INTRODUCTION

Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. The relative impermeability of skin is well known, and this is associated with its functions as a dual protective barrier against invasion by micro-organisms and the prevention of the loss of physiologically essential substances such as water. Elucidation of factors that contribute to this impermeability has made the use of skin as a route for controlled systemic drug delivery possible. Basically, four systems are available that allow for effective absorption of drugs across the skin. The microsealed system is a partition-controlled delivery system that contains a drug reservoir with a saturated suspension of drug in a water-miscible solvent homogeneously dispersed in a silicone elastomer matrix. A second system is the matrix-diffusion controlled system. The third and most widely used system for transdermal drug delivery is the membrane-permeation controlled system. A fourth system, recently made available, is the gradient-charged system. Additionally, advanced transdermal carriers include systems such as iontophoretic and sonophoretic systems, thermosetting gels, prodrugs, and liposomes.1 Many drugs have been formulated in transdermal systems, and others are being examined for the feasibility of their delivery in this manner (e.g., nicotine antihistamines, beta-blockers, calcium channel blockers, non-steroidal anti-inflammatory drugs, contraceptives, anti-arrhythmic drugs, insulin, antivirals, hormones, alpha-interferon, and cancer chemotherapeutic agents). Research also continues on various chemical penetration enhancers that may allow delivery of therapeutic substances.

Transdermal drug delivery system is topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medications. These devices allow for pharmaceuticals to be delivered across the skin barrier.

This approach to drug delivery offers many advantages over traditional methods. As a substitute for the oral route, transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosing due to the shortened metabolism pathway of the transdermal route versus the gastrointestinal pathway. The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications. Multi-day therapy with a
single application, rapid notification of medication in the event of emergency, as well as the capacity to terminate drug effects rapidly via patch removal, are all further advantages of this route. However, this system has its own limitations in which the drug that require high blood levels cannot be administered and may even cause irritation or sensitization of the skin. The adhesives may not adhere well to all types of skin and may be uncomfortable to wear. Along with these limitations, the high cost of the product is also a major drawback for the wide acceptance of this product.[1-3]

Components of Transdermal Drug Delivery Systems

- Polymer matrix or matrices.
- The drug.
- Permeation enhancers.
- Other excipients.

Polymer Matrix
The Polymer controls the release of the drug from the device. Possible useful polymers for transdermal devices are:

Natural Polymers:
- Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

Synthetic Elastomers:
- Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadiene rubber, Neoprene etc.

Synthetic Polymers:
- Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polycrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

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

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 low melting point.

Enhancers
These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

Solvents
These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing 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, N-methyl 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 polar head group and the hydrocarbon chain length.

Anionic Surfactants:
- Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decydecylmethyl sulphoxide etc.

Nonionic Surfactants:
- Pluronic F127, Pluronic F68, etc. Bile Salts: e.g. Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Biary system
These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways, e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

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 sparse. These include eucalyptol, di-o-methyl-β-cyclodextrin and soyabean casein.

Other Excipients

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

TRANSDERMAL PATCHES

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.

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.

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.

Drug Matrix-in-Adhesive

The Matrix system design is characterized by the inclusion of a semi-solid 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.

EVALUATION OF TRANSDERMAL PATCHES

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

1. 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% to 115% of the specified value and one has content not less than 75% to 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.

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

   **Moisture Uptake:**
   Weighed films are kept in a desiccator 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 desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

   \[
   \% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
   \]
**Initial weight**

**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.

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

- \( I_1 \): Final length of each strip
- \( I_2 \): 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.

\[
\text{Tensile strength} = \frac{F}{a \times b} (1 + \frac{L}{l})
\]

- \( F \): Force required to break; \( a \): width of film; \( b \): thickness of film; \( L \): length of film; \( l \): elongation of film at break point

**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.

**2. 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. 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.

**3. 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 lipophilic 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 cm² per sec-
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 is 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 -20°C 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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Type of transdermal patch</th>
<th>Manufacturer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Duragesic</td>
<td>Reservoir</td>
<td>Alza / Janssen</td>
<td>Moderate/ Severe pain</td>
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<tr>
<td>Nitroglycerine</td>
<td>Deponit ,Minitran, Nitrodisc,Nitroderm, Transderm,Nitro</td>
<td>Drug in adhesive, Drug adhesive, Micro reservoir in,Matrix , Reservoir</td>
<td>Schwarz Pharma,3M, Key Pharmaceuticals, Searle, USA</td>
<td>Angina Pectoris</td>
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<td>Nicotine</td>
<td>Prostep ,Nicotrol , Habitrol</td>
<td>Reservoir,Drug in adhesive Drug in adhesive</td>
<td>ElanCorp/Lederie Labs, Cygnus Inc /McNeil Consumer Products Ltd. ,Novartis</td>
<td>Smoking Cessation</td>
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<tr>
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<td>Reservoir ,Reservoir Thera Tech/</td>
<td>GlaxoSmithKline</td>
<td>Hypogonadism</td>
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<td>Catapres-TTS</td>
<td>Membrane matrix hybrid type</td>
<td>Alza/Boeheringer Ingelheim</td>
<td>Hypertension</td>
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<td>Drug in adhesive</td>
<td>Cerner Multum, Inc.</td>
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<td>Transderm Scop</td>
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<td>Motion sickness</td>
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<td>3M Pharmaceuticals/ First</td>
<td>First Postmenstrual</td>
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<td></td>
<td></td>
<td>Berlex,Alza/Novartis,Women Healthcare, Inc.,Johnson &amp;Johnson</td>
<td>Syndrome</td>
</tr>
</tbody>
</table>

4. 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
Considerable time and resources are required to carry out 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 in vivo 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.

CONCLUSION

Transdermal delivery is hardly an old technology, and the technology no longer is just adhesive patches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules.

Transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroperoration (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable.
and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin. It promises to eliminate needles for administration of a wide variety of drugs in the future. Therefore, from the present review it was concluded that there is great possibility in the treatment of many disease and disorders. Also, Table 1 gave information on available medication for transdermal delivery system.

REFERENCES


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