TRANSDERMAL DRUG DELIVERY SYSTEMS
Department of pharmaceutics, Nimra college of pharmacy, Nimranagar, ibbrahimpatnam, Vijayawada, Andhra Pradesh.
*Corresonding author: E. Mail id:debjit_cr@yahoo.com

ABSTRACT

Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. The relative impermeability of skin is well known, and this is associated with its functions as a dual protective barrier against invasion by microorganism and the prevention of the loss of physiologically essential substances such as water. Elucidation of factors that contribute to this impermeability has made the use of skin as a route for controlled systemic drug delivery possible. The market for Transdermal devices is currently estimated at US$ 1.2 billion, approximately 10% of the entire US $ 28 billion drug delivery market. In addition, Transdermal drug delivery market is currently based on only 10 drugs. Hence, Pharmaceutical scientists are striving to add new deliverables to the short list of approved Transdermal products.

Keywords Therapeutic activity, Bioavailability, First pass metabolism, Ionophoresis.

1. INTRODUCTION

For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquid aerosols, injectable and suppositories, as carriers. Recently, several technical advancements have been made. They have resulted in the development of new techniques of drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue. In responses to these advances, several transdermal drug delivery systems have recently been developed, aiming to achieve the objective of systemic medication through topical application on the intact skin surface. The principal of transdermal drug delivery systems is that they could provide sustained drug delivery (and hence constant drug concentrations in plasma) over a prolonged period of time. For these attributes, it is often extrapolated that sustained therapeutic activity will also be obtained with transdermal drug delivery systems. Thus, it is anticipated that transdermal drug delivery systems can be designed to input drugs at appropriate rates to maintain suitable plasma-drug levels for therapeutic efficacy, without the periodic sojourns into plasma concentrations that would accompany toxicity or lack of efficacy. Today, four drugs have been successfully incorporated into transdermal drug delivery systems for clinical use (Scopolamine, Nitroglycerine, Clonidine and Estradiol), which establishes the dermal route for systemic drug delivery. Ultimately, the success of all transdermal systems depends on the ability of the drug to permeate skin in sufficient quantities to achieve its desired therapeutic effect. (Roberts MS, 1997)

1.1. Advantages of TDDS:

1. Avoids the risk and inconveniences of intravenous therapy
2. Bypass the variation in the absorption and metabolism associated with oral administration
3. Permit continuous drug administration and the use of drugs with a short biological half-life.
4. Increase the bioavailability and efficacy of drugs and bypass of hepatic first pass metabolism.
5. Treatment can be continued or discontinued according to the desire of the physician.
6. Greater patient compliance due to the elimination of multiple dosing schedules.

1.2. Selection of drug candidate for transdermal delivery: The transdermal route of administration cannot be employed for a large number of drugs. Judicious choice of the drug substance is the most important decision in the successful development of a transdermal system. The drug candidate should have following ideas characteristics:

1.2.1. Adequate skin permeability:

- Drugs with low molecular weight
- Drugs with low melting point
- Drugs with moderate oil and water solubility

1.2.2. Adequate skin acceptability:
1.2.3. Adequate clinical need:
- Need to prolong administration
- Need to reduce side effects on target tissues
- Need to increase patient compliance

1.3. Factors affecting transdermal permeation: The principle transport mechanism across mammalian skin is by passive diffusion through primarily the transepidermal route at steady state or through trans-appendageal route at initial non-steady state. The factors controlling transdermal permeability can be broadly placed in the following cases

1.3.1. Physico-chemical properties of the penetrant molecules: Partition co-efficient: Drugs possessing both lipid and water solubility are favorably absorbed through the skin. Transdermal permeability co-efficient shows a linear dependency on partition co-efficient. A lipid/water partition co-efficient of one or greater is generally required.

1.3.2. pH conditions: The pH value of very high or very low can be destructive to the skin. With moderate pH values, the flux of ionisable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

1.3.3. Penetrant concentration: Increasing concentration of dissolved drug causes a proportional increase in flux. At higher concentrations, excess solid drug functions as a reservoir and prolonged period of time.

1.3.4. Physico-chemical properties of drug molecule: Release characteristics: solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors. Whether the drug molecules are dissolved or suspended in the delivery system.

1.3.5. Enhancement of transdermal permeation: Majority of drugs will not penetrate the skin at the rates sufficiently high for therapeutic efficacy; the permeation can be improved by the addition of permeation enhancer like dimethyl sulfoxide, dimethyl formamide, propylene glycol, etc into the system.

1.4. Physiological and pathological conditions of skin:

1.4.1. Reservoir effect of horny layer: The horny layer is deeper layer, can sometimes act as depot and modify the transdermal permeation of drugs. The reservoir effect is due to irreversible binding of a part of the applied drug with the skin.

1.4.2. Lipid film: The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

1.4.3. Skin hydration: Hydration of stratum corneum can enhance permeability. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to accumulation of sweat. Increased hydration appears to open up the dense, closely packed cells of the skin and increase its porosity.

1.4.3. Skin temperature: Raising the skin temperature results in an increase in the rate of skin permeation; this may be due to availability of energy required for diffusivity.

1.4.4. Regional variation: Differences in nature and thickness of the barrier of skin causes variation in permeability.

1.4.5. Pathological injuries to the skin: Injuries that disrupt the continuity of the stratum corneum, increases permeability due to increased vasodilatation caused by removal of the barrier layer.

1.4.6. Cutaneous self-metabolism: Catabolic enzymes present in the epidermis may render the drug inactive by metabolism and thus the topical bioavailability of the drug.

1.4.7. Penetration enhancers and their use in transdermal therapeutic system: The transdermal route for drug administration is limited by the barrier properties of the skin. Only the most potent drugs with low daily dose and appropriate physicochemical characteristics are candidates for transdermal delivery. To circumvent the low permeability nature of human skin, pharmaceutical scientists are searching for safe and effective skin penetration enhancers. Development of penetration enhancer is important to improve the low permeability of drug across the skin. Although many penetration enhancers are known, their mode of action is still not fully understood. The penetration enhancers are agents that increase the permeability of the skin or substances that reduce the impermeability of the skin. According to Chien et.al., penetration enhancers or promoters or promoters are agents that...
have no therapeutic properties of their own but can transport the sorption of drugs from drug delivery systems onto the skin and/or their subsequent transdermal permeation through skin. The accelerant causes the keratin to swell and leaches out essential structural material from the stratum corneum, thus reducing the diffusional resistance and increasing the permeability of drugs through skin.

1.5. Mechanisms of transdermal permeation: For a systemically active drug to reach a target tissue, it has to possess some physicochemical properties which facilitate the sorption of the drug through the skin and enter the microcirculation. The rate of permeation, dq/dt, across various layers of skin tissues can be expressed as:

\[
\frac{dq}{dt} = P_s \left( C_d - C_r \right) \quad \ldots \ldots \ldots (1)
\]

Where \( C_d \) and \( C_r \) are respectively, the concentrations of a skin penetrant in the donor phase (stratum corneum) and in the receptor phase (systemic circulation), and \( P_s \) is the overall permeability coefficient of the skin and is defined by

\[
P_s = K_s \frac{D_{os}}{h_s} \quad \ldots \ldots \ldots (2)
\]

Where, \( K_s \) = partition coefficient of the penetrant.
\( D_{os} \) = apparent diffusivity of penetrant,
\( h_s \) = thickness of skin

Thus, permeability coefficient \( (P_s) \) may be a constant, if \( K_s, D_{os} \) and \( h_s \) terms in equation (2) are constant under a given set of conditions. A constant rate of drug permeation is achieved if \( C_d >> C_r \), then the equation (1) may be reduced to

\[
\frac{dq}{dt} = P_c C_d
\]

Molecular penetration through the various regions of the skin is limited by the diffusional resistances encountered. The total diffusional resistance \( (R_{\text{skin}}) \) to permeation through the skin has been described by Chien as:

\[
R_{\text{skin}} = R_{sc} + R_c + R_{pd} \quad \ldots \ldots \ldots (4)
\]

Where \( R \) is the diffusional resistance and subscripts sc, e, pd refer to stratum corneum, epidermis and papillary layer of the dermis respectively. Of these layers, the greatest resistance is put up by the stratum corneum and tends to be the rate limiting step in percutaneous absorption. When more than one phase of the membrane is capable of supporting separate diffusional currents through each transdermal patch, then the pathways are configured in parallel to one another and the total fluxes of matter across the membrane is the sum of the fluxes of each route and is expressed by:

\[
J = A (f_1 p_1 + f_2 p_2 + \ldots \ldots + f_n p_n) \quad C
\]

Where \( J = \) diffusional flux and the term \( f_1 p_1 + f_2 p_2 + \ldots \ldots f_n p_n \) defines the overall permeability coefficient, \( C \) being the concentration drop.

1.6. Components of transdermal devices: Transdermal drug delivery devices have come of age. It is 24 years since the first US patents were issued to these systems; today more than 100 patents describing transdermal devices have been issued. Transdermal devices are of 3 types, they are adhesive device, monolithic matrix device and the reservoir system. These devices basically contain:

1. Backing layer
2. Drug reservoir
3. Release control layer (polymer matrix)
4. Adhesive and peel strip
5. Enhancers and excipients.

The backing layer/membrane is flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin. Eg., metallic plastic laminate, plastic backing with absorbent pad and Occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

The drug reservoir is generally made up of adhesives and allow for the transport of drug at a desired rate. The drug should be selected depending upon clinical need and its physicochemical properties. The following are some of the desirable properties of a drug for transdermal delivery.

1.7. Physicochemical properties:

1. The drug should have a molecular weight less than approximately 1000 daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phases.
3. The drug should have a low melting point.

1.8. Biological properties:

1. The drug should be potent with a daily dose of the order of a few mg/day.
2. The half life \( (t_{1/2}) \) of the drug should be short.
3. The drug must not induce a cutaneous irritant or allergic response.
4. Drugs which degrade in the GI tract or/are inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.
5. Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
6. Drugs which have to administer for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

1.9. Polymer Matrix: The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a transdermal system.

1. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
2. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive.
3. The polymer and its degradation products must be non-toxic or non-antagonistic to the host.
4. The mechanical properties of the polymer should not deteriorate excessively when large amounts of active agent are incorporated into it.

1.10. Possible useful polymers for Transdermal devices are:

1.10.1. Natural Polymers: Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

1.10.2. Synthetic elastomers: Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Neoprene etc.

1.10.3. Synthetic Polymers: Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidine, Polymethylmethacrylate, Epoxy etc.

1.10.4. Adhesives: The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfil the following criteria. Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the skin. It should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc. It should be removed easily from the skin. It should not leave a un washable residue on the skin. It should have excellent (intimate) contact with the skin at macroscopic and microscopic level.

1.10.4.1. The face adhesive system should also fulfill the following criteria:

1. Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
2. Permeation of drug should not be affected.
3. The delivery of simple or blended permeation enhancers should not be affected.
4. Some widely used pressure sensitive adhesives include polyisobutylene, acrylics and silicones.

1.11. Permeation Enhancers: These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Permeation enhancers are hypothesized to affect one or more of these layers to achieve skin penetration enhancement. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability. These may be conveniently be classified under the following main headings

1.11.1. Solvents: These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Eg., water alcohols-methanol and ethanol ; alkyl methyl sulfoxides-dimethyl sulfoxide, dimethyl acetamide and dimethyl formamide, miscellaneous solvents-propylene glycol, glycerol, isopropyl palmitate.

1.11.2. Surfactants: These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. Anionic surfactants can penetrate and interact strongly with the skin. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the 3 major classes of surfactants, the nonionics have long been recognised as those with the least potential for irritation and have been widely studied. Egs., of commonly used surfactants are:
1.11.3. Anionic surfactants: Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecemethyl sulphoxide etc.

1.11.4. Nonionic surfactants: Pluronic F127, Pluronic F68, etc.

1.11.5. Bile salts: Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Binary systems systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways. Eg. Propylene glycol-oleic acid and 1,4-butane dioil-linoleic acid.

1.11.6. Miscellaneous chemicals: Urea, N,N-dimethyl-m-tolualimide, Calcium thioglycolate,

1.11.7. Anticholinergic agents: The enhancers used should be pharmacologically inert, non-toxic, non-allergenic and non-irritating. They should show a quick onset of action, reduction of barrier function of the skin only in one direction. On removal from skin, the tissues should quickly and fully recover normal barrier function. It should be compatible with all the formulation components and should be an excellent solvent for drugs.

2. TECHNOLOGIES OF DIFFERENT TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM

Several technologies have been successfully developed to provide a rate-control over the release and skin permeation of drugs. These technologies can be classified into the following approaches.

2.1. Membrane permeation controlled TDDS: In this system, the drug reservoir is sandwiched between a backing membrane and a rate-controlling membrane, through which the drug is released. In the drug reservoir, drugs are either dispersed uniformly in the solid adhesive matrix (polyisobutylene) or suspended in a viscous, leachable liquid (silicone fluid) or dissolved in a releasable solvent (alkyl alcohol). The rate controlling membrane can be either microporous or non-porous membrane (Ethylene vinyl acetate copolymers)

2.2. Adhesive type TDDS: In this system, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer (polyisobutylene or polyacrylate), then spreading the medicated adhesive by solvent casting or hot melt, onto a backing support to form a single layer or multiple layers of drug reservoir

2.3. Matrix type TDDS: The drug reservoir here is formed by homogeneously dispersing the drug in a hydrophilic or lipophilic polymer matrix and the medicated polymer formed is then moulded into medicated discs with a defined surface area and controlled thickness. This is then mounted onto a backing membrane and the adhesive is applied outside the disc along the circumference to form a strip of adhesive rim.

2.4. Microreservoir TDDS: This type of drug delivery system is formed by first suspending the drug in the aqueous solution of a water-soluble polymer (eg. PEG) and then dispersing homogeneously, the drug suspension in a lipophilic polymer, by high shear force, to form unleachable microscopic drug reservoirs. These are also known as ‘Microsealed Delivery Devices.

2.5. Poroplastic or Molecule Type Devices: These systems, developed at Moleculon, (Cambridge, Massachusetts) utilise poroplastic films. The film is made utilizing the concept of water coagulation of cellulose triacetate solution in organic acids at low temperature. The coagulation is performed under controlled conditions and the extent of water content may be varied to a great condition and degree.

2.6. Penetration enhancement: The permeation of drugs across the skin is enhanced by physical means like pulsed DC iotophorosis or effect of ultrasounds may have synergistic effect depending upon the current density of pulse current applied and ultrasound intensity time (Chien YW, 1992).

2.6.1. Iontophoresis: It is a process that utilizes bipolar electric fields to propel ionic drug molecules across the intact skin into the underlying tissues. Positively charged drug ions in solution are transferred from a positive polarity chamber and vice versa. Delivery of positively charged compounds is easier than negatively charged compounds as the skin itself possesses a net negative charge. Iontophoresis can enhance transport across skin by a number of ways including an electrophoretic driving force and an electro-osmotic driving force and thus transiently increasing skin permeability. The transdermal transport can be increased by orders of magnitude relative to passive diffusion-based methods and can be modulated by controlling electrical parameters.

Food and Drug Adminstration (FDA) has approved a number of products based on this technique like pilocarpine and lidocaine patches. The delivery of
proteins and peptides and other small macromolecules has been demonstrated in various articles. An iontophoretic electrode, Trans-Q has been developed such that the charge is delivered to a hydrogel pad loaded with the drug solution. Most of the work is going on to develop novel bioadhesive drug containing electrodes for use in iontophoretic drug delivery. Iontopatch SP transdermal drug delivery system is a self-constrained ultra-thin technology that eliminates the need of wires or batteries. It has an active area of 15.5 cm² containing 40 mcg of the medicament. Mostly this technology has been introduced as an alternative to traditional treatment with injections. Non-steroidal anti-inflammatory drugs and corticosteroids are delivered by this mechanism. Alza Corporation Ltd., has developed electro transport system (E-Trans) for delivering fentanyl to treat acute and post operative pain. The patient has to push the button on the device which causes current to flow between two electrodes and a predetermined amount of drug is released through the skin. Also, a disposable kind of iontophoretic patch called Power Patch for delivering calcitonin to treat osteoporosis is under clinical trial.

2.6.2. Sonophoresis: It involves the introduction of substance into the body by ultrasound energy. Ultrasound energy vibrates molecules and creates tiny holes in the skin surface through ultrasound technology. The pores remain open for 12 hrs only. SonoPrep transdermal system from Sontra Medical uses low frequency ultrasound for skin permeation of lidocaine. It involves exposing the skin to a coat of lipids and then applying ultrasound at a frequency of 55,000 cycles per second causing creation of tiny bubbles which expands both in the liquid layer applied and the lipids of the skin. Thus, the skin of that area becomes leaky and remains as such. However, the pores get changed once the sound is turned off. Similarly, ImaRx Therapeutics has developed ultrasound assisted transdermal system utilizing ultrasound transducers to activate a drug and to open the skin pores for enhanced transdermal delivery. This technique has been employed for large molecular weight drugs such as peptides or proteins having molecular weight between 6000 to 48000 Daltons.

2.6.3. Electroporation: It is known that the mammalian skin is having intercellular lipids arranged in bilayers, which do not allow the transport of the drug transdermally. Electroporation is the technique by which aqueous pores are created by electric pulse of milliseconds causing transient permeability in the outer membrane which facilitates transport of drug. Flux increase up to four orders of magnitude was observed with human skin in vitro for three polar molecules having charges between −1 and −4 and molecular weights up to slightly more than 1000 daltons. Similar increase in flux was observed in vivo with animal skin. The commercial product MedPulser (Genetronics Biomedical) is used on electroporation therapy system for use in delivering pharmaceuticals and genes. This electroporation system takes about 30 minutes and uses very small dose of the drug. The flux values of the model drugs increases exponentially and reaches the steady state flux. The examples are heparin and leutinizing hormone releasing hormone (LHRH), which show increased transdermal absorption with this technique.

2.6.4. Heat and Microneedles: Heat is also now expected to enhance the transdermal delivery of various drugs by increasing skin permeability, body circulation, blood vessel wall permeability, rate limiting membrane permeability and drug solubility. Heating prior to or during topical application of a drug will dilate penetration pathways in the skin, increase kinetic energy and the movement of particles in the treated area and facilitate drug absorption. Heating the skin after topical application of a drug will increase the drug absorption into vascular network, enhancing the systemic delivery but decreasing the local delivery as drug molecule is carried away from local site. Temperature changes of approximately 5°C are necessary to cause measurable changes in cell permeability. Recently, some researchers have reported the use of pressure driven jets for the intradermal delivery of a variety of drugs. The pressure and velocity of the jet were measured using calibrated pressure transducers and high-speed photography and showed the dependence on the drug delivery. Another innovation in this field is controlled heat aided drug delivery system (CHADD), which uses a thin heating device, attached to the top of the transdermal patch. The heat and temperature are controlled to deliver the drug either as bolus or to match circadian rhythms. S-Caine, a pediatric formulation of lidocaine and tetracaine uses CHADD technology for attaining a dense anesthetic effect in 15 to 20 minutes. Another product-Titragesia, uses the same technology to deliver fentanyl for treating pain.
3. CONCLUSION

The novel drug delivery system has brought renaissance into the pharmaceutical industry for controlled drug delivery. The novel drug delivery systems include transdermal drug delivery system, mucoadhesive drug delivery system, nasal drug delivery system etc. The transdermal route of drug delivery is gaining accolade with the demonstration of percutaneous absorption of a large number of drugs. This type of drug delivery with the intention of maintaining constant plasma levels, zero order drug input and serves as a constant I.V. infusion. Several transdermal drug delivery systems (TDDS) have recently been developed aiming to achieve the objective of systemic medication through application to the intact skin. The intensity of interest in the pontential bio-medical application of transdermal controlled drug administration is demonstrated in the increasing research activities in a number of health care institutions in the development of various types of transdermal therapeutic systems (TTS) for long term continuous infusion of therapeutic agents including antihypertensives, antianginal, anti-histamine, anti-inflammatory, analgesic drugs etc.

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