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Transdermal drug delivery: Past, present, future trends

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Abstract

Transdermal delivery of medications was foreshadowed in earlier eras by the use of certain plasters and ointments. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medicament into the patient. A disadvantage to development however, stems from the fact that the skin is a very effective barrier. A wide variety of pharmaceuticals can be delivered by transdermal patches. The present paper highlights the various aspects of transdermal drug delivery system, their advantages, limitation and applications.

Key-Words: Skin, Transdermal Patch, Drug Delivery

Introduction

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs and avoid partial first-pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms[1-3].

These advantages are offered by the currently marketed transdermal products. One of the most successful, the nicotine patch, releases nicotine over sixteen hours, continuously suppressing the smoker's craving for a cigarette. The scopolamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically. The fentanyl patch acts for seventy-two hours, providing long-lasting pain relief. And an estrogen–progestin contraceptive patch needs to be applied only once a week, a boon for women who find it onerous to take one pill every day[2-3].

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The transdermal route is indeed desirable, but there is one small obstacle: whereas the function of the GI tract is to render ingested material suitable for absorption, the skin's function is to keep things out of the body. The major barrier within the skin is the stratum corneum, the top layer of the epidermis. The stratum corneum consists of keratinized, flattened remnants of once actively dividing epidermal cells. Hygroscopic, but impermeable to water, it behaves as a tough, flexible membrane. The intercellular space is rich in lipids. The stratum corneum is about ten microns thick, but on the palms and soles it ranges up to 600 microns in thickness[1].

Permeation of drug across skin
Characteristics of several drugs delivered transdermally
Transdermal absorption occurs through a slow process of diffusion driven by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin. Thus, the delivery system must be kept in continuous contact with the skin for a considerable time (hours to days).

The major products currently marketed for transdermal absorption are the transdermal therapeutic systems (TTS), popularly known as patches. The functional parts of a patch, proceeding from the visible surface inward to the surface opposed to the skin are:

- An impermeable backing.

- A reservoir holding the active ingredient, together with release-controlling materials.
- An adhesive to hold the patch in place on the skin.
- A protective cover that is peeled away before applying the patch.

Most patches belong to one of two general types – the reservoir system, and the matrix (or drug-in-adhesive) system.

Developing a patch formulation is a complex process. The rate and amount of transdermal absorption depend on many factors, including the nature of the drug, the drug's concentration in the reservoir or matrix, and the area of skin covered by the patch. When several dose-strengths of a drug patch are marketed (e.g., estradiol patches), the formulations used are identical but the patches have different surface areas for different strengths of delivered drug. A large excess of drug is placed in the patches to keep the concentration gradient favorable for absorption. Because the active ingredients act at low dosage and are inexpensive, the cost of wasted excess drug is not economically significant[2-8].

Historical perspecitve

Transdermal delivery of medications was foreshadowed in earlier eras by the use of certain plasters and ointments. The mustard plaster, applied as a home remedy for severe chest congestion, may be considered an example. (This author remembers his mother making mustard plasters for members of the family.) Powdered mustard seed (*Brassica nigra)* was mixed with warm water, and the resulting paste was spread on a strip of flannel, which was applied to the patient's chest with a cloth binding wrapped around the body to hold the plaster in place. The moisture and body warmth activated an enzyme (myrosin) in the mustard that hydrolyzed a glycoside (sinigrin), causing the release of the pungent active ingredient allyl isothio-cyanate ($CH_2=CHCH_2NCS$). This substance possesses the qualifications listed above for transdermal absorption.

It is a low molecular weight liquid (90 Da), lipophilic, and effective at low dosage. The flannel served as an impermeable backing and the mustard paste was the reservoir. Continuous enzymatic action released the active substance over a period of hours, until the plaster was removed. Commercially manufactured mustard plasters were sold at pharmacies.

The history of plasters has been traced back to antiquity. In addition to mustard plasters, several other plasters were recognized in early 20th century editions of the United States Pharmacopeia (USP) and National Formulary (NF). At one time, Belladonna Plaster, containing 0.25–0.30% of belladonna root alkaloids, was believed to act transdermally as an analgesic.

Perhaps the most remarkable forerunner of modern transdermal medication was Stronger Mercurial Ointment, used as a treatment for syphilis when Salvarsan and other arsenicals were in use, before the discovery of penicillin. Even the composition of this ointment was remarkable; it contained 50% of elemental mercury! To make the ointment, liquid mercury was first mixed with mercuric oleate, a mercury soap. Dispersion of the mercury into microscopic globules required a large input of energy, either by hand trituration with mortar and pestle, or by a power mixer. The dispersed mercury was made into an ointment with benzoinated lard, using suet as a stiffening agent. Stronger Mercurial Ointment was applied and rubbed into areas where the skin is thinnest: the groin and the bends of the elbows and knees. The amount applied was two to four grams of ointment, containing one to two grams of mercury.

At the time this product was in use, questions were raised about its mode of action. It was suggested that instead of mercury being absorbed through the skin, the patient was actually inhaling mercury vapor. Schamberg conducted a study in rabbits and concluded that the bulk of mercury absorption was transdermal. A more definitive study, in humans, was reported by Cole, Gericke, and Sollmann . After the ointment was rubbed in, excess ointment was washed off the skin with solvent, eliminating any source of mercury vapor. In this study, 75% of the subjects experienced salivation, one of the known systemic effects of mercury. This study was essentially a crude bio-availability study based on a clinical endpoint[7-14].

The future of transdermal therapy

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. At that time, biotech medicinals were still being developed. During the past decade biotech products have come into their own, but transdermals have essentially remained static. The number of drugs formulated in patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. One reason for this undoubtedly is the fact that only certain specialized firms can manufacture transdermal patches. Companies prefer to have full control of their projects, and to enjoy the higher profits on products developed and manufactured in house. Another reason is that only a limited number of drugs

fit the molecular weight, lipophilicity, and potency requirements for transdermal absorption[8-10].

Molecular absorption enhancement

Considerable research has been done on absorption enhancers, compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives as well as certain phenols seem to improve transdermal absorption. For example, linalool, alpha terpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it to a therapeutic level. Limonene, menthone, and eugenol were found to enhance transdermal absorption of tamoxifen. Phloretin, a polyphenol, enhanced the absorption of lignocaine. In general, absorption enhancement research has been done with excised animal skin (pig or rabbit) or human skin obtained from cadavers or plastic surgery procedures.

In contrast, an interesting clinical trial was reported from Australia where estradiol was formulated as a metered-dose aerosol, using padimate O [a para-aminobenzoic acid (PABA) derivative used as a sunscreen agent] as the penetration enhancer. The volunteer subjects were four healthy, postmenopausal women. The aerosol was applied to the ventral forearm in three sprays, each delivering one milligram of estradiol. Each spray covered 10 cm^2 of skin. After administering the spray, the skin was not touched for two minutes, but then normal activity, including washing and dressing, was resumed. The drug was applied in this way for nine successive days. Plasma estradiol/estrone ratios obtained for the topical aerosol were consistent with those produced by a topical gel and a transdermal patch, showing that a clinically relevant dose of estradiol was delivered. Using the Draize skin irritation test, no irritation was observed. This dosage form appears to be a practical alternative to the patch, unless inadvertent inhalation of the spray turns out to be a problem[11-14].

Absorption enhancement by energy input

The above are potential adjuvants to the existing "passive" transdermal systems. Also under study is the possibility of active transfer of drugs through the skin by the action of electrical or other forms of energy. The most research has been devoted to iontophoresis; sonophoresis and electroporation have been less well studied.

Iontophoresis is a method of transferring substances across the skin by applying an electrical potential difference. It promotes the transfer of charged ionic drugs and possibly high molecular weight substances such as peptides. Electric current is applied through two electrodes, placed on the patient's skin. The first, or donor, electrode (cathode) delivers the negatively charged therapeutic agent (e.g., an organic acid), whereas the second, or receptor, electrode (anode) serves to close the circuit. This setup is named cathodal iontophoresis. For positively charged drugs (e.g., amines or peptides), the cell arrangement is reversed (anodal iontophoresis). The silver (anode) and silver chloride (cathode) electrode system—utilized in both types of iontophoresis—is favored largely because it does not affect the drug solution to the extent that other electrode systems can.

Current commercial applications of iontophoresis include intradermal administration of lidocaine as a local anesthetic and dexamethasone for local inflammation. The devices used are typically bench-top systems with patches connected to a power supply through cables; however, innovations in electronic circuit and battery technology may make small, integrated patch-like systems practicable.

A small number of human trials have been conducted as proof of concept. Thus, fentanyl was tested in twelve healthy volunteers who were protected from its opioid effects by naltrexone administration. Analysis of plasma levels of fentanyl revealed transdermal absorption. Luteinizing hormone-releasing hormone (LHRH), a decapeptide having a molecular weight of about 1200 Da, was tested in eight healthy male volunteers, demonstrating that pulsatile delivery of this hormone *is* feasible.

Electroporation is a technique that delivers high voltage pulses of micro-to-millisecond duration to the skin, causing transient changes in cell membranes or lipid bilayers. It is hypothesized that pretreatment of the skin in this way would enable the passage of large, polar molecules such as heparin and peptides.

Low frequency ultrasound treatment, or sonopheresis, was reported to enhance absorption of mannitol, which was used as a model for highly hydrophilic drugs.

Transdermal patch

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medicament into the patient. A disadvantage to development however, stems from the fact that the skin is a very effective barrier. A wide variety of pharmaceuticals can be delivered by transdermal patches.

An adhesive tape with Fludroxycortide impregnated in the adhesive, for the treatment of the skin itself, was developed in the US and sold as Cordran tape. As a steroid fludroxycortide is absorbed systemically but this is not the desired action.

The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979. These patches administered scopolamine for motion sickness[10-16].

Development

Before these patches go into the market, they have to be carefully studied. One way to study these patches are through the use of Franz Diffusion Cell systems. This system is used to study the effects of temperature on the permeated amount of a specific drug on a certain type of membrane, which in this case would be the membrane that is used in the patches. A Franz Diffusion Cell system is composed of a receptor and a donor cell. In many of these research studies the following procedure is used. The donor cell is set at a specific temperature (the temperature of the body), while the receptor cell is set at different one (temperature of the environment).

Different runs are performed using different temperatures to study the impact of temperature on the release of a certain medicament through a certain type of membrane. Although different concentrations of the medicament are used in this study, they do not affect the amount permeated through the membrane (the process is constant). From Chemical kinetics it's concluded that these studies are zero order, since the concentration plays no role in the permeated amount through the membrane.

Some pharmaceuticals must be combined with substances, such as alcohol, within the patch to increase their ability to penetrate the skin in order to be used in a transdermal patch. Others can overwhelm the body if applied in only one place, and are often cut into sections and applied to different parts of the body to avoid this, such as nitroglycerin. Many molecules, however, such as insulin, are too large to pass through the skin.

Popular uses

The highest selling transdermal patch in the United States was the nicotine patch which releases nicotine to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.

Fentanyl, an analgesic for severe pain

Other skin patches administer estrogen for menopause. This also seems to prevent osteoporosis after menopause.

Nitroglycerin patches for angina are available.

Lidocaine patches, marketed as Lidoderm, relieve the peripheral pain of shingles (*herpes zoster*). It is also now commonly used off-label, for pain from acute injuries and chronic pain, although limited by its requirement to be removed for 12 hours, after 12 hours of use.

Flector (Diclofenac epolamine) patch is an NSAID topical patch for the treatment of acute pain due to minor strains, sprains, and contusions. It is also being used in the treatment of pain and inflammation for chronic conditions benefiting from NSAIDs, including fibromyalgia and arthritis.

Clonidine has also been administered transdermally.

Buprenorphine, marketed as BuTrans, as analgesia for moderate to severe chronic pain

Recent developments expanded their use to the delivery of hormonal contraceptives, antidepressants and even pain killers and stimulants for Attention Deficit Hyperactivity Disorder/ADHD.

Vitamin B_1 and Aloe patches are also available as insect repellents[11-17].

Adverse events

In 2005, the FDA announced that they are investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. The Duragesic product label was subsequently updated to add safety information in June 2005.

In 2009, the FDA announced a public health advisory warning of the risk of burns during MRI scans from transdermal drug patches with metallic backings. Patients should be advised to remove any medicated patch prior to an MRI scan and replace it with a new patch after the scan is complete.

Technologies for developing transdermal drug Delivery systems[10-16]

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 and are discussed in this section.

Polymer Membrane permeation-controlled TDDS

In this system the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate-controlling polymeric membrane. The drug molecules are permitted to release only through the rate-controlling polymeric membrane. In the drug reservoir compartment the drug solids are dispersed homogeneously in a solid polymer matrix, suspended in a unleachable, viscous liquid medium (e.g., silicone fluid) to form a paste like suspension, or dissolved in a releasable solvent (e.g., alkyl alcohol) to form a clear drug solution

The rate controlling membrane can be either a microporous or a nonporous polymeric membrane with specific drug permeability. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure-sensitive adhesive polymer, may be applied to provide intimate contact of the TDD system with the skin surface. The rate of drug release from this TDD system can be tailored by varying the composition of the drug reservoir formulation and the permeability coefficient and/or thickness of the rate-controlling membrane.

Polymer matrix diffusion-controlled TDDS

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 disk is then mounted onto an occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating the adhesive polymer directly on the surface of the medicated disk, as shown earlier in the first type of TDD systems, in this system the adhesive polymer is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk.

Drug reservoir gradient-controlled TDDS

To overcome the non-zero-order (Q versus t ½) drug release profiles, polymer matrix drug dispersion-type TDD systems 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 multilaminate adhesive layers. The rate of drug release from this type of drug reservoir gradient controlled TDDS can be expressed by

$$dQ/dt = K_{a/r}\, D_a/h_a(t) * L_d(h_a)$$

In this system the thickness of diffusional path throw which drug molecules diffuse increases with time.

Microreservoir Dissolution- Controlled TDDS[30]

This type of drug delivery system can be considered a hybrid of the reservoir- and matrix dispersion-type drug delivery systems. In this approach the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water –miscible drug solubilizer, e.g., polyethylene glycol, and then homogeneously dispersion 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 chains in situ, which produces a medicated polymer disk with a constant surface area and a fixed thickness.

A TDDS is then produced by mounting the medicated disk at the center of an adhesive pad.

Basic components of transdermal drug delivery systems[11-17]

The components of transdermal devices includes:

➢ Polymer matrix or matrices.
➢ The drug.
➢ Permeation Enhancers.
➢ Liner - Protects the patch during storage. The liner is removed prior to use.
➢ Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.
➢ Membrane - Controls the release of the drug from the reservoir and multi-layer patches.
➢ Backing - Protects the patch from the outer environment.
➢ **Polymer matrix:** The polymer controls the release of drug from the devices. The following criteria should be satisfied for a polymer to be used in a transdermal system.
A. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that specific drug diffuses properly and gets released through it.
  ▪ The polymer should be stable.
  ▪ The polymer must be non reactive with the drug.
  ▪ The polymer can be easily manufactured.
  ▪ It can be fabricated easily into the desired product.
  ▪ It must be economic.
  ▪ The polymer and its degradation product must be non-toxic.
  ▪ They are not antagonistic to the host.
  ▪ The mechanical properties of the polymer should not deteoriate excessively when large amount of active agent or incorporated into it.

Polymers used in transdermal system:

A polymer is a very large organic molecule made up from many smaller molecules joined together. The small molecules are known as monomers and most polymers are made up of one or two different types of monomer.

➢ **The Drug** – Drug solution in direct contact with release liner. For successfully developing transdermal delivery system, the drug should be choosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.
(a) Physiochemical Properties

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

(b) Biological Properties

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

➢ **Permeation Enhancers**

These are compounds which promotes skin permeability by altering the skin as barrier to the flux of a desired penetrant. The flux J of drugs across the skin can be written as:

J= D dc/dx, Where, D is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusing molecules as well as the membrane resistance. C is the conc. of the diffusion species. X is the spatial coordinate.

The permeation enhancers may be classified under the following categories:

a. Solvents
b. Surfactants
c. Binary systems
d. Miscellaneous chemicals

Solvents: These compounds increased penetration possibly by swelling the polar pathway or by fluidizing lipids.

Selection criteria for the solvents: The solvent must be possessed following criteria:
  ➢ The solvent must be non reactive with the drug.
  ➢ The solvent can be easily vapourised.
  ➢ It must be economic.
  ➢ The solvent must be non-toxic.
  ➢ They are not antagonistic to the host.

Examples:
  Water

Organic Solvents- Chloroform, methanol, ethanol, acetone etc.

Alkylmethylsulfoxides- Dimethylsulfoxides, alkylhomologs of methylsulfoxide, dimethyl acetamide and dimethylformamide.

Pyrrolidones- 2-pyrrolidone, N-methyl 2pyrrolidone.

Laurocapram (azone)

Miscellaneous solvents- Propylene glycol, glycerol, silicon fluids, isopropyl palmitate.

Surfactants: They enhance polar pathway transport of hydrophilic drugs. Examples: Pluronic F127.

Binary system: These systems apparently open up the heterogeneous multilaminate pathways as well as the continuous pathways. e.g: oleic acid and propylene glycol.

Miscellaneous chemicals: These mainly include urea, a hydrating and crytolytic agents

Other Excipients:

Adhesives: The adhesive must be fulfill the following criteria:
  a) Should not irritate or sensitized the skin during the contact time.
  b) Should adhere to the skin aggressively.
  c) Its position should not be disturbed by the activities such as bathing, exercise etc.
  d) Should be easily removed.
  e) Should not leaved and unwashable residue on the skin.
  f) Should have excellent contact with the skin at microscopic and macroscopic level.

The phase adhesive system should also fulfill the following criteria:

1. Physical and Chemical compatibility of the drug, excipients and enhancers device of which it is a part.
2. Permeation of drug should not be effected.
3. The delivery of simple or blended permeation enhancers should not be effected.

Backing membrane: Backing membranes are:

1. Flexible.
2. They provide a good bond to the drug reservoir.
3. Prevent drug from leaving the doses form through the top.
4. It is permeable substance that protects the product during use on the skin.

Types

Sample transdermal patches. On left is a 'reservoir' type, on the right a 'Single-layer Drug-in-Adhesive' version. Both contain exactly the same level of the same active ingredient with identical release rates.

There are five main types of transdermal patches.

Single-layer Drug-in-Adhesive
The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Multi-layer Drug-in-Adhesive
The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

Reservoir
Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

Matrix
The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

Vapour Patch
In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapour patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

Regulatory aspects
A transdermal patch is classified by the U.S. Food and Drug Administration as a combination product, consisting of a medical device combined with a drug or biological product that the device is designed to deliver. Prior to sale in the United States, any transdermal patch product must apply for and receive approval from the Food and Drug Administration, demonstrating safety and efficacy for its intended use.

Plasticizers
Plasticizers play an important role in the film formation process. The degree of latex particle coalescence and the quality of the resulting film are dependent on the type and amount of plasticizer added to the coating. The efficiency of a plasticizer is related to its chemical structure and the extent of interaction with the polymer. The plasticizers currently employed in pharmaceutical coatings include polyols like glycerin, organic esters such as citrate esters and dibutyl sebacate, and oils such as castor oil. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch. It reduce the brittleness, increase the flexibility, and improve the toughness and tensile strength of polymers.

Evaluation of transdermal patches[8-14]
Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed 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 ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

Physicochemical evaluation
Thickness: The thickness of transdermal film is determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination: An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% - 115% of the

specified value and one has content not less than 75%-125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

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

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

Moisture Uptake: Weighed films are kept in a desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

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

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

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

I_2 = Final length of each strip
I_1 = Initial length of each strip

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. 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 weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted.

The tensile strength can be calculated using the following equation.

Tensile strength= F/a.b (1+L/l)

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point

In another study, Tensile strength of the film was determined with the help of texture analyzer. The force and elongation were measured when the films broke.

Water vapor transmission studies (WVT): For the determination of WVT, Rao *et al.*, (1997) weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch.

In other reported method, desiccators were used to place vials, in which 200 ml of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated.

WVT = W/ ST

W is the increase in weight in 24 h; S is area of film exposed (cm^2); T is exposure time

Microscopic studies: Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope.

Adhesive studies: The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors:

- **Peel Adhesion properties**: It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied

to substrate at 180° angle. The test is passed if there is no residue on the substrate. Minghetti *et al.*, (2003) performed the test with a tensile testing machine Acquati model AG/MC 1.

- **Tack properties**: It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

Thumb tack test: The force required to remove thumb from adhesive is a measure of tack.

Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90∘ at the speed of 12 inch/min.

Probe tack test: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

- **Shear strength properties or creep resistance** : Shear strength is the measurement of the cohesive strength of an adhesive polymer *i.e.*, device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti et al., (2003) performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.

In vitro release studies
Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system *e.g.*, Higuchi, First order, Zero order and Peppas and Korsenmeyer model. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug.
There are various methods available for determination of drug release rate of TDDS.

- **The Paddle over Disc**: (USP apparatus 5/ PhEur 2.9.4.1) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C

- **The Cylinder modified USP Basket**: (USP apparatus 6 / PhEur 2.9.4.3) This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C.

- **The reciprocating disc**: (USP apparatus 7) In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method (PhEur 2.9.4.2) may be used.

- **Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell**: In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid *i.e.,* buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically.
The pH of the dissolution medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). Ph Eur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models in order to ascertain the release mechanism.

In vitro permeation studies
The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages.

Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux *i.e.,* drug permeated per cm^2 per second.

Preparation of skin for permeation studies: Hairless animal skin and human cadaver skin are used for permeation studies. Human cadaver skin may be a logical choice as the skin model because the final product will be used in humans. But it is not easily available. So, hairless animal skin is generally favored as it is easily obtained from animals of specific age group or sex.

Intact Full thickness skin: Hair on dorsal skin of animal are removed with animal hair clipper, subcutaneous tissue is surgically removed and dermis side is wiped with isopropyl alcohol to remove residual adhering fat. The skin is washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20C till further use. The skin is defrosted at room temperature when required.

Separation of epidermis from full thickness skin: The prepared full thickness skin is treated with 2M sodium bromide solution in water for 6 h. The epidermis is separated by using a cotton swab moistened with distilled water. Then epidermis sheet is cleaned by washing with distilled water and dried under vacuum. Dried sheets are stored in desiccators until further use.

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 following models

Animal models: Considerable time and resources are required to carryout human studies, so animal studies are preferred at small scale. 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. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for evaluation of transdermal drug delivery in man.

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. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

Skin irritation studies: White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin. Mutalik and Udupa (2005) carried out skin irritation test using mice. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of group I was served as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals were sacrificed and skin samples were processed for histological examination. The results of this study showed that the prepared

systems (both blank and drug loaded) and USP adhesive tape produced negligible erythema and edema. While standard irritant, formalin produced severe edema and erythema. The histopathologic examination of the skin also indicated that adhesive tape and prepared patches produced mild inflammation and edema.

Stability studies: The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines.

Regulatory requirements: A transdermal patch is classified by U.S. Food and Drug Administration (FDA) as a combination product, consisting of a medical device combined with drug or biologic product that the device is designed to deliver. Prior to sale, any transdermal patch product must receive approval from FDA, demonstrating safety and efficacy for its intended use.

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