g. ethanol; solubilizing the drug in the donor, in case of poor soluble substances, e.g. surfactants [17,18].

5. Solid and Lipid nanocarriers in transdermal drug delivery

In general, solid colloidal nano-carriers systems have been extensively studied as drug delivery systems

(DDS), mostly for oral and parenteral applications, and have shown to be one of the most promising strategies to achieve site-specific drug delivery [20]. As potential human drug delivery systems requires that the material has to be biocompatible, preferentially biodegradable, or at least should be able to be excreted [21]. This may be the reason why only a limited number of biodegradable polymeric nanoparticles, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been studied with respect to their potential for drug systemic and topical administration.SLN and NLC are composed of physiological and biodegradable lipids, which possess a low cytotoxicity and also low systemic toxicity [22].The high pressure homogenization methods, which can be performed under hot or cold conditions depending on the drug stability, and the microemulsion technique are two main preparation methods described for SLN. the protection against chemical degradation of the drug and the modulating capacity of the active compound release are some advantages of SLN , when compared with liposomes and emulsions. In these nano-carriers, solid and liquid lipid are mixed in such a combination that the particle solidifies upon cooling but does not re-crystallize, remaining in amorphous state[23].

6. Polymeric nanocarriers in transdermal drug delivery

Not as extensively as SLN the potential of polymeric nanocarriers have been studied for skin drug delivery. Polymeric nanoparticles are particles of less than 1000 nm in diameter that can be prepared from natural or synthetic polymers [24, 25]. The enhancement effect can also act indirectly, for example: modifying the thermodynamic activity of the drug in the formulation at the moment of the application, e.g. ethanol; solubilizing the drug in the donor, in case of poor soluble substances, e.g. surfactants [26, 27].

PLGA microparticles were described as vehicles for topical drug delivery, providing a reservoir system for release into the skin [28, 27]. Other polymeric nanoparticles examples have been: poly (ε-caprolactone) NP, used by Alvarez-Román (2004) et al to increase the availability of octyl methoxycinnamate within the SC [29]; and chitosan NP, used by Cui and Mumper (2001) for vaccine delivery to the viable epidermis [30].

Despite of the apparent advantages compared with other DDS, polymeric nanoparticles appear rather unexplored for drug delivery to the skin.

7. Nanocarrier toxicology

Nanocarriers are present in different dermatological and cosmetic formulations.The most commonly used carriers are liposomes; solid poorly soluble materials as titanium dioxide and zinc oxide; polymer particles and SLN.The small size of the carriers give them an increased ratio surface to total atoms or molecules exposed to the interaction with cellular systems, increasing its biological activity. This large activity can either positive (e.g. antioxidant, carrier capacity for therapeutics, penetration of cellular barriers for drug delivery) or negative (e.g. toxicity,induction of oxidative stress or of cellular disfunction), or a mixture of both. However, in strong ontrast to the efforts to increasing its positive properties for improving the human health are the limited attempts to valuate the potentially undesirable effects of nanoparticles when administered for medical or cosmetical purposes [31].

Some of the studies undertaken to evaluate the toxicological potential of dermatologically applied nanoparticles have reported the following results:

Titanium dioxide nano- and microparticles have been studied by Lademann et al who report that micro-sized particles get through the human SC and into the hair follicles [32]; on other study, carried by Menzel et al, using commercially available sunscreen creams and pig skin has reported the penetration of nanoparticles (approximately 15 nm in diameter) in the SC and into the underlying stratum granulosum through the intercellular space [33]. Gamer et al studied the penetration of zinc oxide by tape-stripping method on porcine skin and found that approximately 100% of the applied amount remains in the uppermost layers of the SC, only a few samples showing the presence of particles in the deeper layers [34].

PLGA microparticles (1-10 μm in diameter) have been studied by de Jalón et al using pig skin and were found to penetrate into the viable epidermis [35].

Solid lipid nanoparticles have shown lower toxicity than poly (lactide-coglycolide) or polyalkylcyanoacrylate nanoparticles when administered intravenously [36], but there are no studies performed when topically applied.

Limited literature or qualitative information about penetration and effect of nanoparticles during the skin transport is available, only in the case of liposomes, zinc oxide and titanium dioxide nanoparticles toxicological information is available. In general,only a few conclusions can be made about the toxicological potential of nanocarriers:

Penetration of the skin layers is size dependent.

Different type of particles has different behaviour with respect to the dermal membrane, and it is not possible to predict either its permeation or toxicological behaviour.

Parts or materials which can dissolve or leach from the particles can possibly penetrate the skin.

There are other studies, using particles not intended for dermatological use that have shown that particles can be phagocytized by macrophages or Langerhans cells, and this process can induce a sensitation response.

There is no evidence that particle applied to the skin can penetrate and enter the systemic circulation when applied to normal skin [37].The available data suggest

that dematologically applied nanoparticles have a low human risk, but is necessary more information about the real effects under in vivo conditions.

8. Nanocarrier – skin interaction mechanism

Following the topical application of a dermatological formulation the absorption of the active compound could follow the transcellular, intercellular (paracellular) and transappendageal pathway through the epidermal barrier.

The mechanism of interaction of the nanoparticulated carrier systems and the skin and also the transport pathways within the membrane of the drug and/or the carrier, are required to establish the possibility of using such systems to optimize the drug transport process [9]. It has been described that SLN, due to its particle size, are able to ensure a high adhesion to the SC enhancing the amount of drug which penetrates into the viable skin. Furthermore, for SLN particles between 200 and 400 nm an occlusive effect has been described on artificial membranes [30], and reducing the trans-epidermal water loss and increasing the penetration of a occlusion sensitive drug into the skin layers [29, 37].In another hand, in vivo studies indicated that NLC have been able to increase the anti-inflamatory effect of indomethacin on the time, correlated well with an increased permanence of the drug in the SC layers studied using tape stripping method [23]. The role of the hair follicles in the penetration process is often neglected based on the fact that the orifices of the hair follicles occupy only approximately 0.1% of the total skin surface area. However it is not considered that the hair follicles is an invagination of the epidermis extended deep into the dermis, increasing the absorption area below the skin surface [38, 39]. In the case of polymeric carriers, Rolland et al have demonstrated hair follicle targeting using 5 μm PLGA-adapalen-loaded microparticles [38], as well as de Jalon et al have shown PLGA-microparticles penetration into porcine skin [36]. In other studies, copolymer nanoparticles have been shown by Shim et al to deliver monoxidil through the skin in a size dependent form when hairy rats where used [20]. Using polystyrene nanoparticles of 20 and 200 nm in diameter and porcine ear skin, Alvarez-Román et al General Introduction have demonstrated that particles accumulate in the follicular opening and that smaller particles favour this localization [40]. Bigger particles of the same polymer (0.75 – 6 μm) were tested by Lademann's group showing in vitro and in vivo size dependent particle penetration that was independent of the hair type (terminal vs. vellus hairs). A massage increased the penetration into the hair follicle [41]. Finally, the same group have extensively studied the follicle penetration of particles using human skin and titanium dioxide microparticles which were found to reach only the outer layers of the SC as well as deep into the hair follicles. They stated out that particle

penetration was dependent on the "activity" of the hair follicle, i.e. hair growth and sebum production will influence the particle penetration process [42-45].
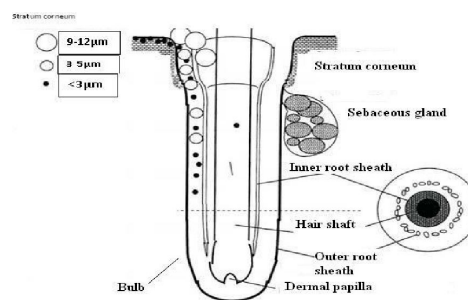

Figure 2- Size dependence of hair follicle particle penetration

The hair follicle delivery has several pharmacokinetic advantages as a reduction or bypass of the tortuous pathway of the transepidermal absorption, decrease of the drug systemic toxicity when the follicle act as long term delivery reservoir and increasing additionally the therapeutic index of some drugs as well as reducing the applied dose or frequency of administration. Micro- as well as nanoparticles have been demonstrated to reach deep into the hair follicles, where the barrier posses only a few layers of differentiated corneocytes and can be considered highly permeable, and additionally the hair follicles can act as long-term reservoir, beneficial condition when transdermal delivery is intended.Techniques as confocal laser scanning microscopy (CLSM) offer the possibility of visualizing the distribution of fluorescent probes in a skin sample by optical sectioning without previous cryofixation or embedding of the tissue, and it is considered as a valuable method for reporting the extent of penetration of molecules into the skin and for identifying the transport pathways [9]. Multi-photon fluorescence imaging can also be applied as technique for determinations in vivo tissue absorption/accumulation of dermatological and cosmetical preparations, such as interaction of nanoparticulated systems with the skin [46, 47].

9-Conclusion

Transdermal drug delivery is used require a lot of considerations in mind about the nature and function of the site. It must always remember that the main functions and keeping the skin is protected.

Because of these rules, as it is exceptionally difficult to pass through the skin for systemic absorption.

However, with ongoing discoveries about the composition, operation, and physical and chemical properties of the skin, more and more new products for the skin transmission between distributed. The Safe and drug discovery transfer ultimate goal is for all new technologies.

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