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A Review ArNovel Approaches For Transdermal Drug Delivery System

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ABSTRACT

From thousands of years, human civilizations have applied substances to the skin as cosmetic and medicinal agent. Transdermal patches are the relatively recent concept in medical and pharmaceutical Practice, That the patient provides a controlled release of medication in to the patient, usually through either a porous membrane. Topical administration of therapeutic agents offers many advantages over Conventional oral and invasive methods of drug delivery and also provide controlled release of drug for Extended period of the tissue, and the main dis- advantage to TDDS. Stems from the fact that skin is a very effective barriers as a result only medications whose molecule and small Can easily Penetrate the skin, so that it can be delivery through this method.

Key words: Drug delivery, Matrix, Reservoir, Transdermal, Permeation pathways, Hydrin rubber, Silicon rubber.

INTRODUCTION

Now a day many drugs are administered orally, but they are observed not more effective as desired so to upgrade such character TDDS was created. Drug delivery administered by the skin and attain a systemic effect of drug is called as transdermal drug delivery system. These are kind of dosage form which includes drug transport to reasonable epidermis and potentially dermal tissue of the skin locally therapeutic effect. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a three-day period.Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation & neurological disorders such as Parkinson's disease.

ADVANTAGES:
1. Self-medication is possible
2. Side effect gets reduced
3. Plasma drug concentration becomes maintained
4. Drug duration of action are extendable
5. GIT incompatibilities get avoided
6. Number of dosage frequency reduced
7. Easier to remember and used
8. Large area of application in comparison with nasal and buccal cavity

DISADVANTAGES:
1. Chances to allergic reaction
2. High molecular drug level cannot to attain therapeutic level

3. It is deliver to ionic drug
4. It requires significant lag time
5.It is limited only to potent drug molecule.
6.Drugs must not be locally irritating or sensitizing.
7. or drug formulation may cause skin irritation or Sensitization.
8. Drugs with short biological half lifes that are subject to large First pass metabolism.

ANATOMY AND PHYSIOLOGY OF SKIN:

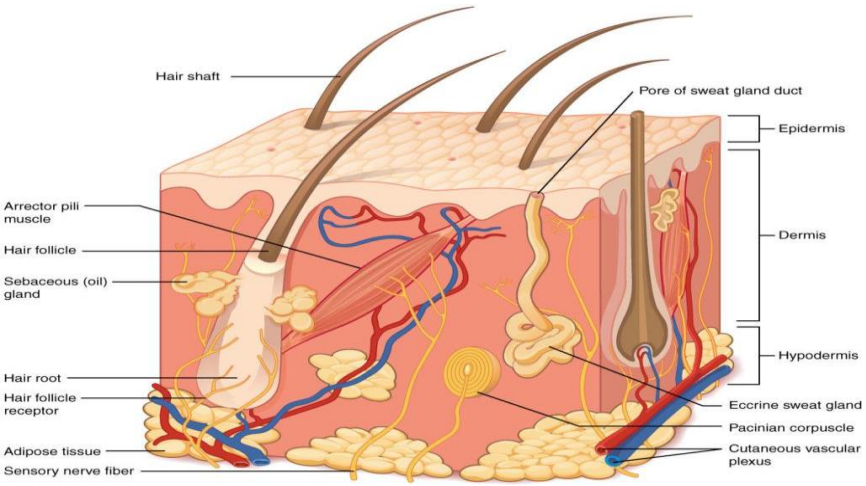

Figure No:1.1 Structure of Skin

Epidermis:
The epidermis is a stratified, squamous, keratinizing epithelium. The complex layer of epidermis varies in contingent upon cell size, thickness and number of cell layers of epidermis which are going from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. About 90% epidermal cells are keratinocytes or chest rated in five layers and creates keratin protein and 8% melanocytes are available. They create melanina yellow or dark colored dark shade that adds to skin shading and ingests harming UV light. A Langerhans cell emerges from red bone marrow and moves to epidermis, where they constitute little portion of epidermis cells. Markel cells are slightest several of epidermal cells.

Dermis:
Dermis is 3 to 5 mm thick layer and is made out of a lattice of connective tissue, which contains veins, lymph vessels and nerves. The cutaneous blood supply has basic capacity in direction of body temperature. It additionally gives supplements and oxygen to the skin while removing toxins and squander items. Vessels reach to inside 0.2 mm of skin surface and give sink conditions to most atoms entering the skin hindrance. The blood supply in this manner keeps the dermal centralization of a saturate low and the subsequent fixation contrast over the epidermis gives fundamental focus inclination to transdermal penetration.

Hypodermis:
The hypodermis or subcutaneous fat tissue underpins the dermis and epidermis. It fills in as a fat storage area. This layer controls temperature, gives wholesome help and mechanically security. It conveys chief veins and nerves to skin and may contain tangible weight organs. For transdermal medication conveyance, sedate needs to infiltrate through all these three layers and venture into foundational flow while if there should be an occurrence of topical medication conveyance just entrance through stratum corneum is fundamental and after that maintenance of medication in skin layers is desired.

ROUTES OF DRUG ADMINISTRATION

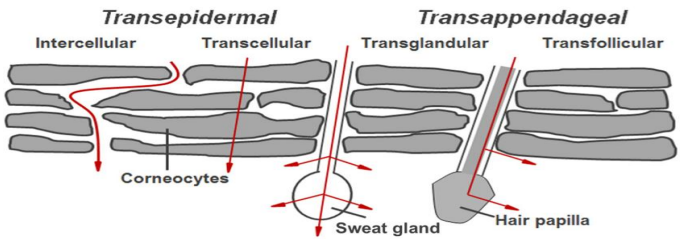

Figure No:1.2 Possible path ways for permeation of drug across the skin barrier.

Tran follicular route :
Tran follicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs.

Tran cellular route:
Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway. The drug passes through the comeocytes of stratum corneum.

Intercellular route:
In intercellular pathway the drug diffuses through the continuous lipid matrix present between the cells.

MECHANISM OF TRANSDERMAL PERMEATION

Transdermal permeation of a drug delivery system based on the

1. Permeation of drug by feasible epidermis.
2. Sorption through stratum corneum.
3. Take up of the drug moiety through the capillary system in the dermal papillary layer.

The rate of transdermal drug permeation, dQ/dt, through several layers of skin tissues which can be expressed as

$$dQ/dt = Ps(Cd-Cr) \text{.....eq (1)}$$

Where,
dQ/dt = Rate of skin permeation
Cd and Cr =the concentrations of skin penetrate in the donor phase (stratum corneum) and the receptor phase(systemic circulation)
Ps=overall permeability coefficient of the skin
Ps is defined as by L john

$$Ps = KsDss/Hs \text{.....eq (2)}$$

Where,
Ks = Partition coefficient of the penetrant)
Dss = Apparent diffusivity of penetrant
Hs = Thickness of skin At constant rate of drug permeation is achieved when Cd>Cr Then equation (1) becomes

$$dQ/dt = PS.CD. \text{.....eq (3)}$$

(dQ/dt) becomes as constant when Cd value remains genuinely constant done the span of skin permeation. To retain the Cd at a constant value, it is simple to make the drug to be released at a rate (Rr) which is regularly more prominent than the rate of skin take-up (Ra) therefore Rr>>Ra.

Thusly, the drug concentration on the skin surface (Cd) is kept up at a level which is constantly more prominent than the equilibrium (or saturation) solubility of the drug in the stratum corneum (Ces), i.e., Cd>>Ce s ; and a most extreme rate of skin permeation (dQ/dt)m, as written by equation.

$$(dQ/dt)m = PSCes$$

Where,
(dQ/dt)m = Magnitude of Rate of skin permeation.
Ps = the skin permeability coefficient of drug.
Ces - equilibrium solubility in the stratum corneum .

TYPES OF TRANSDERMAL PATCHES:

There are four main types of TDDS

- Single-layer Drug-in-Adhesive.
- Multi-layer Drug-in-Adhesive.
- Drug Reservoir-in-Adhesive.
- Drug Matrix-in-Adhesive.

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.

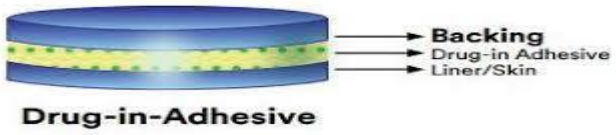

Figure No:1.3

Multi-layer Drug-in-Adhesive:

- 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.

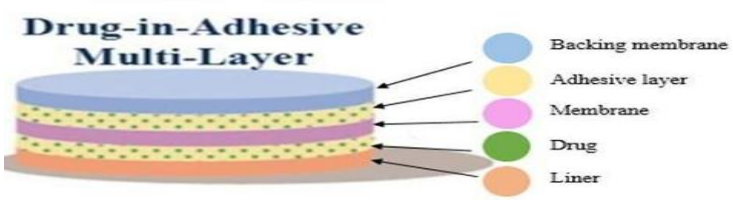

Figure No:1.4

Drug Reservoir-in-Adhesive

- 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.

Figure No:1.5

Drug Matrix-in-Adhesive:

- 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.

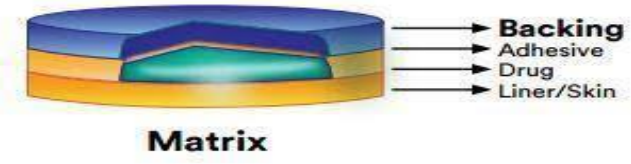

Figure No:1.6

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM:

Polymer Matrix/ Drug Reservoir:
It is prepared by dispersing the drug in liquid or solid state synthetic polymer base. It should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status. Polymers used in Transdermal drug delivery systems are classified as-

a) Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
b) Synthetic Elastomers: e.g.polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.
c) Synthetic Polymers: e.g. polyvinylchloride, polyethylene, polyvinylalcohol, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

Drugs:
Some of ideal properties of drug & some factors to be consider during preparation of Transdermal patches are as follows:

a. Ideal Properties of Drugs: (Table 1)

Table No:1.1 Ideal Properties of Drugs.

S.No.	Parameter	Properties
1	Dose	Should be Low in weight (less than 20mg/day).
2	Half-life	10/less (hrs).
3	Molecular weight	<400da.
4	Skin permeability coefficient	>0.5*10-3cm/h.
5	Skin Reaction	Non irritating, Non sensitizing
6	Oral bioavailability	Low.

b. Factors Affecting: (Table 2)

Table No:1.2 Factors Affecting

Physicochemical	Pharmacokinetic	Biological
Solubility	Half-life	Skin toxicity
Crystalinity	Volume of distribution	Site of application
Molecular weight	Total body clearance.	Allergic Reaction
Polarity	Theraputic plasma con.	Skin metabolism
Meting point	Bioavailable factor	

Permeation Enhancers:
Permeation enhancers 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. The flux, of drugs across the skin can be written as J=D Xdc/dx

Where, D is the diffusion coefficient and is a function of size, shape and flexibility of the diffusing molecule as well as the membrane resistance; C is the concentration of the diffusing species; x is the spatial coordinate.

Although the solution for J with various boundary conditions and membrane heterogeneities can be very complex, the basic concepts regarding flux enhancement can be found in above equation. The concentration gradient is thermodynamic in origin, and the diffusion coefficient is related to the size and shape of penetrate and the energy required to make a hole for diffusion. Thus enhancement of flux across membranes reduces to considerations of:

- Thermodynamics (lattice energies, distribution coefficients).
- Molecular size and shape.
- Reducing the energy required to make a molecular hole in the membrane.
- Permeation enhancers are hypothesized to affect one or more of the layers to achieve skin penetration enhancement. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability. These conveniently classified under the following main headings:

Solvents:
These compounds increase penetration possibly by
1). Swelling the polar pathways in the skin.
2). Fluidization of lipids.

Examples include water alcohols-methanol and ethanol; alkyl methyl sulfoxides-dimethyl sulfoxide, alkyl. homologs of methyl sulfoxide, dimethyl acetamide and dimethyl formamide; pyrrolidones-2-pyrrolidone, laurocapram (Azone), miscellaneous solvents-propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

Surfactants:
These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the head group and the hydrocarbon chain length. These compounds are skin irritants, therefore, a balance between penetration enhancement and irritation have to be considered. Anionic surfactants can penetrate and interact strongly with the skin. Once these surfactants have. penetrated the skin, they can induce large alterations. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the three major classes of surfactants, the nonionic have long been recognized as those with the least potential for irritation and have been widely studied.

Examples of commonly used surfactants are:

Anionic Surfactants: Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.
Nonionic Surfactants: Pluronic F127, Pluronic F68, etc.
Bile Salts: Sod taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Miscellaneous Chemicals: These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m toluamide; Calcium thioglycolate; Anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on their effectiveness are sparse. These include eucalyptol, di-o-methyl-beta cyclodextrin and soyabean casein.

Backing Laminate:
It is a supportive material which is impermeable to drugs and also to permeation enhancers. They should chemically compatible with the drug, enhancer, adhesive and other excipients.
Ex: Vinyl, Polyethylene and Polyester films.

Release Liner: This is the primary packaging material that can protect the patch during application. It is made up of base layer which may be

a) Non-Occlusive (e.g. paper fabric)
(OR)
b) Occlusive (e.g. polyethylene, polyvinylchloride)

It is made up of silicon or Teflon. Release liner should be chemically inert & it should be permeable to drug, penetration enhancers & water.

Other Excipients Like Plasticizers and Solvents:

a) Solvents: Chloroform, methanol, acetone, isopropanol and dichloromethane.

b) Plasticizers: Dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol.

PARAMETERS:

- Dose should be low i.e <20mg/day.
- Half life should be 10 h or less.
- Molecular weight should be <400.
- Partition coefficient should be Log P (octanol-water) between 1.0 and 4.

- Skin permeability coefficient should be <0.5 X 10-3cm/h.
- Drug should be non-irritating and non sensitizing to the skin.
- Oral bioavailability should be low.
- Therapeutic index should be low.

FACTORS AFFECTING TRANSDERMAL PATCHES:

There are various factors which affects the action of transdermal patches. These are given below:

a. Physicochemical Properties

i. Partition coefficient.
ii. Molecular size.
iii. Solubility/melting point.
iv. Ionization.

b. Physiological & Pathological Conditions of Skin

i. Reservoir effect of horny layer.
ii. Lipid film.
iii. Skin hydration.
iv. Skin temperature.
v. Regional variation.
vi. Pathological injuries to the skin.
vii. Cutaneous self-metabolism.
viii. Skin barrier properties in the neonate and young infant.
ix. Skin barrier properties in aged skin.
x. Race.
xi. Body site.
xii. Penetration enhancers used.

EVALUATION TESTS FOR TRANSDERMAL PATCHES

Development of controlled release transdermal dosage form is a complex process. Transdermal patches have been developed in order to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to find out their desired performance and reproducibility under the specified environmental conditions.

1. Physical evaluation of transdermal system:

1.Film Thickness: The thickness of film is measured by using electronic vernier calipers, with a least count of 0.01mm. Thickness is measured at five different points on the film and average of five readings is taken.

(ii) Percentage flatness: Film is cut into strips, two from either end and one from the center. The length of these strips is measured to the nearest centimeter without applying any additional pressure. The percent flatness of the strips is selected as the average percent of length calculated from the 7 cm strips.

(iii) Patch Thickness: Patch thickness can be measured using digital micrometer screw gauge at three different places and the mean value is calculated.

(iv) Folding endurance : Folding endurance of patches can be determined by repeatedly folding a small strip of film (2 x 2 cm) at the same place till it breaks. The number time the film could be folded at the same place without breaking is the folding endurance value.

(v) Tensile strength: The tensile strength can be determined by using a modified pulley system. Weight is gradually increased so as to increase the pulling force till the patch breaks. The force required to break the film is considerd as a tensile strength and it is calculated as kg/cm².

2.Weight variation:
Weight variation is studied by individually weighing 10 randomly selected patches. Such determination is performed for each formulation.

3.Drug content:
A 5 cm^2 film is cut into small pieces, put into a 100 ml buffer (pH 7.4), and shaken continuously for 24 hours. Then the whole solution is ultrasonicated for 15 min. After filtration, the drug is estimated spectrophotometrically and the drug content is determined.

4.Moisture content:
The prepared films are weighed individually and kept in desiccators containing calcium chloride after a specified time of 24 hours at room temperature. These films are weighed again after a specified interval until they show a content weight. The percent moisture content is calculated by using following formula.

$$\% \text{ moisture content} = \frac{\text{Initial weight-final weight}}{\text{Final weight}} \times 100$$

5.Moisture uptake:
First weigh the films and then the films are kept in desiccators at room temperature for 24 hours. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators until a constant weight is achieved. The percentage of moisture up take can be calculated by using following formula.

$$\%\text{moisture uptake} = \frac{\text{Final weight-initial weight}}{\text{Initial weight}} \times 100$$

6.Flatness:
This study is being performed because the transdermal patch should possess a smooth surface and should not constrict with time. For, flatness determination one patch is cut from the centre and two from each side of patches. The length of each patch is measured and variation in length is measured by determining percent constriction. 0% constriction is equivalent to 1005 flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_2} \times 100$$

I_2 = initial length of each strip

I_2= final length of each strip

7. Folding endurance:
Evaluation of folding endurance involves determining the folding capacity of the films after subjecting them to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value of that particular patch.

8.Tensile strength:
To determine tensile strength, the polymeric films are sandwiched separately by corked linear iron plates. In this test, one end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weight is added gradually to the pan that is attached with the hanging end of the thread. A pointer on the thread is used to assess the elongation of the film. The weight which is just sufficient to break the film is noted. The tensile strength can be calculated by using the following equation.

Tensile strength = F/aLb (1+L/1)
F = Force required to break
A = Width of film
B= Thickness of film
L = Length of film
I= Elongation of film at break point.

9. Skin irritancy studies:
The skin irritancy (erythema) can be conducted on mice/albino rat and potential of transdermal systems can be evaluated by modified Draize test. The scores are given from 0 to 4 depending on the degree of erythema as follows: no erythema-0, slight erythema (barely perceptible-light pink)-1, moderate erythema (dark pink) 2.

10. In vitro skin permeation:
The in vitro skin permeation of transdermal system can be studied using Franz diffusion cell (Fig. 6.10) with an effective permeation area and receptor cell volume of 1.0cm² and 10mL, respectively. The temperature is maintained at 32 ± 1°C. The receptor compartment is filled with 10 ml PBS and is constantly stirred in a magnetic stirrer at 100 rpm. The skin is then carefully checked through a magnifying glass to ensure that samples are free from any surface irregularity such as tiny holes or cervices in the portion that. The skin is mounted on a receptor compartment with the stratum corneum side facing upward into the donor compartment. The transdermal system is applied the skin in donor compartment. Samples are withdrawn through the sampling port of the diffusion cell at predetermined time intervals over 24 hours and are analyzed. Receptor

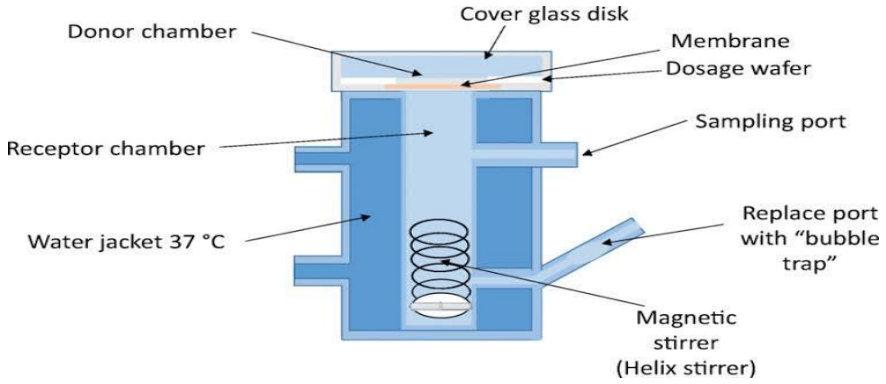

Figure No:1.7schematic of Franz diffusion cell

11. In vivo Studies:
In vivo evaluation is the true depiction to assess the drug performance. The variables that cannot be taken into account during in vitro studies can be assessed during in vivo studies. In vivo evaluation carried out by using TDDS can be

- Animal models
- Human volunteers

12. Stability Studies:
The stability studies are conducted in order to investigate the influence of temperature and relative humidity on the drug content in various formulations. These transdermal formulations are subjected to stability studies as per IC guidelines.

CONCLUSION

Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. Wide range of drugs can be delivered improved drug uptake Minimal complications and side effects low cost and easy to use. Example Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches used by over a million patients per year. Transdermal delivery of a drug product which is currently approved as oral dosage form, allows for the avoidance of first pass metabolism. Dermal patches are the most common form of transdermal delivery of drugs. However, the transdermal technologies have limitations due to the relatively impermeable thick of outer stratum corneum layer. Researchers are trying to overcome this hurdle of poor permeability by physical and chemical means.

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