Review Article

Transdermal Drug Delivery System: A Review

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Abstract

The transdermal route has numerous advantages over the more traditional drug delivery routes. These include high bioavailability, absence of first pass hepatic metabolism, steady drug plasma concentrations, and the fact that therapy is non-invasive. The main obstacle to permeating drug molecules is the outermost layer of the skin, the stratum corneum. Consequently, research into enhancing transdermal drug delivery (TDD) by overcoming this layer is an area of prime interest. This review article is written to provide a coverage commentary of the recent advancements in TDD enhancement techniques. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. This review describes enhancement techniques based on drug/vehicle optimisation such as drug selection, prodrugs and ion-pairs, supersaturated drug solutions, eutectic systems, complexation, liposomes, vesicles and particles. Enhancement via modification of the stratum corneum by hydration, chemical enhancers acting on the structure of the stratum corneum lipids and keratin, partitioning and solubility effects are also discussed. The mechanism of action of penetration enhancers and retarders and their potential for clinical application is described.

Keywords

Transdermal delivery, skin penetration, enhancer, Evaluation and Applications.

Introduction

Transdermal drug delivery is 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 system (TDDS) established itself as an integral part of novel drug delivery systems.

Advantages of Transdermal Drug Delivery Systems

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., gastro-intestinal 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 diphase is not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.

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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 of Transdermal Drug Delivery Systems

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.

Skin as a Site for Drug Infusion

The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. 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 (Fig 1). 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.
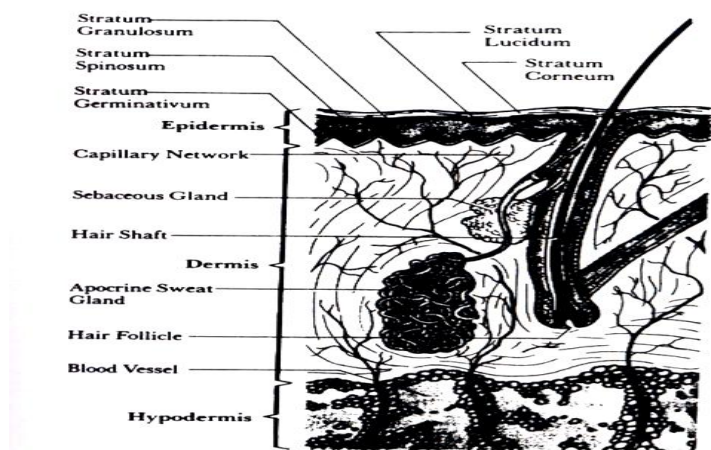

Fig 1: A cross-section of human skin, showing various skin tissue layers and appendages.

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-appendage 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 (Fig 2), the various skin tissue layers can be represented by a simplistic multilayer model as shown in Fig 2. 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.
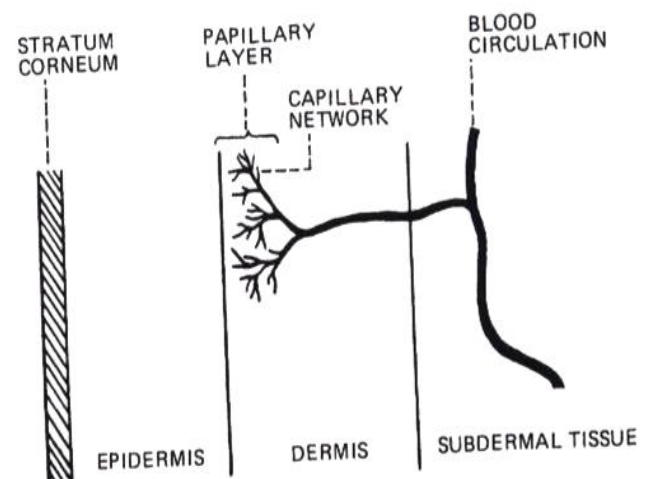

Fig 2: Simplified model of the human skin for mechanistic analysis of skin permeation.

Mechanisms of Transdermal Permeation[3]

For a systemically-active drug to reach a target tissue, it has to possess some physico-chemical properties which facilitate the absorption of the drug through the skin (Fig 1), and also the uptake of the drug by the capillary network in the dermal papillary layer (Fig 2). The rate of permeation, dQ/dt, across various layers of skin tissues can be expressed as.

$$\frac{dQ}{dt} = P_s(C_d - C_r) - - - - - (1)$$

Where, C_d and C_r are, respectively, the concentrations of skin penetrate 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

$$P_s = \frac{K_s D_{ss}}{h_s} \ - - - - -(2)$$

Where,

K_s = Partition coefficient of the penetrant
D_{ss} = Apparent diffusivity of penetrant
h_s = Thickness of skin

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

$$\frac{dQ}{dt} = P_s . C_d \ - - - - -(3)$$

And the rate of skin permeation (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_r) which is always greater than the rate of skin uptake (R_a), i. e., $R_r \gg R_a$ (Fig 3).
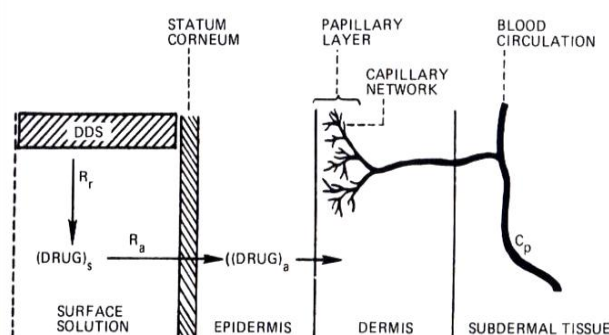

Fig 3: Relationship between the rate of drug release (R_r) from a transdermal drug delivery system (TDDS) and the rate of drug uptake (R_a) by the skin.

By doing so, the drug concentration on the skin surface (C_d) 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., $C_d \gg C^e_s$; and a maximum rate of skin permeation $(dQ/dt)_m$,

as expressed by equation (4),is thus reached:

$$\left(\frac{dQ}{dt} \right)_m = P_s C_s^e$$

Apparently, the magnitude of $(dQ/dt)_m$ is determined by the skin permeability coefficient (P_S) of the drug and its equilibrium solubility in the stratum corneum (C^e_s).

Types of Transdermal Patches [1-5]

Four Major Transdermal Systems

1. Single-layer Drug-in-Adhesive

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin. The intrinsic rate of drug release from this type of drug delivery system is defined by

$$dQ/dT = \frac{Cr}{1/Pm + 1/Pa}$$

Where Cr is the drug concentration in the reservoir compartment and Pa and P m are the permeability coefficients of the adhesive layer and the rate controlling membrane, Pm is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. Pm and Pa, respectively, are defined as follows.

$$Pm = \frac{Km/r.\ Dm}{hm}$$

$$Pa = \frac{Ka/m.\ Da}{ha}$$

where $K_{m/r}$ and $K_{a/m}$ are the partition coefficients for the interfacial partitioning of drug from the reservoir

to the membrane and from the membrane to adhesive respectively; Dm and Da are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and hm and ha are the thicknesses of the rate controlling membrane and adhesive layer, respectively.

2. Multi-layer Drug-in-Adhesive

Backing
Drug-in-Adhesive
Membrane
Drug-in-Adhesive
Liner
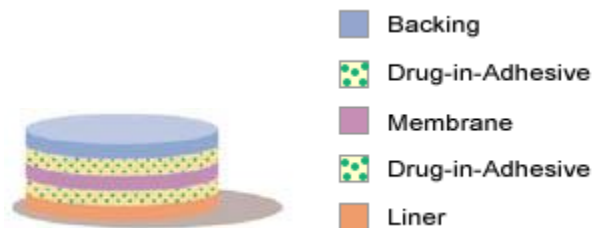
The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer
encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single   backing film. The rate of drug release in this system is defined by,

$$dQ/dt = \frac{Ka/r.\ Da}{ha}\ Cr$$

Where $K_{a/r}$ is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

3. Drug Reservoir-in-Adhesive

Backing
Drug
Membrane
Adhesive
Liner
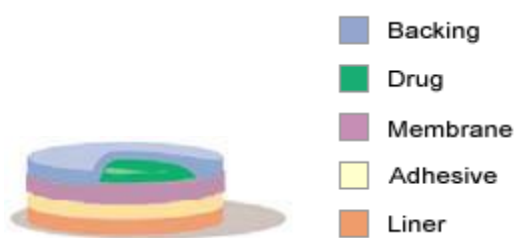
The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

The rate of drug release from this drug reservoir gradient controlled system is given by,

$$dQ/dt = \frac{Ka/r.\ Da}{ha\ (t)}\ A\ (\ ha\ )$$

In the above equation, the thickness of the adhesive layer for drug molecules to diffuse through increases with time ha (t). To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusional path A (ha).

4. Drug Matrix-in-Adhesive

Backing
Adhesive
Drug
Liner

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix. The rate of drug release from this type of system is defined as,

$$\frac{dQ}{dt} = \frac{AC_P\ D_P^{1/2}}{2t}$$

Where A is the initial drug loading dose dispersed in the polymer matrix and C_p and D_p are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, C_p is essentially equal to C_R, where C_R is the drug concentration in the reservoir compartment[8,9].

Basic Components of TDDS [1, 2.8,11,12]

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner and other excipients like plasticizers and solvents

Polymer matrix / Drug reservoir

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status. Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber. Similarly Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethyl cellulose for isosorbide dinitrate matrix. The polymers utilized for TDDS can be classified as,

- **Natural Polymers**: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc*.
- **Synthetic Elastomers**: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc*.
- **Synthetic Polymers**: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

Drug

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non-compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day). Table 1 enlists the currently available drugs for transdermal delivery. In addition drugs like rivastigmine for Alzheimer's and Parkinson dementia, rotigotine for Parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

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. 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 (SC) 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 SC to enhance the drug penetration (and absorption) through the skin can be categorized as (1) Chemical and (2) physical methods of enhancement[15].

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 SC.

➢ 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 SC to promote drug diffusion.

➢ Promoting penetration and establish drug reservoir in the SC.

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.

Pressure sensitive adhesives

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physic chemically and biologically compatible and should not alter drug release.

Backing Laminate

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipients compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusive to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films.

Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (*e.g.* paper fabric) or occlusive (*e.g.* polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates.

Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

Approaches to Development Transdermal Therapeutic Systems[1, 2.8,11,12]

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.

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 micro porous 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 homogenously 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.
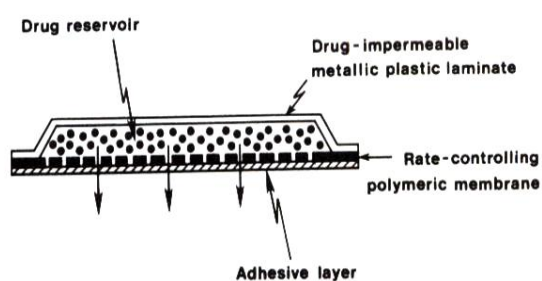

Fig 4: Membrane-moderated Transdermal drug delivery system.

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. 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. Examples of this system are

Transderm – Nitro

Nitroglycerin – releasing transdermal system for once a day medication in angina pectoris.

Transderm – Scop

Scopolamine – releasing transdermal system for 72 hrs. Prophylaxis of motion sickness.

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.

Adhesive Dispersion – Type Systems

This is a simplified form of the membrane-permeation controlled system. As represented in Fig 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.

Frandol tape

Releases Isosorbide dinitrate for once-a-day medication of angina pectoris.

Deponit

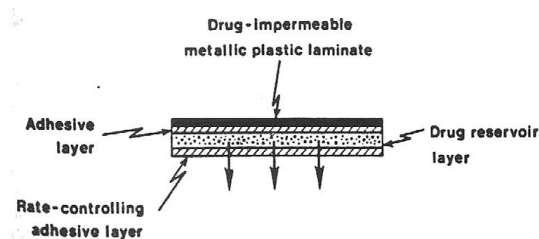Delivers nitroglycerine for the treatment of angina pectoris.

Fig 5: adhesive diffusion-controlled Transdermal drug delivery system.

Matrix Diffusion- Controlled Systems

In this approach, the drug reservoir is formed by homogenously dispersing the drug solids in a hydrophilic or lipophillic polymer matrix. The resultant medicated polymer is then molded 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. e.g. Nitro-Dur: Delivers nitroglycerin for the treatment of angina pectoris.
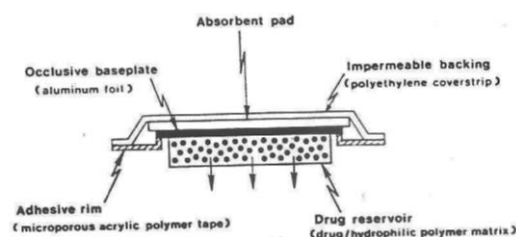

Fig 6: Matrix dispersion-type transdermal drug delivery system

Micro reservoir type or Micro sealed Dissolution

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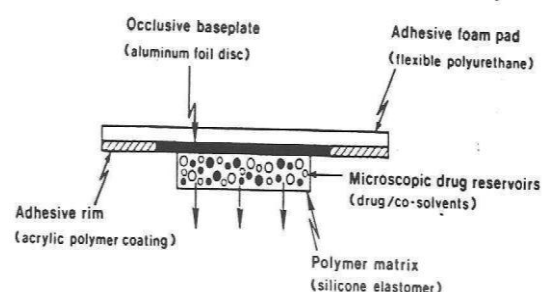

Fig 7: Micro reservoir-type transdermal drug delivery system.

Evaluation of Transdermal Films [15-30]

In-Vitro **Skin Permeation and Release Kinetics Studies**

The design and development of transdermal drug delivery systems is greatly aided by invitro 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. 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 9). Keshary and Chien have pointed out certain deficiencies in the Franz cell and modified to obtain closer approximation to in vivo conditions[17].Some diffusion cells are designed to hold the skin at a vertical position between donor and receptor chambers. 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 solutions and suspensions. Various types of in vitro apparatus for measuring drug permeation profiles across the skin have been reported in the literature. 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
      • Noncirculation system
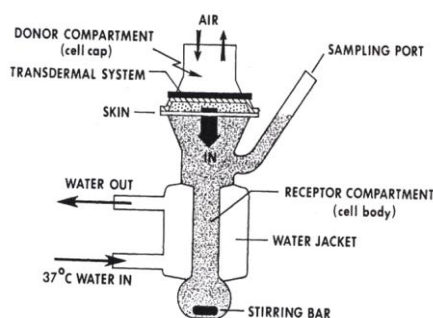 ➢ Intermittent system: rotating agitation systems

Fig 8: 8-cell Franz diffusion apparatus

1. Donor Compartment
  1. Easy access to deliver the penetrant to the skin.
  2. Stirred were possible.
  3. Temperature controlled (32 ^{O}C + 1 ^{O}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 ^{0}C + 1^{0}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, 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.

In-Vitro Dissolution Studies

Apparatus: Two-sided open ended tube
Temperature   37 + 0.5 ^{O}C

In-vivo Evaluation of Transdermal Drug Delivery Systems:
In-vivo evaluation of TDDS can be carried out using,

  A. Animal models
  B. Human volunteers
  C. Biophysical models

A. Animal models

In vivo animal models are preferred because considerable time and resources are required to carry out 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 volunteers

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

**Applications of Transdermal Patches [1, 2, 8]**

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).

- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).

- Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.

- The anti-hypertensive drug Clonidine is available in transdermal patch form.

- Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.

- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

Transdermal Market Product [13, 14]

The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally.

Advance Development in TDDS[13, 14]
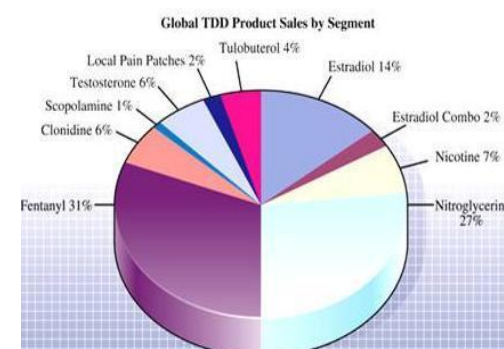
Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin

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adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch. A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called "active" transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

Conclusion

The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

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