



## FORMULATION AND EVALUATION ASPECTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

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Accepted on: 06-12-2010; Finalized on: 10-02-2011.

### ABSTRACT

The conventional oral dosage forms has significant drawbacks of poor bioavailability due to hepatic first pass metabolism and tendency to produce rapid blood level spikes (Both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To improve such characters transdermal drug delivery system (TDDS) was emerged which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body thereby reducing both the size and number of doses. TDDS is such a mode of delivery which has been explored extensively over the last 25 years, with therapeutic success. TDDS is ideally suited for diseases that demand chronic treatment. Topical administration of drugs offers many advantages over conventional oral dosage form. Important advantages of TDDS are limitation of hepatic metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.

**Keywords:** Transdermal drug delivery system (TDDS), Bioavailability, Hepatic first pass metabolism, therapeutic efficacy.

### 1. INTRODUCTION

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin<sup>1, 2</sup>. Conventional systems of medication which require multi dose therapy have numerous problems and complications. The design of conventional dosage form, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient<sup>3, 4</sup>. The impetus for the development of novel drug delivery systems, apart from therapeutic efficacy is cost. Redesigning the modules and means to transport medicine into the body is less demanding and more lucrative task. To address these problems, controlled release drug delivery system, a novel drug delivery approach evolves, which facilitates the drug release into systemic circulation at a pre-determined rates<sup>5-7</sup>. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time<sup>7-10</sup>.

For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin<sup>7</sup>. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs<sup>12</sup>.

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged<sup>3</sup>. In comparison to conventional pharmaceutical dosage forms, TDDS offer many advantages, such as elimination of first pass metabolism, enhancement of therapeutic efficiency and (maintenance of steady plasma level of the drug sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance<sup>12, 13</sup>, reduces the load that the oral route commonly places on the digestive tract and liver<sup>14, 15</sup>. Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy. Designing and development of transdermal patches can be described as state of the art<sup>14, 15</sup>.

### 2. FORMULATION ASPECTS OF TDDS

#### 2.1 Basic Components of TDDS:

- 2.1.1 Polymer matrix / Drug reservoir
- 2.1.2 Drug
- 2.1.3 Permeation enhancers
- 2.1.4 Pressure sensitive adhesive (PSA)
- 2.1.5 Backing laminates
- 2.1.6 Release liner
- 2.1.7 Other excipients like plasticizers and solvents



### 2.1.1 Polymer matrix / Drug reservoir

Polymers are the heart of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have good stability and compatibility with the drug and other components of the system and they should provide effective release of a drug throughout the device with safe status<sup>16</sup>.

The polymers used for TDDS can be classified as:

**Natural polymers:** e.g. cellulose derivatives, zein, gelatine, shellac, waxes, gums, natural rubber and chitosan *etc.*

**Synthetic elastomers:** e.g. polybutadiene, hydriin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc.*

**Synthetic polymers:** e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc.*

The polymers like polyethylene glycol<sup>17</sup>, eudragits<sup>18</sup>, ethyl cellulose, polyvinylpyrrolidone<sup>19</sup> and hydroxypropyl methylcellulose<sup>20</sup> are used as matrix type TDDS.

The polymers like EVA<sup>21</sup>, silicon rubber and polyurethane<sup>22</sup> are used as rate controlling TDDS.

### 2.1.2 Selection of drugs

The selection of drug for TDDS is based on physicochemical properties of drug. Transdermal drug delivery system is much suitable for drug having<sup>23, 24</sup>,

- Extensive first pass metabolism.
- Narrow therapeutic window.
- Short half-life which causes non-compliance due to frequent dosing.
- Dose should be less (mg/day)<sup>25</sup>.
- Low molecular weight (less than 500 Daltons).
- Adequate solubility in oil and water (log P in the range of 1-3).
- Low melting point (less than 200°C).

### 2.1.3 Permeation enhancers

These compounds are useful to increase permeability of stratum corneum by interacting with structural components of stratum corneum *i.e.*, proteins or lipids to attain higher therapeutic levels of the drug<sup>26</sup>. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability<sup>27</sup>.

Some example are Dimethyl sulfoxide, Propylene glycol, 2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Pluronic,

Cardamom oil, Caraway oil, Lemon oil, Menthol, d-limonene, Linoleic acid.<sup>14</sup>

### 2.1.4 Pressure sensitive adhesives

The pressure-sensitive adhesive (PSA) affixes the Transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue<sup>28, 29</sup>. Adhesives must be skin-compatible, causing minimal irritation or sensitization, and removable without inflicting physical trauma or leaving residue. In addition, they must be able to dissolve drug and Excipient in quantities sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability.

PSAs used in commercially available Transdermal systems include polyacrylate, polyisobutylene, and polysiloxane<sup>30</sup>.

*Polyacrylates*, are most widely used. In general, all acrylic adhesives are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of polyacrylate matrices.

*Polyisobutylenes (PIBs)*, in contrast, are characterized by a low solvent capacity for drugs. PIBs are often used in membrane-controlled systems where the initial burst of drug released from the adhesive layer should be limited. PIB-based adhesives are mixtures of high and low molecular weight polymers, which provide cohesion and tackiness, respectively. By adjusting the composition of the PIB formulation, cold flow and adhesiveness can be customized for each system.

*Silicone*, adhesives are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicones, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups. To address this problem, special silicones have been developed that are rendered resistant to amine-catalyzed condensation through end-capping of silanol functional groups.

*Hot Melt Pressure Sensitive Adhesives (HMPSA)*, HMPSA melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flowless state. They are thermoplastic in nature. Compounded HMPSA are Ethylene vinyl acetate copolymers, Paraffin waxes, Low density polypropylene, Styrene-butadiene copolymers, Ethylene-ethacrylate copolymers. Uncompounded HMPSA are Polyesters, Polyamides and Polyurethanes.

### 2.1.5 Backing laminate

Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear,



pigmented, or metallized form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability. In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate<sup>31, 32</sup>.

Examples of some backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethylene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate

### 2.1.6 Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metalised laminates<sup>29, 33</sup>.

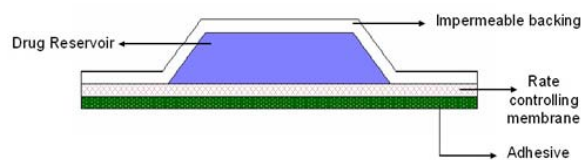
### 2.1.7 Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir<sup>21, 35</sup>. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch<sup>35, 36</sup>.

## 2.2 Methods of Preparation of TDDS

### 2.2.1 Polymer membrane permeation-controlled TDDS

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied (Figure-1). The rate of drug release from this type of Transdermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate controlling membrane<sup>9, 37</sup>.

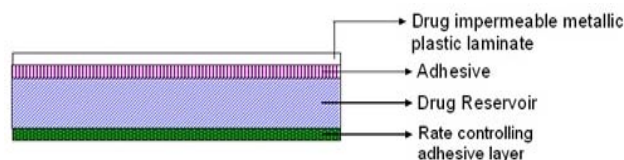


**Figure: 1** Polymer membrane permeation-controlled TDDS

**TransdermScop** (Scopolamine) for 3 days protection of motion sickness and **TransdermNitro** (Nitroglycerine) for once a day medication of angina pectoris.

### 2.2.2 Adhesive diffusion controlled TDDS

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in case of hot-melt adhesives) onto an impervious backing layer (Figure-2). The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlling drug delivery system<sup>9, 37</sup>.

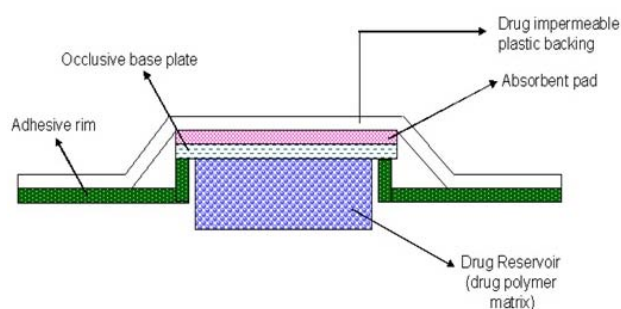


**Figure: 2** Adhesive diffusion controlled TDDS

**Deponit** (Nitroglycerine) for once a day medication of angina pectoris.

### 2.2.3 Matrix diffusion controlled TDDS

The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer (Figure-3). Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim<sup>9, 37</sup>.



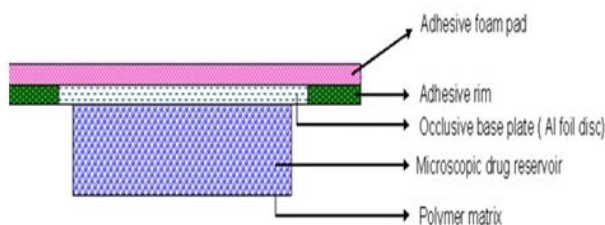
**Figure: 3** Matrix diffusion controlled TDDS

**Nitro Dur** (Nitroglycerine) used for once a day medication of angina pectoris.

### 2.2.4 Microreservoir controlled TDDS

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the

solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs (Figure 4). The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ. A Transdermal system therapeutic system thus formed as a medicated disc positioned at the center and surrounded by an adhesive rim<sup>9, 37</sup>.



**Figure 4:** Microreservoir controlled TDDS

**Nitro-dur® System** (Nitroglycerin) for once a day treatment of angina pectoris.

### 3. EVALUATION METHODS

The evaluation methods for transdermal dosage form can be classified into following types:

- 3.1 Physicochemical evaluation
- 3.2 *In vitro* evaluation
- 3.3 *In vivo* evaluation

#### 3.1 Physicochemical Evaluation

##### 3.1.1 Interaction studies

The drug and the excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are taken out by Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, absorption maxima<sup>3, 38, 39</sup>.

##### 3.1.2 Thickness of the patch

The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch<sup>40</sup>.

##### 3.1.3 Weight uniformity

The prepared patches are to be dried at 60°C for 4hrs 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<sup>40</sup>.

##### 3.1.4 Folding endurance

A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance<sup>40</sup>.

##### 3.1.5 Percentage moisture content

The prepared patches are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature. After 24 hrs the films are to be reweighed and determine the percentage moisture content by below formula<sup>40</sup>.

Percentage moisture content =  $\frac{[\text{Initial weight} - \text{Final weight}]}{\text{Final weight}} \times 100$ .

##### 3.1.6 Percentage moisture uptake

The prepared patches are to be weighed individually and to be kept in a desiccator 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 by below formula<sup>40</sup>.

Percentage moisture uptake =  $\frac{[\text{Final weight} - \text{Initial weight}]}{\text{Initial weight}} \times 100$ .

##### 3.1.7 Water vapour permeability (WVP) evaluation

Water vapour permeability can be determined by a natural air circulation oven. The WVP can be determined by the following formula<sup>41</sup>.

$$\text{WVP} = \frac{W}{A}$$

Where, WVP is expressed in gm/m<sup>2</sup> per 24 hrs,

W is the amount of vapour permeated through the patch expressed in gm/24 hrs

A is the surface area of the exposure samples expressed in m<sup>2</sup>.

##### 3.1.8 Drug content

A specified area of 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). Then take the average of three different samples<sup>41</sup>.

##### 3.1.9 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<sup>14</sup>.

### 3.1.10 Uniformity of dosage unit test

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2µm membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated<sup>42</sup>.

### 3.1.11 Polariscopic examination

A specific surface area of the piece is to be kept on the object slide of Polariscopic and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch<sup>42</sup>.

### 3.1.12 Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength<sup>42</sup>.

### 3.1.13 Adhesive studied

**Peel Adhesion test:** In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion (Figure-5). Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured<sup>42</sup>.



Figure: 5 Peel Adhesion test

**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<sup>42</sup>.

**Thumb tack test:** It is a qualitative test applied for tack property determination of adhesive. The thumb is simply

pressed on the adhesive and the relative tack property is detected<sup>42</sup>.

### 3.1.14 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% flatness<sup>39</sup>.

$$\% \text{ constriction} = \frac{l_1 - l_2}{l_1} \times 100$$

where,  $l_1$  = Initial length of each strip.

$l_2$  = final length of each strip.

### 3.1.15 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 formula<sup>43</sup>.

$$\text{Elongation percentages} = \frac{L_1 - L_2}{L_2} \times 100$$

Where,  $L_1$  = is the final length of each strip.

$L_2$  = is the initial length of each strip.

### 3.1.16 Rolling ball tack test

This test measures the softness of a polymer that relates to tack. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive (Figure-6). The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch<sup>9</sup>.

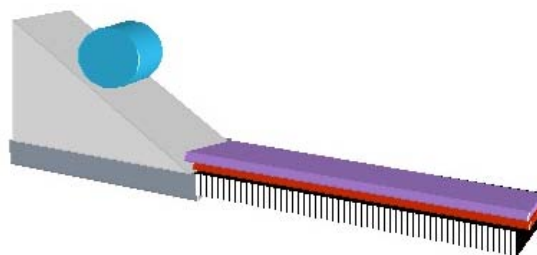


Figure: 6 Rolling ball tack test

### 3.1.17 Quick stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90° at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured (Figure-7) and recorded as tack value, which is expressed in ounces or grams per inch width<sup>9</sup>.

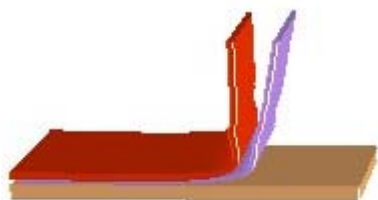


Figure: 7 Quick stick (peel-tack) test

### 3.1.18 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 (Figure-8). The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams<sup>9</sup>.

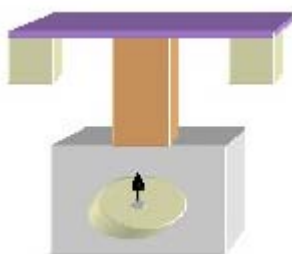


Figure: 8 Probe Tack test

### 3.1.19 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 (Figure-9) which was fabricated according to PSTC-7 (pressure sensitive tape council) specification<sup>14</sup>.

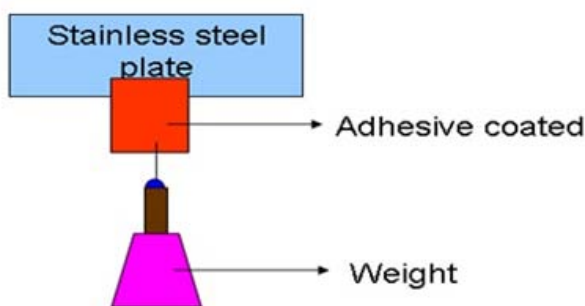


Figure: 9 Shear strength properties or creep resistance

### 3.1.20 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<sup>44</sup>.

## 3.2 *In vitro* Evaluation of TDDS

### 3.2.1 *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  $32 \pm 0.5^\circ\text{C}$ . 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 HPLC. The experiment is to be performed in triplicate and the mean value can be calculated<sup>44</sup>.

### 3.2.2 *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 gm. 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 dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at  $32 \pm 0.5^\circ\text{C}$  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 HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated ( $\text{mg cm}^2$ ) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load ( $\text{mg cm}^2$ )<sup>44</sup>.

## 3.3 *In vivo* Evaluation

**3.3.1 *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<sup>14</sup>.

**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<sup>14</sup>.

### 3.3.2 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 cm<sup>2</sup>) 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 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury<sup>42</sup>.

## 4. CONCLUSION

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

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