Transdermal Drug Delivery System: An Update of Upcoming Evolution

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ABSTRACT

These days about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Delivery of drugs through the skin has been always a challenging area for research due to barrier properties exhibit by the outermost layer of skin stratum corneum. In the last two decades, the transdermal drug delivery system has become a proven technology that offers significant clinical benefits over other dosage forms. Because transdermal drug delivery offers controlled as well as predetermined rate of release of the drug into the patient, it able to maintain steady state blood concentration. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. It’s a desirable form of drug delivery because of the obvious advantages e.g. convenient and pain-free self-administration for patients, and the GI tract for poorly bioavailable drugs over other routes of delivery. The outlook for continued growth of the TDD market is very optimistic. Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. This review emphasizes the three generations of transdermal drug delivery which start a new era of delivery of drug.

KEY WORDS: Transdermal drug delivery, Poorly bioavailable, Stratum corneum.

1. INTRODUCTION

In recent years considerable attention has been focused on the development of controlled release drug delivery systems. Controlled release drug delivery systems are designed to release one or more drugs continuously in a predetermined pattern for a fixed period of time either systemically or to a specified target organ. Drug release from this system should be at a desired predictable and reproducible rate. The primary objectives of controlled release drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. Controlled release drug delivery systems have been designed for oral parental, implantable and transdermal route. The benefits of intravenous infusion closely duplicated, without its hazards by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation.

Transdermal drug delivery systems (TDDS) are defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. In comparison to conventional pharmaceutical dosage forms, TDDS offer many
advantages, such as elimination of first pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance.

To provide continuous drug infusion through the intact skin, membrane moderated systems, adhesive diffusion controlled systems, matrix dispersion type systems and micro reservoir systems have been developed for the topical application on to the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue. In membrane moderated systems, drug reservoir is encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate controlling polymeric membrane. Membrane moderated systems were developed in this investigation, as they are easy to fabricate in a wide range of sizes and the constant release rate of the drug is the major advantage of membrane permeation controlled system.

Continuous intravenous infusion is recognized as a superior mode of drug delivery not only to bypass hepatic “first-pass” elimination, but also to maintain a constant, prolonged and therapeutically effective drug level in the body. A closely monitored intravenous infusion can provide the advantage of drug into the systemic circulation and control of circulating drug levels. However this mode of drug delivery involves certain risks.

Recently there has been a growing recognition that the benefits of intravenous infusion can be closely duplicated without its hazards, by using the intact skin as the port of drug administration to provide continuous drug delivery into the systemic circulation [1]. This is known as transdermal administration and the drug delivery systems are known as “transdermal therapeutic systems” or popularly as “transdermal patches”.

Transdermal therapeutic systems [2] are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery systems [3] are adhesive drug containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended period of time thus eliminating numerous problems associated with oral dosing including product stability, bioavailability and the peaks and troughs of pulse dosing.

1.1 Advantages & Disadvantages Transdermal Drug Delivery Systems [4, 5, 6, 7]:

Advantages:
1. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
2. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastrointestinal irritation, low absorption, decomposition due to hepatic “first-pass” effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.
3. Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.
4. The simplified medication regimen leads to improved patient compliance and reduced inter & intra-patient variability.
5. At times the maintenance of the drug concentration within the biophase is not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.
6. Self administration is possible with these systems.
7. The drug input can be terminated at any point of time by removing transdermal patch.

Disadvantages:
1. The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
2. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin’s impermeability.
3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

1.2 Drug Permeation through Skin:

1.2.1 Skin as a Site for drug infusion:

The skin of an average adult body covers a surface area of approximately 2 square meters and receives about one-third of the blood circulating through the body [8]. The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis, and the hypodermis. Microscopically, the epidermis further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. The various skin tissue layers can be represented by a simplistic multilayer model as shown in Figure 1.1.

An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimeter of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface. Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendageal route of percutaneous absorption has, at steady state, a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules can, thus, be considered as, a process of passive diffusion through the intact stratum corneum in the inter follicular region. So, for the sake of mechanistic analysis of transdermal drug infusion [9] from stratum corneum the following model (Figure 1.2) can be used.

Figure 1.1: A cross-section of human skin, showing various skin tissue layers and appendages.

In the case that the skin serves as the point of administration for systemically active drugs, the drug applied topically will be absorbed, first into the systemic circulation and then transported to target tissues.

1.2.2 Mechanisms of Transdermal Permeation:

For a systemically active drug to reach a target tissue, it has to posses some physico-chemical properties which facilitate the sorption of the drug through the skin (Figure: 1.1), and also the uptake of the drug by the capillary network in the dermal papillary layer (Figure: 1.2). Various events governing percutaneous absorption are shown in Figure: 1.3.

Figure 1.2: Simplified model of the human skin for mechanistic analysis of skin permeation.

Figure 1.3: Events governing percutaneous absorption
The rate of permeation, \( \frac{dQ}{dt} \), across various layers of skin tissues can be expressed as:

\[
\frac{dQ}{dt} = P_s (C_d - C_s) \quad \ldots \ldots (1)
\]

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

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

Where, \( K_s = \) Partition coefficient of the penetrant
\( D_s = \) Apparent diffusivity of penetrant
\( h_s = \) Thickness of skin

Thus, permeability coefficient \( (P_s) \) may be a constant since \( K_s; D_s \) and \( h_s \) terms in equation (2) are constant under the given set of conditions.

A constant rate of drug permeation achieved, if \( C_d > C_s \), then the equation (1) may be reduced to

\[
\frac{dQ}{dt} = P_s C_d \quad \ldots \ldots (3)
\]

And the rate of skin permeation \( (\frac{dQ}{dt}) \) becomes a constant, if the \( C_d \) value remains fairly constant throughout the course of skin permeation. To maintain the \( C_d \) at a constant value, it is critical to make the drug to be released at a rate \( (R_s) \) which is always greater than the rate of skin uptake \( (R_a) \), i.e., \( R_s > R_a \).

By doing so, the drug concentration on the skin surface \( (C_s) \) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum \( (C^{e}_s) \), i.e., \( C_s >> C^{e}_s \), and a maximum rate of skin permeation \( (\frac{dQ}{dt})_{m} \) as expressed by equation (4), is thus reached:

\[
\left( \frac{dQ}{dt} \right)_{m} = P_s C_d \quad \ldots \ldots (4)
\]

Apparently, the magnitude of \( (\frac{dQ}{dt})_{m} \) is determined by the skin permeability coefficient \( (P_s) \) of the drug and its equilibrium solubility in the stratum corneum \( (C^{e}_s) \).

1.3.1 Polymer matrix or matrices:
It is the rate controlling polymeric membrane which regulates the release rate of drug during a predetermined time interval. The following criteria should be satisfied for a polymer to be used in the transdermal system [11].

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 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 amount of active agents are incorporated into it.

1.3.2 The Drug:
For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

A. Physicochemical Properties:
1. The drug should have molecular weight less than approximately 1000 Daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful delivery via the skin.
3. The drug should have a low melting point.

B. 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 / allergic response.
4. Drugs which degrade in the GIT or which 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 be administered for a long period time or which cause adverse effects to non target tissue can also be formulated for transdermal delivery.
1.3.3 Permeation Enhancers:

Three pathways are suggested for drug penetration through the skin: polar, non-polar, and polar/non-polar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers increase the fluidity of the lipid portion of the stratum corneum [12, 13]. Some enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multilaminate pathway for penetrants. Enhancers can increase the drug diffusivity in the stratum corneum by dissolving the skin lipids or by denaturing skin proteins. The type of enhancer employed has a significant impact on the design and development of the product.

The success of dermatological drug products that are intended for systemic drug delivery, such as the transdermal, depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve its desired therapeutic effect. The methods employed for modifying the barrier properties of the stratum corneum to enhance the drug penetration (and absorption) through the skin can be categorized as (1) Chemical and (2) physical methods of enhancement [14].

A. Chemical Enhancers:

Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, or penetration enhancers. Chemical enhancers act by

- Increasing the drug permeability through the skin by causing reversible damage to the stratum corneum.
- Increasing (and optimizing) thermodynamic activity of the drug when functioning as co-solvent.
- Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin.
- Conditioning the stratum corneum to promote drug diffusion.
- Promoting penetration and establish drug reservoir in the stratum corneum.

B. Physical enhancers:

The iontophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents.

1.3.4 Other Excipients:

A. Adhesives:

The fastening of all transdermal devices to the skin has 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. The adhesive used in transdermal drug delivery system should fulfill the following criteria [11].

1. Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the skin.
2. Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.
3. Should be easily removed
4. Should not leave an unwashable residue on the skin.
5. Should have excellent contact with the skin at macroscopic and microscopic level.

The face of 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 the drug should not be affected.

B. Backing membrane:

Backings membranes are 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 e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminum foil), adhesive foam pad (flexible poly urethane) with occlusive base plate (aluminum foil disc) etc.

1.4 APPROACHES TO DEVELOPMENT OF TRANSDERMAL THERAPEUTIC SYSTEMS:

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies can be classified into four approaches as follows:

1. Membrane permeation – controlled systems
2. Adhesive dispersion – type systems.
3. **Matrix diffusion – controlled systems.**

4. **Micro reservoir type or micro sealed dissolution controlled systems.**

### 1.4.1 Membrane Permeation – Controlled Systems:

In this type of system drug reservoir is encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be microporous or non-porous. The drug molecules are permitted to release only through the rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogeneously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in an unbleachable, viscous liquid medium (e.g. Silicon fluids) to form a paste like suspension.

The rate of drug release from this type of system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive [15]. The constant release rate of the drug is the major advantage of membrane permeation controlled system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or rapid release of entire drug content (Figures 1.4, 1.5). Examples of this system are

- Transderm – Nitro: Nitroglycerin releasing transdermal system for once a day medication in angina pectoris.
- Catapres: Clonidine releasing transdermal system for 7 day therapy of hypertension.
- Estraderm: Estradiol releasing transdermal system for treatment of menopausal syndrome for 3 - 4 days.

The membrane permeation controlled technology has also been used for controlled percutaneous absorption of prostaglandin derivatives.

### 1.4.2 Adhesive Dispersion – Type Systems:

This is a simplified form of the membrane permeation controlled system. As represented in Figure: 1.6, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.

On the top of the drug reservoir layer, thin layers of non medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion – controlled delivery system. Examples are

- Frandol tape: Releases Isosorbide dinitrate for once-a-day medication of angina pectoris.
- Deponit: Delivers nitroglycerine for the treatment of angina pectoris.
1.4.3 Matrix Diffusion- Controlled Systems:
In this approach, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophillic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross-linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can also be formed by dissolving the drug and the polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. This drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing membrane. Instead of applying the adhesive polymer directly on the surface of the medicated disc as discussed earlier in the first two types of transdermal delivery systems, the polymer is spread along the circumference of the patch to form an adhesive rim around the medicated disc (Figure 1.7).

E.g., Nitro-Dur: Delivers nitroglycerin for the treatment of angina pectoris.

This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim (Figure 1.8).

E.g., Nitroglycerin: Releasing transdermal therapeutic system for once a day treatment of angina pectoris

1.4.4 Micro Reservoir Type or Micro Sealed Dissolution Controlled Systems
The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer (e.g. Polyethylene glycol) and then dispersing the drug suspension homogeneously in lipophillic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable micro spheres of drug reservoirs.

This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim (Figure 1.8).

E.g., Nitroglycerin: Releasing transdermal therapeutic system for once a day treatment of angina pectoris

EVALUATION OF TRANSDERMAL FILMS:

1.5.1 In-Vitro Skin Permeation and Release Kinetics Studies:
The design and development of transdermal drug delivery systems is greatly aided by in-vitro studies. In-vitro studies can help in investigating the mechanism of skin permeation of drug before it can be developed into a transdermal therapeutic system. The methodology used in the in-vitro study is relatively easy to follow and generally affords the investigator better control over the experimental conditions than is possible in-vivo.

The factors that require consideration when selecting an in vitro system include:

1. The rate limiting process: Drug solubilization or diffusion in the vehicle, partitioning from the vehicle, diffusion through the test membrane or partitioning and removal by the receptor phase.
2. The intrinsic diffusivity of the permeate and apparent diffusivity.
3. The predominating route of diffusion during the experiment and the relative contents of drug binding and metabolism, occurring in the membrane, delivery and receptor phases.
4. The predominating route of diffusion during the experimentation and the relative extents of drug binding.
5. The intrinsic barrier potential of the membrane and the effects that vehicle components may have on retardative properties. Hydration of the membrane and the presence of penetration enhancers may be important here.

(A). Diffusion study:
The kinetics of skin permeation can be more precisely analyzed by studying the time course for the permeation of drug across a freshly excised skin mounted on a diffusion cell, such as the Franz diffusion cell (Fig 1.9). Keshary and Chien have pointed out certain deficiencies in the Franz cell and modified to obtain closer approximation to in-vivo conditions [16].

Some diffusion cells are designed to hold the skin at a vertical position between donor and receptor chambers [17]. A more recent example is the valia-Chien cell, which is superior to similar earlier models in that it does not expose both, the donor and the receptor phases to the same temperature, and does not allow solvent loss from either phase. Moreover, the design overcomes another inadequacy of the Franz cell, namely the susceptibility of its donor phase to the changes in ambient temperature. Finally the donor compartment contents may be stirred which makes the cell suitable for transdermal drug delivery from solution and suspensions [18].

Various types of in-vitro apparatus for measuring drug permeation profiles across the skin have been reported in the literature [19, 20]. They can be broadly classified into two categories as shown below.

A. Physical design of diffusion cell
   ➤ Horizontal type
   ➤ Vertical type
   ➤ Flow-through type

B. Method of sampling and measurement
   ➤ Continuing system
      • Fluid circulation system
      • Non circulation system
   ➤ Intermittent system: rotating agitation systems.

Franz diffusion apparatus is showed in Figure 1.9.
The components of the diffusion cell are showed below [21].

1. Donor Compartment:
   1. Easy access to deliver the penetrant to the skin.
   2. Stirred where possible.
   3. Temperature controlled (32 °C ± 1 °C)
   4. Control of evaporation for vehicles and penetrants.

2. Membrane:
   1. For the study of penetration kinetics, only human skin should be used.
   2. For vehicle/device release studies other barrier may be used.
   3. The skin sample should contain both stratum corneum and viable epidermis.
   4. A molecule of known penetration kinetics should used prior to the test molecule, to assess barrier function.
   5. Where applicable metabolic viability of epidermis may be assessed.

3. Receptor Compartment:
   1. Either, flow – through or static.
   2. Temperature controller (32 °C ± 1 °C)
   3. Sufficient volume to maintain infinite sink conditions
   4. Stirred without obvious formations of boundary layers.

4. Receptor Fluid:
   1. Should not compromise barrier function.
2. Should be of favorable partitioning.
3. Capable of maintaining epidermal viability where ever necessary.
4. Must be contained once collected.

Majority of In-vitro experiments are conducted in animal skin i.e. hairless mouse, guinea pig, rabbit etc. Although these exist a number of similarities there is as yet no animal skin that complete mimics the penetration characterization of human skin.

(B) Dissolution Studies:

The methodology [22] involved in drug release studies from transdermal films was specified in USP apparatus 5 (Paddle over Disc). Its description was given in Figure 1.10.

1.5.2 In-vivo Evaluation of Transdermal Drug Delivery Systems:

The following models are useful for in-vivo evaluation of TDDS.

A. Animal models:

In-vivo animal models are preferred because considerable time and resources are required to carryout studies in humans. Some of the species that have been used for in-vivo testing include; mouse, rat, guinea pig, rabbit, hairless mouse, hairless rat, hair less dog, cat, dog, miniature pig, pig, horse, goat, squirrel, monkey, rhesus monkey, chimpanzee, etc. Various experiments have been carried out to determine which of the animal models provide the best prediction of the behavior of the device, being tested, in humans.

B. Human models:

The final stage in the development of transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the device to human volunteers. An in-vivo evaluation using human subjects should give pertinent information with minimum risk to the subjects within a reasonable period of time. In-vivo evaluation using human models involve determination of percutaneous absorption by an indirect method of measuring radio activity in excreta following topical application of the labelled drug. $^{14}$C is generally used for radio-labeling. Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the body, or excreted by routes not monitored. This necessitates measurement of dose absorbed.

The percentage of dose absorbed transdermally is calculated by the following formula.

$$\text{% dose absorbed} = \frac{\text{Total radio activity excreted after Topical administration}}{\text{Total radio activity excreted after IV administration}} \times 100$$

However this method has certain limitations, to overcome the limitations inherent in this method, various refinements have been made. These are described below,

1. “Reservoir” Technique:

This method involves a simple, short exposure of the skin to the (radio-labelled) compound under study followed by removal of the stratum corneum by tape stripping and analysis of the content of the compound in the stratum corneum. From this analysis, it is possible to predict the amount of drug that will penetrate over a longer period of time.

2. “Mass balance” technique:

This method involves the application site is covered with an occlusive chamber, the chamber being replaced by a new one after a particular time interval. The site is also subjected to washing at these times. Radio-labeling techniques are used and the chambers, washings and the faeces and urine of the patients are subjected to analysis. Advantage of this technique include achievement of mass balance between the applied dose and excretion levels and the use of surface wash measurements for predicting percutaneous absorption.
C. Biophysical Models:
Models based on steady state mass balance equation, solution of Fick’s second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been described in the literature [23, 24].

It can be concluded that many techniques for in-vivo evaluation of transdermal systems have been put forward but there is scope for further refinement. Some of the unresolved issues include the change in barrier function of the skin with age, skin metabolism, in-vivo functioning of permeation enhancers etc.

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