

REVIEW ARTICLE

TRANSDERMAL DRUG DELIVERY PATCHES: A REVIEW

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For thousands of years, human civilizations have applied substances to the skin as cosmetic and medicinal agents. However, it was not until the twentieth century that the skin came to be used as a drug delivery route. In fact, Merriam Webster dates the word "transdermal" to 1944 highlighting that it is a relatively recent concept in medical and pharmaceutical practice. Transdermal drugs are self-contained, discrete dosage form. Drug delivery through the skin to achieve a systemic effect without producing any fluctuations in plasma concentration of the drug. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. And also provide controlled release of the drug for extended period of the time. This review article covers brief outline advantages, skin pathways for transdermal drug delivery systems (TDDS), various components of transdermal patch, and approaches for preparation of transdermal patches, evaluation of transdermal system, general clinical considerations in the use of tdds and limitation of tdds.

Key words: Transdermal, Permeation pathways, Drug delivery, Matrix, Reservoir

INTRODUCTION:

Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system. 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. This is achieved by better control of plasma drug levels and less frequent dosing. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation^{1, 2}.

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 period³.

Advantages:

There are many advantages associated with Transdermal drug delivery systems^{4, 5}.

- The drugs by pass the hepatic and pre systemic metabolism thereby increasing bioavailability.
- Risks and inconveniences of IV therapy are avoided.
- Reduced dose frequency and predictable sustained and extended duration of action.
- Easy termination of drug therapy.
- It gives greater patient compliance due to elimination of multiple dosing intervals.
- Enhanced therapeutic efficiency by avoiding the peaks and troughs in systemic drug levels associated with conventional delivery.
- Self-administration is possible.

PHYSIOLOGY OF THE SKIN:

Skin of an average adult body covers a surface of approximately 2 m² and receives about one-third of the blood circulating through the body. Skin contains (Figure 1) an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body^{5, 6}.

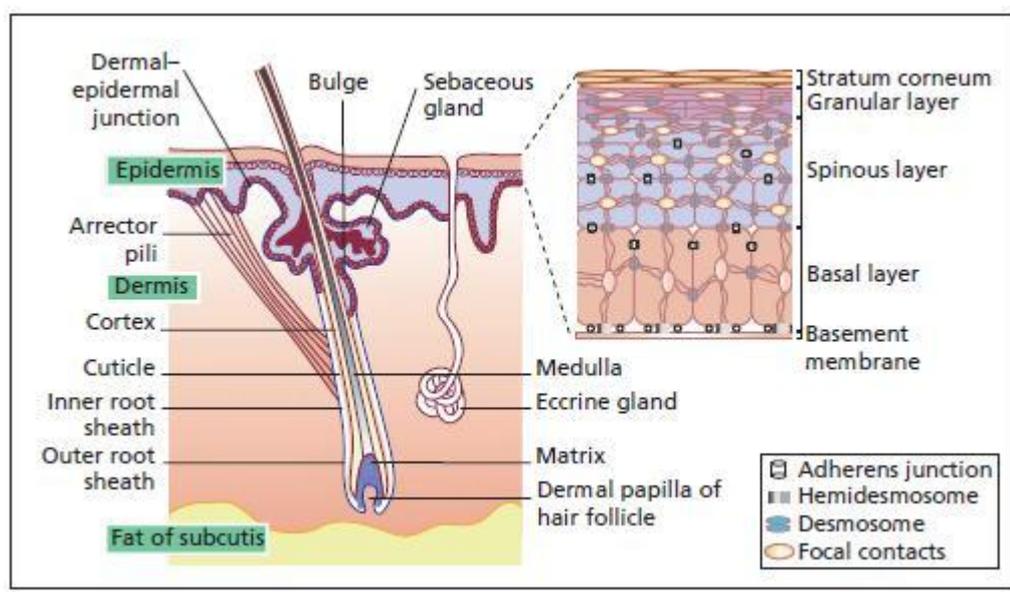


Figure 1: Anatomical and physiological Structure of skin

SKIN PATHWAYS FOR TRANSDERMAL DRUG DELIVERY SYSTEMS:

When drugs are applied on the skin surface, penetration into and through the skin can occur via various routes. Drugs penetrate either via the stratum corneum (transepidermal) or via the appendages (transappendageal) (Figure 2). During penetration through the stratum corneum, two possible routes can be distinguished, Penetration alternating through the corneocytes and the lipid lamellae (transcellular route) and ii) Penetration along the tortuous pathway along the lipid lamellae (intercellular route).

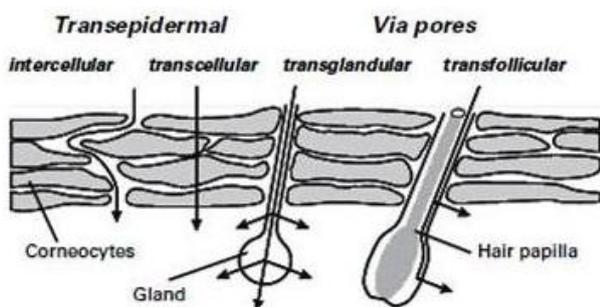


Figure 2: Possible pathways for permeation of drug across the skin barrier

Generally it is accepted that the predominant route of penetration through the stratum corneum is the

intercellular route. This is mainly caused by the densely cross-linked cornified envelope coating the keratinocytes. However transcellular transport for small hydrophilic molecules such as water cannot completely be excluded. The appendage route or shunt route includes either the duct of the eccrine sweat glands or the follicular duct. The content of the eccrine sweat glands is mainly hydrophilic, while the content of the follicular duct is lipophilic. This is mainly due to the sebum excreted into the opening of the follicular duct. It is generally accepted that due to its large surface area, passive skin permeation mainly occurs through intact stratum corneum⁷⁻¹⁰.

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

The components of Transdermal device include¹¹⁻¹³.

- Polymer matrix
- Drug
- Permeation enhancers
- Other excipients

Polymer Matrix:

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a Transdermal system. Possible useful polymers for Transdermal devices are;

Table 1: Showing different types of polymers

Natural Polymers:	Synthetic Elastomers	Synthetic Polymers
Cellulose derivatives, Zein, Gelatin, Waxes, Proteins, Gums, Natural rubber, Starch.	Polybutadiene, Hydrin rubber, polysiloxane, silicone rubber, Nitrile, Acrylonitrile, Butylrubber, Styrenebutadiene, Neoprene etc.	Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyvinylpyrrolidone, Polymethyl methacrylate, Epoxy, Polyurea, etc.

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.

Physicochemical Properties:

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

Biological Properties:

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

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.¹¹ 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, Decylmethyl sulphoxide etc.

Nonionic Surfactants: Pluronic F127, Pluronic F68, etc.

Bile Salts : Sodium 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.

Other Excipients:

Adhesives: The fastening of transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally.

Both adhesive systems should fulfill the following criteria.

- Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora.
- Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.

- Should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should have excellent (intimate) contact with the skin at macroscopic and microscopic level.

Backing Membrane: Backing 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 and 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 polyurethane) with occlusive base plate (aluminum foil disc) etc.

Release Liner: During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

DESIGN OF TRANSDERMAL DELIVERY SYSTEM:

The basic components of any transdermal delivery system include the drug dissolved or dispersed in an inert polymer matrix that provides support and platform for drug release. There are two basic designs of the patch system that dictate drug release characteristics and patch behavior:

1) **Matrix or Monolithic:** The inert polymer matrix binds with the drug and controls its release from the device.

2) **Reservoir or Membrane:** The polymer matrix does not control drug release. Instead, a rate controlling membrane present between the drug matrix and the adhesive layer provides the rate limiting barrier for drug release from the device¹⁴.

TECHNOLOGIES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS:

Several technologies have been successfully developed to provide rate control over the release and skin permeation of drugs. These technologies can be classified into four basic approaches^{5,15}.

Polymer membrane permeation-controlled TDD Systems:

In this system the drug reservoir is sandwiched between a drug-impermeable metallic plastic laminate and a rate-controlling polymeric membrane. The drug molecules are permitted to release only through the rate-controlling polymeric membrane. The rate-controlling membrane can be either a microporous or nonporous polymeric membrane, e.g., ethylene-vinyl acetate copolymer, with drug permeability. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure-sensitive adhesive polymer, e.g., silicone adhesive, may be applied to provide intimate contact of the TDD system with the skin surface (Figure

3). Ex: Transderm-Nitro system, Transderm-Scop system, the Catapres TTS system, the Estraderm system, and the Duragesic system.

Polymer matrix Diffusion-Controlled TDD Systems:

In this approach the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and the medicated polymer formed is then molded into medicated disks with a defined surface area and controlled thickness. This drug reservoir-containing polymer disc is then mounted onto an occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. In this system the adhesive polymer is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disc (Figure 4). Ex: Nitro-Dur system and the NTS system.

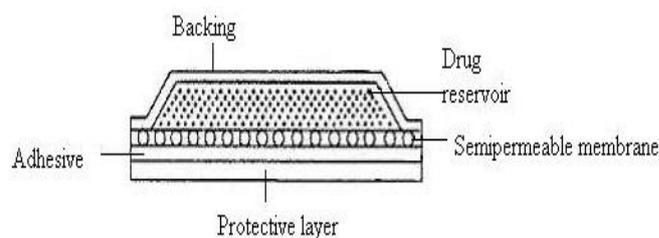


Figure 3: Transderm-Nitro system

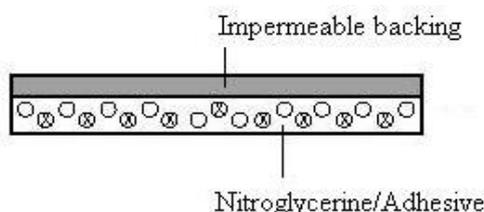


Figure 4: Nitro-Dur Transdermal System

Drug Reservoir Gradient-Controlled TDD Systems:

To overcome the non zero-order drug release profiles, polymer matrix drug dispersion-type TDD system can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multilaminar adhesive layer (Figure 5). Ex: Deponit system.

Microreservoir Dissolution-Controlled TDD Systems:

This type of the delivery system can be considered a hybrid of the reservoir and matrix dispersion type delivery systems. In this approach the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-miscible drug solubilizer, e.g., polyethylene glycol, and then homogeneously dispersing the drug suspension, with controlled aqueous solubility, in a lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chain in situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness (Figure 6).

Ex: Nitrodisc system.

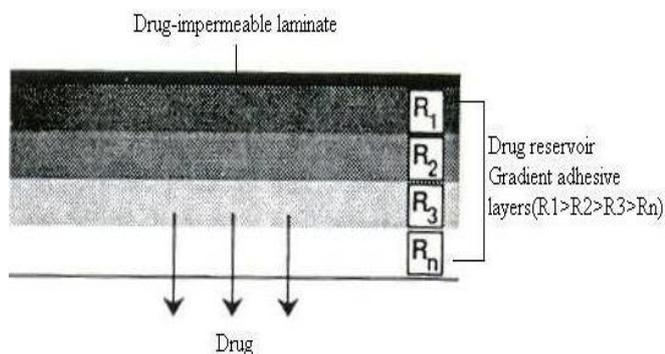


Figure 5: Drug Reservoir Gradient-Controlled TDDS

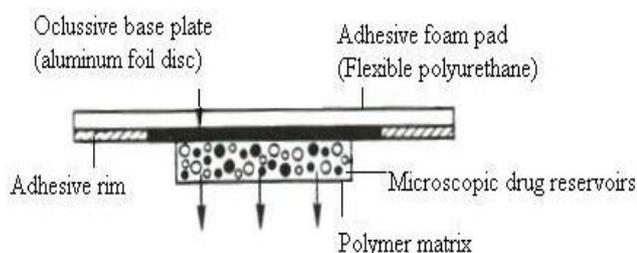


Figure 6: Microreservoir Dissolution-Controlled TDDS

PREPARATION OF TRANSDERMAL PATCHES:

Transdermal drug delivery patches can be prepared by various methods

Mercury Substrate Method:

In this method required amount of drug is dissolved in predetermined amount of polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is kept aside until air bubbles removed completely and then poured in to a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The dried films are to be stored in a desiccator¹⁶⁻²⁰.

Circular Teflon Mould Method:

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Plasticizer added into drug polymer solution. The total contents are to be stirred and then poured into a circular teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in a desiccator^{21, 22}.

Glass Substrate Method:

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and dry anumbra petriplate. The rate of solvent evaporation is controlled by inverting a glass funnel over the petriplate. After over night, the dried films are taken out and stored in a desiccator²³⁻³⁰.

By Using IPM Membranes Method:

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane^{28, 29}.

By Using EVAC Membranes Method:

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device^{28, 29}.

Aluminium Backed Adhesive Film Method:

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks^{30, 31}.

Asymmetric TPX Membrane Method:

A prototype patch can be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive³².

GENERAL CLINICAL CONSIDERATIONS IN THE USE OF TDDS:

The patient should be advised of the following general guidelines. Rotating of site of application is important to allow the skin to regain its normal permeability and to prevent skin irritation¹⁵.

- TDDS should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken. Wet or moist skin can accelerate drug permeation time.
- Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.

- Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug.
- Patient should not physically alter TDDS, since this destroys integrity of the system.
- The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds.
- A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement. TDDS should be left on when showering, bathing or swimming.
- A TDDS should be worn for full period as stated in the product's instructions followed by removal and replacement with fresh system.
- The patient or caregiver should clean the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system.
- If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation.
- Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused. The used patch discarded in a manner safe to children and pets.
- Use of transdermal patch It is important to use a different application site everyday to avoid skin irritation. Suggested rotation is:

Day 1 – Upper right arm, Day 2 – upper right chest, Day 3 – Upper left chest, Day 4 – Upper left arm, then repeat from Day 1.

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE USED:

Transdermal patch is used when:

- When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.
- Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia^{33, 34}.

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE NOT USED:

The use of transdermal patch is not suitable when:

- (1) Cure for acute pain is required.
- (2) Where rapid dose titration is required.
- (3) Where requirement of dose is equal to or less than 30 mg/24 hrs^{33, 34}.

EVALUATION TEST OF TRANSDERMAL PATCH:

Drug Excipients Interaction Studies:

The drug and excipients should be compatible to produce a stable product, and it is mandatory to detect any possible

physical and chemical interaction. Interaction studies are commonly carried out using thermal analysis, FT-IR studies, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, and absorption maxima etc³².

Drug Content: A specified area of the patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique). Each value represents average of three samples³⁵⁻³⁷.

Weight Uniformity: The prepared patches are to be dried at 60°C for 4 hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights^{37, 38}.

Thickness of the Patch: The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch³⁸⁻⁴¹.

Flatness Test: Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness³³.

Percentage Moisture Uptake: The weighed films are to be kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula^{41, 42}.

Percentage moisture uptake = [Final weight-Initial weight/initial weight] × 100.

Moisture Loss: The prepared films are to be weighed individually and to be kept in a desiccator containing calcium chloride at 40°C. After 24 hrs the films are to be reweighed and determine the percentage of moisture loss from the below formula⁴³.

% Moisture Loss = [Initial wt – Final wt/ Final wt] × 100

Water Vapor Transmission Rate (WVTR) Studies:

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in oven at 100 °C for some time. About 1g anhydrous calcium chloride was placed in the cells and respective polymer film was fixed over brim. The cell were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after storage. The amount of water vapor transmitted was found using following formula^{43, 44}.

Water Vapor Transmission Rate = Final Weight –Initial Weight/ Time X Area

It is expressed as the number of grams of moisture gained/hr/cm.sq.

Swellability: The patches of 3.14 cm² was weighed and put in a petri dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed⁴⁵.

The degree of swelling (S) was calculated using the formula,

$$S (\%) = \frac{W_t - W_o}{W_o} \times 100$$

Where S is percent swelling

W_t is the weight of patch at time t and W_o is the weight of patch at time zero.

Folding Endurance: A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be fold at the same place without breaking gave the value of the folding endurance⁴⁶.

Polariscope Examination: This test is to be performed to examine the drug crystals from patch by Polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch²¹.

Percentage Elongation Break Test: The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula⁴⁷.

Elongation percentage = $[(L1 - L2) / L2] \times 100$ Where, L1 is the final length of each strip and L2 is the initial length of each strip.

Tensile Strength: Tensile strength of the film determined with universal strength testing machine. The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one is fixed and upper one is movable. The test film of size (4 × 1 cm²) is fixed between these cell grips and force is gradually applied till the film broke³¹. The tensile strength of the film is taken directly from the dial reading in kg. Tensile strength is expressed as follows.

Tensile strength = Tensile load at break / Cross section area

Probe Tack test: In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams⁴⁷.

Skin Irritation Study: Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50 cm²) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hrs and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury³⁸.

In-vitro drug release studies: The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-ml of the dissolution medium or phosphate buffer (pH 7.4) and the apparatus was equilibrated to 32 ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or high performance liquid chromatography (HPLC). The experiment is to be performed in triplicate and the mean value can be calculated⁴⁸.

In-vitro skin permeation studies: An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male wistar rats weighing 200 to 250 g. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in diffusion medium or phosphate buffer pH 7.4 before starting the experiment.

Diffusion cell filled with diffusion medium and placed on a magnetic stirrer with a small magnetic bead for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or high performance liquid chromatography (HPLC)⁴⁹⁻⁵⁸.

Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm⁻²) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm⁻²).

In-vivo studies: *In-vivo* evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in-vitro* studies can be fully explored during *in-vivo* studies. *In-vivo* evaluation of TDDS can be carried out using:

Animal models

Human volunteers

Animal models:

The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc.

Human models:

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch

to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc.

Stability Studies: Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at $40\pm 0.5^\circ\text{C}$ and $75\pm 5\%$ RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content^{38,59}.

LIMITATIONS FOR SELECTION OF TDDS:

All types of drugs cannot be administered through this route; the drug must have some desirable Physico-Chemical properties.¹¹

- Not suitable for drugs that require high plasma levels.
- Not suitable for drugs that produce skin irritation and contact dermatitis.
- Not suitable for drugs with high molecular weight.
- Not suitable for drugs that undergo metabolism during the passage through the skin.
- The Transdermal route cannot be employed for a large number of drugs, as the skin is a very efficient barrier for penetration of drugs. Only with low dose can be administered.

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