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Reviewed Article

Transdermal drug delivery system: Formulation aspects and evaluation

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The conventional oral dosage forms have significant setbacks of poor bioavailability due to hepatic first pass metabolism. To improve characters of transdermal drug delivery system (TDDS) was emerged, which will improve the therapeutic efficacy and safety of drugs by specific sites within the body, thereby reducing both the size and number of doses. Skin is an effective medium from which absorption of the drug takes place and enters into systematic circulation over a period of time. The present article reviews the selection of drug candidates and polymers suitable to be formulated as transdermal system, advantages, disadvantages of formulation design and the methods of evaluation.

Key words: Transdermal drug delivery system (TDDS), bioavailability, hepatic first pass metabolism.

INTRODUCTION

Recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven to be effectively delivered through the skin, typically cardiac drugs such as nitroglycerin and hormones such as estrogen. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. The basic components of any transdermal delivery system include the drug(s) dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil, and a pressure-sensitive adhesive that anchors the patch to the skin. The adhesive is covered by a release liner which needs to be peeled off before applying the patch to the skin. Drugs administered via skin patches include scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine.

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.

Advantages

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea (Finnin and Morgan, 1999).
3. They avoid the first-pass effect, that is, the initial passage of “s” drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes (Allen et al., 2005; Barry, 2002).

4. They are non invasive, avoiding the inconvenience of Parenteral therapy (Allen et al., 2005; Barry, 2002).
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration (Allen et al., 2005).
6. The activity of drugs having “s” short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release (Barry, 2002; Cleary).
7. Drug therapy may be terminated rapidly by removal of its application from the surface of the skin (Barry, 2002).
8. They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.

At the same time, transdermal drug delivery has few disadvantages that are limiting the use of transdermal delivery (Barry, 2002).

Disadvantages

1. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin’s impermeability (Allen et al., 2005; Barry, 2002).
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation (Barry, 2002).
3. The delivery system cannot be used for drugs requiring high blood levels (Allen et al., 2005).
4. The use of transdermal delivery may be uneconomical (Barry, 2002).

For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways (Barry, 2002; Vyas and Khar, 2002). This is shown in Figure 1- 3

Anatomy and physiology of skin

Human skin comprises of three distinct but mutually dependent tissues (Tortora and Grabowski, 2006; Wilson and Waugh, 1996), namely:

1. The stratified, a vascular, cellular epidermis;
2. Underlying dermis of connective tissues and;
3. Hypodermis.

Epidermis

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis, also called viable epidermis, cover a major area of skin (Tortora and Grabowski, 2006).

Stratum corneum: This is the outermost layer of skin, also called horney layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane (Tortora and Grabowski, 2006; Wilson and Waugh, 1996).

Viable epidermis: This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basale layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratumcorneum (Tortora and Grabowski, 2006; Wilson and Waugh, 1996).

Dermis

Dermis is a 3 to 5 mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels, and nerves. The continuous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation (Tortora and Grabowski, 2006; Wilson and Waugh, 1996).

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area.

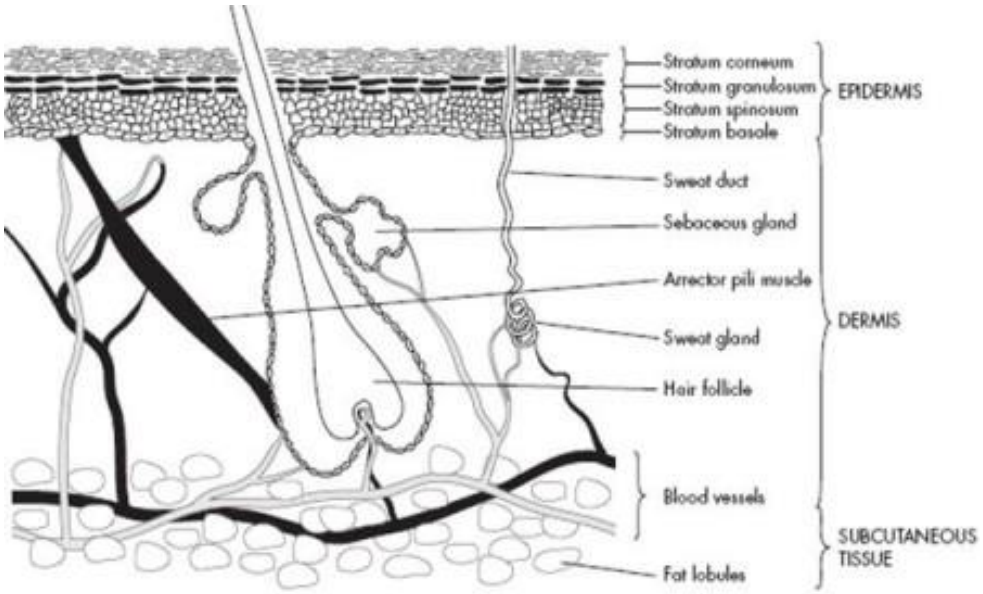

Figure 1. Structure of human skin.

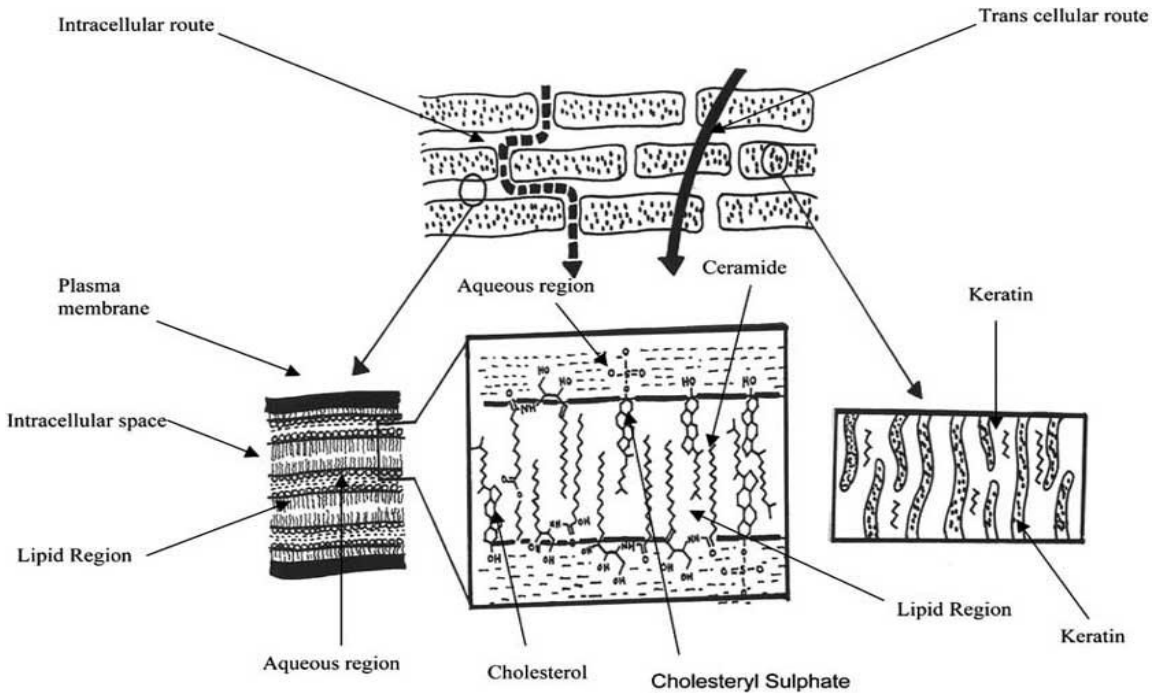

Figure 2. Simplified diagram of skin structure and macro routes of drug barrier at a penetration. Source: Allen et al. (2005).

This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired (Tortora and Grabowski, 2006; Wilson and Waugh, 1996).

ROUTES OF PENETRATION

The diffusant has two potential entry routes to the blood vasculature; through the epidermis itself or diffusion

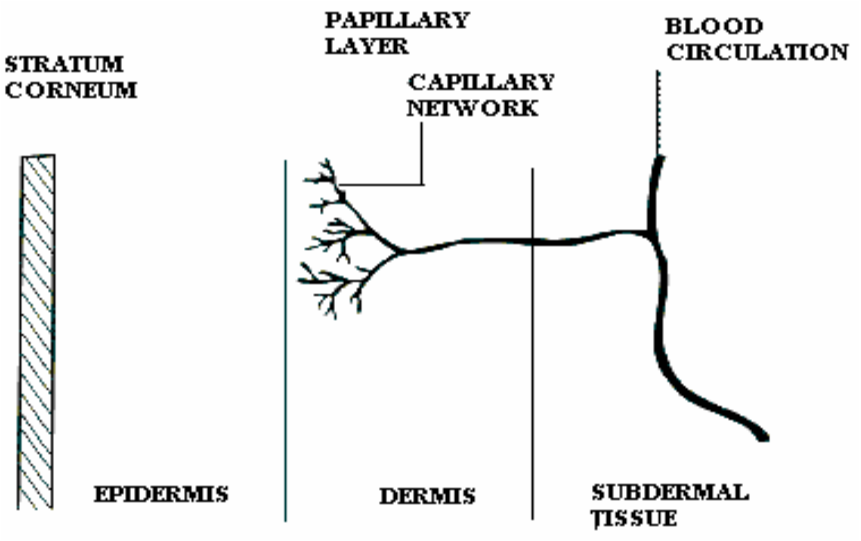

Figure 3. Simplified model of the human skin for mechanistic analysis of skin permeation. Source: Cleary (1984).

through shunt pathway, mainly hair follicles with their associated sebaceous glands and the sweat ducts (Barry, 1987). Therefore, there are two major routes of penetration (Bodde et al., 1991; Heisig et al., 1996).

Transcorneal penetration

Intra cellular penetration

Drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

Intercellular penetration

Non-polar substances follow the route of intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments.

Transappendegeal penetration

This is also called as the shunt pathway (Bodde et al., 1991; Heisig et al., 1996). In this route, the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands (Barry, 1987). The transappendegeal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). However this route may be of some importance for large polar compounds.

The route through which permeation occurs is largely dependent on physico-chemical characteristics of penetrant, most importantantly being the relative ability to partition into each skin phase. The transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis into the microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step (Scheuplein, 1965). The stratum corneum acts like a passive diffusion medium. So for transdermal drug diffusion, the various skin tissue layers can be represented by a simple multilayer model as shown in Figure 2.

FORMULATION DESIGN

A transdermal therapeutic system is essentially a multilaminate structure that is composed of following constituents:

1. Drug;
2. Polymer matrix;
3. Penetration enhancers;
4. Adhesives;
5. Backing membrane;
6. Release linear.

Table 1. Polymers useful for transdermal devices.

Polymer	Category	Role
Gelatin		Base, adhesive
Na-alginate		Base, adhesive
Gum Arabic	Natural polymer	Base with adhesive
Gum tragacanth		Adhesive
Natural rubber		Base with adhesive
Carmellose		Base, adhesive
Methyl and ethyl cellulose	Semi synthetic polymer	Base, adhesive
Hydroxyl propyl cellulose		Base, adhesive
Styrene-butadiene rubber	Synthetic elastomers	Base with adhesive
Silicone rubber		Base with adhesive
Polyvinyl alcohol		Base, adhesive
polyethylene		Linear, backing
polypropylene		Membrane, linear
polystyrene	Synthetic polymer	Co-adhesive
Polyhydroxyethyl methacrylate (PHMA)		Linear, backing
Polyvinyl chloride (PVC)		Base, adhesive
Ethylene vinyl acetate		Membrane

Source: Sugibayashi and Morimoto (1994), Valenta and Auner (2004) and Enclyopedia of polymer science and technology (1976).

Drug

Transdermal route of administration cannot be employed for all types of drugs. It depends upon optimal physicochemical properties of the drug, its biological properties. In addition, consideration of the pharmacokinetic and pharmacodynamic properties of drug is necessary. The most important requirement of drug to be delivered transdermally is demonstrated by need for controlled delivery, such as short half-life, adverse effect associated with other route or a complex oral or I.V. dose regimen (Barry, 1983). The drug parameter required for ideal drug candidate for transdermal drug delivery can be divided into:

Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 Daltons;
2. The drug should have affinity for both- lipophilic and hydrophilic phases. Extreme partitioning characteristic are not conducive to successful drug delivery via the skin;
3. The drug should have a low melting point;
4. Since the skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin. However for a number of drugs, there may also be significant transdermal absorption at pH values at which the unionized form of the drug is predominant.

Biological properties

1. The drug should be potent with a daily dose of the order of a few mg/day;
2. The half life $t_{½}$ of the drug should be short;
3. The drug should be non-irritating and non allergic;
4. Drugs which degrade in the gastro intestinal (GI) tract or inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.

Polymer

Advances in transdermal drug delivery technology have been rapid because of the sophistication of polymer science that now allows incorporation of polymers in transdermal system (TDS) in adequate quantity. The release rate from TDS can be tailored by varying polymer composition. Selection of polymeric membrane is very important in designing a variety of membrane permeation controlled TDS (Siepmann et al., 1998). The criteria for the polymers are (Chien, 1987; Vyas and Khar, 2002; Mishra, 1998).Table 1

1. The polymer should be chemically non reactive or it should be an inert drug carrier;

2. The polymer must not decompose on storage or during the life span;
3. Molecular weight, physical characteristic and chemical functionality of the polymer must allow the diffusion of the drug substance at desirable rate;
4. The polymer and its decomposed product should be nontoxic. It should be biocompatible with skin;
5. The polymer must be easy to manufacture and fabricate into desired product. It should allow incorporation of large amounts of active agent.

Penetration enhancer

An approach commonly researched for promoting permeation through the skin poorly penetrating drug molecules is the incorporation of chemical penetration enhancer to the TDDS (Barry, 1987). Alternatively, physical mechanism such as intophorosis and phonophoresis can be used for certain cases of drug. There are mainly three approaches for the penetration enhancement (Walker and Smith, 1996).

Chemical approach according to Barry (1987)

This includes:

(a) Synthesis of lipophilic analogs;
(b) Delipidization of stratum corneum;
(c) Co-administration of skin permeation enhancers.

This chemical approach can further be classified according to their chemical class;

(i) Sulfoxides: Dimethyl sulfoxide, decylmethal sufoxide;
(ii) Alcohols: Ethanol;
(iii) Polyols: Propylene glycol;
(iv) Alkenes: Long chain alkanes (C_7-C_{16});
(v) Fatty acids: oleic acid;
(vi) Esters: Isopropyl myristate;
(vii) Amines and amides: Urea, dimethyl acetamide, dimethyl formamide;
(viii) Pyrrilidones: N-methylpyrrilidone, azones;
(ix) Terpenes: Eugenol;
(x) Surface active agents: Cationic surfactants;
(xi) Cyclodextrines.

Biochemical approach

This includes:

(a) Synthesis of bio-convertible pro-drugs and;
(b) Co-administration of skin metabolism inhibitors.

Physical approach

This includes:

(a) Iontophoresis;
(b) Sonophoresis: Ultrasonic energy;
(c) Thermal energy;
(d) Stripping of stratum corneum and;
(e) Hydration of stratum corneum.

Adhesive layer according to Hock and William (1999), Qvist et al. (2002), Govil et al. (1993) and Govil (1988)

The adhesive must posses' sufficient property so as to firmly secure the system to the skin surface and to maintain it in position for as long as desired, even in the presence of water. After removal of patch, any traces of adhesive left behind must be capable of being washed with water and soap. Pressure sensitive adhesives are used to achieve contact between the transdermal patch and the skin. Adhesion is understood to be the net effect of three phenomenon's namely;

1. Peel: The resistance against the breakage of the adhesive bond;
2. Track: The ability of a polymer to adhere to a substrate with little contact Pressure and;
3. Creep: The viscous relaxation of the adhesive bond upon shear.

The ideal characters of adhesive materials are (Qvist et al., 2002);

1. High biocompatibility (low irritancy, toxicity, allergic reaction etc.);
2. Good adhesive to oily, wet, wrinkled and hairy skin;
3. Good environment resistance against water and humidity;
4. Easy to remove from the skin;
5. High permeability of moisture to avoid excessive occlusion and for the drug itself and;
6. Non-reactive towards drug.

There are three types of adhesive used mainly (Qvist et al., 2002; Govil et al., 1993);

1. Silicone type adhesive;
2. Polyisobutylene adhesive and;
3. Polyacrylate based adhesive.

Backing layer according to Govil (1988)

The backing layer must be impermeable to drug and permeation enhancers. The backing membrane serves the purpose of holding the entire system together and at the same time protects the drug reservoir from exposure to the atmosphere, which could result in the breakage or loss of the drug by volatilization. The most commonly used backing materials are polyester, aluminized polyethylene terapthalate, siliconised polyethylene

terapthalate and aluminum foil of metalized polyester laminated with polyethylene.

Release liner

The peel strip prevents the loss of the drug that has migrated into the adhesive layer during storage and protects the finished device against contamination. Polyesters foils and other metalized laminates are typical materials which are commonly used.

EVALUATION METHODS

The evaluation methods for transdermal dosage form can be classified into following types: Physicochemical evaluation, *In vitro* evaluation and *In vivo* evaluation

Physicochemical evaluation

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, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV) and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, and absorption maxima (Allen et al., 2005; Aarti et al., 1995; Lec et al., 1991).

Thickness of the patch

The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and this determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch (Reddy et al., 2003).

Weight uniformity

The prepared patches are to be dried at 60°C for 4 h before testing. A specified area of patch is to be cut in different parts of the patch and weighed in digital balance. The average weight and standard deviation values are to be calculated from the individual weights (Reddy et al., 2003).

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 (Reddy et al., 2003).

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 h, the films are to be reweighed and the percentage moisture content determined by below formula (Reddy et al., 2003):

Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

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% Rhesus factor (RH). After 24 h, the films are to be reweighed and the percentage moisture uptake determined by the formula (Reddy et al., 2003).

Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100

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 (Shaila et al., 2006):

WVP = W/A

Where, WVP is expressed in g/m^2 per 24 h, W is the amount of vapour permeated through the patch expressed in g/24 h, A is the surface area of the exposure samples expressed in m^2.

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 the drug content analyzed with the suitable method (UV or HPLC technique).Then, the average of three different samples is taken (Shaila et al., 2006).

Content uniformity test

Ten (10) patches were selected and content 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 (Wolff, 2000).

Flatness test

Three longitudinal strips were 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 percentage constriction, with 0% constriction equivalent to 100% flatness (Lec et al., 1991).

Constriction (%) = I1 - I2 × 100 I1

Where, I1 = initial length of each strip. I2 = final length of each strip.

Percentage elongation break test

The percentage elongation break was determined by noting the length just before the break point and determined from the formula (Lec et al., 1991).

Elongation percentages = L1 - L2 / L_2 × 100

Where L1 = final length of each strip; L2 = initial length of each strip.

Stability studies

Stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines by storing the TDDS samples at 40 ± 0.5°C and 75 ± 5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyzed suitably for the drug content (Singh et al., 1993).

In vitro evaluation of TDDS

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 were cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500 ml of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment was performed in triplicate and the mean value calculated (Singh et al., 1993).

In vitro skin permeation studies

An *in vitro* permeation study can be carried out by using diffusion cell on thick abdominal skin of male Wistar rats weighing 200 to 250 g. Hair from the abdominal region is 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 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume was removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was replaced. Samples were filtered through filtering medium and analyzed spectrophotometrically or using HPLC. Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm^2) versus time in hours, and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^2) (Singh et al., 1993).

In vivo evaluation

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^2) of the rabbit is to be cleaned and the hair removed from the clean dorsal surface by shaving and the surface cleaned by using rectified spirit with the representative formulations applied over the skin. The patch is to be removed after 24 h and the skin observed and classified into 5 grades on the basis of the severity of skin injury (Aarti et al., 1995).

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 effective. This article provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems. TDDS is a realistic practical application as the next generation of drug delivery system.

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