Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Suppl 5, 2011

Review Article

RECENT ADVANCEMENT IN TRANSDERMAL DRUG DELIVERY SYSTEM

KHUSHBU ANSARI[1], A. K. SINGHAI[1], GAURAV. K. SARAOGI[1]

[1]Lakshmi Narain College of Pharmacy, Kalchuri Nagar, Bhopal, (M.P.) India. Email: khushbuansari1may@gmail.com

Received: 26 Aug 2011, Revised and Accepted: 6 Oct 2011

ABSTRACT

There is considerable concern in the skin as a site of drug application both for local as well as for systemic effect. However, the skin, in particular the stratum corneum, poses a formidable obstacle to drug penetration thereby limiting topical and transdermal bioavailability. Transdermal drug delivery systems (TDDS) involve penetration enhancement techniques to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. TDDS differs from traditional drug delivery & had many advantages over conventional dosage forms such as non-invasive, ease of use, withdrawal (increase of side effect), avoidance of first pass metabolism, better patient compliance. However, the major limitation of this route is difficulty of permeation which can be overcome by using different combination of permeation enhancer's. This review article provides an overview of types of transdermal patches, method of preparation & its evaluation parameters.

Keywords: Transdermal delivery, Patches, Drug delivery systems, Topical delivery

INTRODUCTION

Conventional systems of medication which require multidose 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. 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 rate. 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[1].

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Controlled drug delivery has become increasingly important in the pharmaceutical industry now-a-days. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action. Skin of an average adult body covers a surface of approximately 2 m^2 and receives about one-third of the blood circulating through the body. Skin contains an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets[1,2]. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimetres of the skin area. It is one of the most readily accessible organs of the human body. The potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades, but skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. Transdermal drug delivery—the delivery of drugs across the skin and into systemic circulation—is distinct from topical drug penetration, which targets local areas[2].

Transdermal drug delivery system is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration MEC nor exceed the minimum toxic dose[3].

Aim of TDDS

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[1].

The steady permeation of drug across the skin allows for more consistent serum drug levels, often a goal of therapy [2].

Advantages of Transdermal Drug Delivery [4]

1. Avoidance of peak-and-trough blood concentrations associated with conventional oral administration.
2. Avoidance of first-pass metabolism in the gastrointestinal tract.
3. Reduced variability of absorption between and within patients.
4. Prolonged duration of action after application of one dosage form and lower frequency of dosing.
5. Improved compliance (particularly of drugs with short half-lives).
6. Concentration-dependent selectivity of drug action.
7. Drowsiness, confusion and blurred Vision, and have a relatively short duration of action.
8. Rate-controlled delivery might prolong the effect and minimize these adverse effects.

Disadvantages of Transdermal Drug Delivery[4]

The possibility of local irritation may develop at the site of application like Erythema, itching, and local oedema can be caused by the drug, the adhesive, or other excipients from the patch formulation. For most patients, site rotation can minimize irritation. However, some patients develop severe allergic reactions to transdermal patches, and in these cases, therapy must be discontinued.

It is that the skin's low permeability limits the number of drugs that can be delivered in this manner. Because the skin serves protective functions, it inhibits compounds from crossing it. Many drugs with a hydrophilic structure permeate the skin too slowly to be of therapeutic benefit. Drugs with a lipophillic character, however, are better suited for transdermal delivery. Many of the recent developments in transdermal drug delivery target the more hydrophilic compounds that were previously undeliverable via this method.

Damage to a transdermal patch, particularly a membrane or reservoir patch, can result in poor control over the release rate. The release rate

from a damaged patch would more likely be controlled by the skin than the patch, resulting in a higher, perhaps toxic, rate of drug delivery. Patients should be advised to discard a patch if the outer packaging or the patch itself appears damaged or altered in any way.

In order to maintain consistent release rates, transdermal patches contain a surplus of active molecule. A stable concentration gradient is the mechanism used to maintain consistent release rates and constant serum drug levels. Most transdermal patches contain 20 times the amount of drug that will be absorbed during the time of application. Thus, after removal, most patches contain at least 95% of the total amount of drug initially in the patch. Therefore; patients must exercise care when disposing of patches. Each patch should be folded in half and the adhesive sides should be stuck together. As an additional precaution, patches may be flushed down the toilet rather than discarded in household trash, where children and pets may find them and ingest the remaining drug. [2,5,6,7]

Product Development

Because of the uniqueness of this dosage form, the following questions need to be answered to define the final product

1. Target therapeutic concentration
2. Dose to be delivered
3. Maximum patch size acceptable
4. Preferred site of application
5. Preferred application period (daily, biweekly, weekly, etc)

Once the preferred final product description has been established, an evaluation of the drug candidate begins. Because of the limitation of loading dose in a patch and a practical patch size, not all drugs can be candidate for transdermal drug delivery (Table 1)

Table 1: Ideal properties of a transdermal drug delivery system

S No	Properties	Comments
1.	Shelf life	Up to 2 years
2.	Patch size	< 40 cm^2
3.	Dose frequency	Once a daily to once a week
4.	Aesthetic appeal	Clear, tan or white colour
5.	Packaging	Easy removal of release liner & minimum number of steps required to apply
6.	Skin reaction	Non irritating & non-sensitizing
7.	Release	Consistent pharmacokinetic & pharmacodynamics profiles over time

The product development of a transdermal formulation generally includes the following stages:

- Selection of drug candidate.
- Selection of the appropriate physical form (e.g., acid, base, or salt)
- Selection of the desired design (e.g., reservoir, matrix, etc.)
- Preparation of prototype formulations and testing of their physicochemical properties (tack, shear, peel adhesion, skin adhesion, etc.).
- Evaluation of *in vitro* permeation.
- Development of analytical methods to quantitate drug in the formulation, skin layers, release medium, and blood (if applicable).
- Evaluation of potential for systemic adverse events (e.g., carcinogenicity, teratogenicity, mutagenicity, etc.).
- Evaluation of skin toxicity (irritation, sensitization. etc.) in animals and humans.
- Microbial and preservative testing, if necessary.

Selection of Drug Candidate

The transdermal route of administration cannot be employed for a large number of drugs, only a small number of drug products are currently available via transdermal delivery. In many cases, a drug's physical properties, including molecular size and polarity, have limited its capacity to be delivered transdermally. Similarly, the biological properties of drug molecules, including dermal irritation and insufficient bioavailability, have been problematic. In the product development the focus must be on the rationality of drug selection based on pharmacokinetic parameters and physicochemical properties of the drug. Physiochemical factors such as solubility, crystallinity, molecular weight <400, polarity, melting point <200, partition coefficient Log P (octanol-water) between -1.0 to 4 must be considered. Biological factor should also be considered such as skin irritation, site of application of the patch e.g. scopolamine patch for motion sickness is applied backside of the ear and Transderm-Nitro is applied on the chest. When a pharmacologically active material has to be presented to the skin, an occlusive or allergic response is significant, limits have to be determined for the acceptability of the undesired effect. The pharmacokinetic information of the drug is a critical factor in deciding its suitability for delivery by the transdermal route as it is suitable only for drugs whose daily dose is in few milligrams. The resulting plasma concentration of active agent depends on the clearance; however, if one assumes a small volume of distribution and relatively long half-life, plasma level in excess of few micrograms per millilitre is very unlikely (Table 2 and Table 3). Another important factor is the half-life, (e.g., nitro-glycerine $t_{1/2}$ is 3 min) which provides information on the disposition of a drug in our body other parameters such as effective plasma level; also determine whether a transdermal delivery can be developed or not [6,8,9].

Table 2: Factors to Be Considered for Transdermal Dose Calculation

Physiochemical	Pharmacokinetic	Biological
Solubility	Half life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular Weight	Total body clearance	Allergic reactions
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting Point	Bioavailable factor	Skin permeability

Table 3: Ideal Properties of Drug Candidate For Transdermal Drug Delivery

Parameter	Properties
Dose	Should be low
Half life in hours	10 or less
Molecular weight	< 400
Partition coefficient*	Log P (octanol-water) between –1.0 and 4
Skin permeability coefficient*	> 0.5 x10-3cm/hr
Skin reaction	Non irritating and non sensitizer
Oral bioavailability	Low
Therapeutic index	Low

Penetration-Enhancing Adjuvants

For transdermal drug delivery to be successful, the dermal microcirculation must carry the drug from the skin to the systemic circulation (TABLE 4). Substances that act as vasodilators, such as nitro-glycerine, nicotine, and caffeine, can increase the transdermal absorption of a drug, reportedly by temporarily increasing blood flow to the application site. When applied transdermally, most drugs form a local depot in the skin and are absorbed slowly depending on their structure. However, when a vasodilator is added, the formation of a depot is limited, and the systemic rate of absorption increases. Nitro-glycerine and nicotine, both vasodilators, may enhance their own penetration rate through local vasodilation.[2]

Table 4: Variations in Human Skin

Human skin is not all the same. There are numerous differences among patient groups as well as between various regions of the body.
Permeability varies among individuals based upon:
• Age: The skin of neonates and the elderly is more permeable than that of other age groups
• Ethnicity: For example, the skin of Caucasians is more permeable than that of African-Americans
Permeability varies among regions of the body:
• The most permeable areas are the mucous membranes, scrotal skin, and eyelids.
• Areas of intermediate permeability include the face/head, chest/back, buttocks, abdomen, and upper arms/legs
• The least permeable areas are the palmar/plantar surfaces and nails.

Permeability varies according to skin status or conditions:

- Hydration: Hydrated skin is more permeable than dry skin
- Broken or irritated skin: Drugs can more easily bypass the stratum corneum, increasing permeability.
- Temperature: Warmer skin is more permeable
- Sunburn: Initially skin is less permeable; after peeling occurs it becomes more permeable
- Eczema: Regions exhibit increased permeability
- Psoriasis: Areas are thicker and show decreased permeability
- Thermal burns: Skin is more permeable
- Chemical peels: Removal of the stratum corneum increases permeability

Components of Transdermal Patches

The major parts of TDS are a controlled release device composed of polymers, the drug, excipients and enhancers, a fastening system, usually a pressure-sensitive adhesive (PSA), to fix the device to the skin, and a hermetically sealed package composed of impervious film. Advances in transdermal drug delivery technology have been rapid because of the sophistication of polymer science which now allows incorporation of polymers in TDS in adequate quantity. The importance of polymer selection can be appreciated more if one considers the different design criteria which must be fulfilled. In this review paper, typical polymers in topical drug formulation are introduced (Tables 5 and 6), and their usefulness is discussed.

The common ingredients which are used for the preparation of TDDS are as follows.

Drug: Drug is in direct contact with release liner. Ex: Nicotine, Methotrexate and Estrogen.

Liners: Protects the patch during storage. Ex: polyester film.

Adhesive: Serves to adhere the patch to the skin for systemic delivery of drug. Ex: Acrylates, Polyisobutylene, Silicones.

Permeation enhancers: Controls the Release of the drug. Ex: Terpenes, Terpenoids, Pyrrolidones, Solvents like alcohol, Ethanol, Methanol. Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.

Backing layer: Protect patch from outer environment. Ex: Cellulose derivatives, poly vinylalcohol, Polypropylene Silicon rubber. [10,11]

Categorization of polymeric systems for controlled release [12]

Physical systems

1. Reservoir systems with rate-control

- Membrane systems
- Adhesive membrane systems
- Micro reservoir systems (Microencapsulation or Macro encapsulation)

2. Reservoir systems without rate-contro*l*

- Hollow fibres
- Porous film

3. Monolithic systems

- Physically dissolved in nonporous, polymeric, or elastomeric matrix (Non erodible, erodible, environmental agent, or degradable)
- Physically dispersed in nonporous, polymeric, or elastomeric matrix
- Laminated structure
- Other physical methods (Osmotic pumps, Adsorption onto ion-exchange resins)

4. Chemical Systems

- Chemical erosion of polymer matrix: Heterogeneous, Homogeneous
- Biological erosion of polymer matrix: Heterogeneous, Homogeneous

Table 5: Polymers possibly useful for transdermal devices [12]

Polymer	Role
Natural polymer	
Gelatine	base, adhesive
Na-alginate	base, adhesive
Gum Arabic	base with adhesive
Starch	base, adhesive
Gum tragacanth	Adhesive
Shellac	Adhesive
Paraffin waxes	Adhesive
Proteins	Adhesive
Casein	Adhesive
Natural rubber	base with adhesive
Semi-synthetic polymers	
Carmellose	base, adhesive
Cellulose acetate phthalate	
Methyl- &ethylcellulose	base, adhesive
Nitrocellulose	
Hydroxypropylcellulose(HPC)	base, adhesive
Synthetic elastomers	
Polybutadiene	
Polyisoprene	base with adhesive
Polysiloxane	
Styrene-butadiene rubber	base with adhesive
Silicone rubber	base with adhesive
Synthetic polymers	
Polyvinyl alcohol	aq. base, adhesive
Polyethylene	linear, backing membrane, linear co-adhesive foam, backing
Polypropylene (PP)	linear, backing membrane, linear co-adhesive foam, backing
Polystyrene	co-adhesive
Polyurethane	linear, backing membrane, linear co-adhesive foam, backing
Polyvinylpyrrolidone	linear, backing membrane, linear co-adhesive foam, backing
Polymethylmethacrylate (PMMA)	Base
Polyvinylacetate	Base
Polyhydroxyethyl methacrylate(PHMA)	linear, backing membrane,
Polyvinyl chloride (PVC)	base, adhesive
Polyacrylate	base, adhesive
Polyacrylamide (PAA)	base, adhesive
Polyethyleneglycol (PEG)	base,
Polyester (PE)	linear, backing membrane,
Polyamide & polyuria	Foam
Epoxy	Foam
Ethylene vinyl acetate(EVA) co-polymer	Membrane
Polybutne	viscosity modifier
Polyisobutylene	viscosity modifier

Types of Transdermal Patches

a) Single layer drug in adhesive

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi -layer drug in adhesive

This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) Vapour patch

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system

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 nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system

i. Drug-in-adhesive system: In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting(in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system: In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive baseplate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) Micro reservoir system

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoirs 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. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents. [10,13,14,15,16,17]

Various methods for preparation tdds

a. Asymmetric TPX membrane method

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

Asymmetric TPX membrane preparation

These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and non-solvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardener knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.[12]

b. Circular Teflon mould method

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.[18]

c. Mercury substrate method

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10- 15 minutes to produce a homogenous dispersion and poured in to a levelled mercury surface, covered with inverted funnel to control solvent evaporation.[19]

d. By using "IPM membranes" method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.[20]

e. By using "EVAC membranes" method

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.[21]

f. Aluminium backed adhesive film method

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom-made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.[22]

g. Preparation of TDDS by using Proliposomes

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.[23, 24]

h. By using free film method

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.[10, 25]

Evaluation parameters

1. Interaction studies

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can 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 commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.[26, 27]

2. Thickness of the patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.[28]

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.[28]

4. Folding endurance

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

5. Percentage Moisture content

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula

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

6. Percentage Moisture uptake

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula[28].

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

7. Water vapour permeability (WVP) evaluation

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

$$WVP=W/A$$

Where, WVP is expressed in gm/m^2 per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m^2.[29]

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 contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples. [29]

9. 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. [30]

10. Polariscope examination

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

11. 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.[30]

12. Peel Adhesion test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. 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 180º angle, and the force required for tape removed is measured.[30]

13. 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.

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.

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 mentioned formula.

$$\text{Elongation percentage} = [L_1\text{-}L_2 / L_2] \times 100$$

Where, $L_1$is the final length of each strip and L_2 is the initial length of each strip.[26]

16. Rolling ball tack test

This test measures the softness of a polymer that relates to talk. 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. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.[31]

17. Quick Stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.[31]

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. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.[31]

19. *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 cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate 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 can be withdrawn at appropriate time intervals up to 24 h and analysed by UV spectrophotometer or HPLC. [26]

20. *In vitro* skin permeation studies

An *in vitro* permeation study can be carried out by using diffusion cell using full thickness abdominal skin of male wistar rats. The temperature of the cell should maintain at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is generally mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is 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 analysed 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 (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^{-2}).[27]

21. 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 ($50cm^2$) 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.[27, 30]

22. Stability studies

Stability studies are to be conducted according to the 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 analyze suitably for the drug content.[26]

Applications

Delivering drugs by the transdermal route.This list of table 7 includes transdermal patches and delivery systems approved by the FDA. Only the first approved product for a given drug or drug combination administered by a given delivery method is shown. Topical creams, ointments, gels and sprays are not included.[32,33]

Table 7: Transdermal drugs approved by the US FDA [34-42]

Approal year	Drug	Indication	Product Name	Marketing company
1979	Scopolamine	Motion sickness	Transderm-Scop	Novartis Consumer Health (Parsippany, NJ)
1981	Nitroglycerin	Angina pectoris	Transderm-Nitro	Novartis (East Hannover, NJ)
1984	Clonidine	Hypertension	Catapres-TTS	BoehringerIngelheim (Ridgefield, CT)
1986	Estradiol	Menopausal symptoms	Estraderm	Novartis (East Hannover, NJ)
1990	Fentanyl	Chronic pain	Duragesic	Janssen Pharmaceutica (Titusville, NJ)
1991	Nicotine	Smoking cessation	Nicoderm, Habitrol, ProStep	GlaxoSmithKline (Philadelphia, PA), Novartis Consumer Health (Parsippany, NJ) Elan (Gainesville, GA)
1993	Testosterone	Testosterone deficiency	Testoderm	Alza, Mountain View, CA
1995	Lidocaine/ epinephrine (iontophoresis)	Local dermal analgesia	Iontocaine	Iomed (Salt Lake City, UT)
1998	Estradiol/norethidrone	Menopausal symptoms	Combipatch	Novartis (East Hannover, NJ)
1999	Lidocaine	Post-herpetic neuralgia pain	Lidoderm	Endo Pharmaceuticals (Chadds Ford, PA)
2001	Ethinyl estradiol/norelgestromin	Contraception	Ortho Evra	Ortho-McNeil Pharmaceutical (Raritan, NJ)
2003	Estradiol/levonorgestrel	Menopausal symptoms	Climara Pro	Bayer Healthcare Pharmaceuticals (Wayne, NJ)
2003	Oxybutynin	Overactive bladder	Oxytrol	Watson Pharma (Corona, CA)
2004	Lidocaine (ultrasound)	Local dermal anesthesia	SonoPrep	Echo Therapeutics (Franklin, MA)
2005	Lidocaine/tetracaine	Local dermal analgesia	Synera	Endo Pharmaceuticals (Chadds Ford, PA)
2006	Fentanyl HCl (iontophoresis)	Acute post operative pain	Ionsys	Alza, Mountain View, CA
2006	Methylphenidte	Attention deficit hyperactivity disorder	Daytrana	Shire (Wayne, PA)
2006	Selegiline	Majordepressivedisorder	Emsam	Bristol-Myers Squibb (Princeton, NJ)
2007	Rotigotine	Parkinson's disease	Neupro	Schwarz Pharma (Mequon, WI)
2007	Rivastigmine	Dementia	Exelon	Novartis(EastHannover,NJ)

Future Prospects

The advantages of the transdermal approach should increasingly be recognized by the Pharmaceutical Industry. Although some quarter century after their introduction, the use of TDS devices has not been as extensive as one might of expected this is despite:

- The synthesis of more efficient penetration enhancers for particular pharmaco-therapeutic purposes.
- The use of non-irritating and non-sensitizing materials for the TDDS. There can be little doubt that some way of avoiding or counteracting these reactions would be extremely welcome to manufacturers and patients alike.
- Existence of prototypes of 'intelligent' TDS. A major boost to the TDS product range will be the arrival of these devices that release more or less of the drug or hormone contained when needed and as determined by an osmotically driven device or by an analytical 'chip' contained in the TDS itself.
- A further major step forward will be production of TDS units delivering peptide and even protein substances including insulin, growth hormone, and vaccines.

Perhaps it is understandable that the rate of progress is slow – after all, the technical problems are significant and the development costs correspondingly high. It may be that the way ahead will increasingly utilize one or more of the 'physical technologies' (range from microneedles to electroporation and from iontophoresis to sonophoresis) that enable drugs to reach the skin barrier.

CONCLUSION

The researches shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophillic 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 as a realistic practical application as the next generation of drug delivery system. An ideal dosage regimen in the drug therapy of any disease is one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency. But as reported in literature conventional drug delivery has its own limitations, which switch over the formulator to developed new formulation. This overcomes the number of drawbacks associated with conventional dosage drug delivery system. The past decade has seen major advances in developing a drug through concept and technique of controlled and targeted drug delivery system.

Therefore an ideal controlled drug delivery system is the one, which delivers the drug at a predominant rate, locally or systematically, for a specific period of time. Despite of number of approaches to deliver a drug in systemic circulation at predetermined rate and maintain clinically effective concentration over prolong period of time. This allows one to control the overall release of drug via an appropriate choice of polymers. Different penetration enhancer combinations were incorporated in the transdermal system because it significantly enhanced the permeation rate of drug.

REFERENCES

1. Shivaraj A, Panner Selvam R, Tamiz Mani T and Sivakumar T Design and evaluation of transdermal drug delivery of Ketotifen Fumarate, Int. J. of Pharm Biomed Res 2010; 1(2): 42-47**.**
2. Keleb E, Sharma RK, Mosa EB, Abd-alkadar, Aljahwi Z Transdermal Drug Delivery System- Design and Evaluation, Int. J. of Adv. in Pharm. Sci., 2010; 1: 201-211.
3. Uttam B, Panna T Effect of chemical enhancers on in vitro release of Salbutamol Sulphate from transdermal patches**,** Kathmandu University J. Sci. Eng. Technology, 2005; i(1).
4. Nimmo WS: Recent clinical experience with Transdermal Systems, In Prescott L.F. Nimmo W.S. (eds) Novel Drug Delivery, Chichester: John Wiley 1989, 209-222.
5. Baker H The skin as barrier, In: Rook A, Wilkinson D.S., Ebling F.J.G., Champion R.H., Burton J.L., editions Text Book of Dermatology Volume I, 4th edition, Oxford: Blackwell Scientific Publications, 1986, 355-66.
6. Chandrashekar NS, Shobha Rani RH, Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery, Indian J Pharm Sci, 2008; 70: 94-96.
7. Barr M, Percutaneous absorption, J Pharm Science, 1962; 61: 395-409.
8. Riviere JE, Papich MG, Potential and problems of developing transdermal patches for veterinary applications, Advance Drug Deliv. Rev., 2001; 50: 175-203.
9. Prochazka AV, New developments in smoking cessation Chest, 2000; 117: 169-175.
10. Kumar A, Pullakandam N, Lakshmanaprabu S. Gopal V, Transdermal drug delivery system: an overview", Int. J. Pharm. Sci. Rev. Res. 2010; 1: 50-54
11. Chein YW, Advances in transdermal systemic drug delivery drugs of future, 1988; 13: 343-62.
12. Sadashivaiah R, Dinesh BM, Patil UA, Desai BG, Raghu KS, Design and *in vitro* evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers, Asian J Pharm 2008; 2: 43-49.
13. Willams AC, Barry BW, Penetration Enhancers, Adv Drug Del Rev 2004; 56: 603-618.
14. Pellet M, Raghavan SL, Hadgraft J, Davis AF, The application of supersaturated systems to percutaneous drug delivery, In: Guy R.H. and Hadgraft J, Transdermal drug delivery, Marcel Dekker Inc, New York, 2003; 305-326.
15. Brown MB, Jones SA, Hyaluronic acid: a unique topical vehicle for localized drug delivery of drugs to the skin, JEDV, 2000; 19: 308-318.
16. Baker W, Heller J, Material Selection for Transdermal Delivery Systems", In Transdermal Drug Delivery: Developmental Issues and Research Initiatives, Hadgraft J. Guys RH,(Eds) Marcel Dekker, Inc, New York 1989, 293-311.
17. Berner B, John VA, Pharmacokinetic characterization of Transdermal delivery systems, J Clinic Pharmacokinetics, 1994; 26 (2): 121-134.
18. Wiechers J, Use of chemical penetration enhancers in Transdermal drug delivery-possibilities and difficulties, Acta Pharm 1992; 4: 123-127.
19. Yamamoto T, Katakabe K, Akiyoshi K, Kan K, Asano T, Topical application of glibenclamide lowers blood glucose levels in rats, Diabetes Res Clin Pract, 1990; 8: 19-22.
20. Al- Khamis K, Davis SS, Hadgraft J, Micro-viscosity and drug release from topical gel formulations, Pharm Res, 1986; 3: 214-217.
21. Anon K, Transdermal delivery systems-general drug release standards, Pharmacopeial Forum, 1980; 14: 3860-3865.
22. Mayorga P, Puisieux F, Couarraze G, Formulation study of a Transdermal delivery system of Primaquine, International J Pharm, 1996; 132: 71-79.
23. Yan-Yu X, Yunmei S, Zhi-Peng C, Qinerg P, Preparation of Silymarinproliposomes; A new way to increase oral bioavailability of silymarine in beagle dogs, Int J Pharm 2006; 319: 162-168.
24. Deo MR, Sant VP, Parekh SR, Khopade AJ, Banakar UV, Proliposome-based Transdermal delivery of levonorgestrel, Jour Biomat Appl, 1997; 12: 77-88.
25. Crawford RR, Esmerian OK, Effect of plasticizers on some physical properties of cellulose acetate phthalate films, J Pharm Sci, 1997; 60: 312-314.
26. Wade A, Weller PJ, Handbook of Pharmaceutical Excipients, Washington, DC: American Pharmaceutical Publishing Association, 1994; 362-366.
27. Singh J, Tripathi KT, Sakia TR, Effect of penetration enhancers on the *in vitro* transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations, Drug Dev Ind Pharm, 1993; 19: 1623-1628.
28. Rhaghuram RK, Muttalik S. and Reddy S, Once daily sustained-release matrix tablets of nicorandil: formulation and *invitro* evaluation, AAPS PharmSciTech, 2003; 4: 4-14.
29. Shaila L, Pandey S, Udupa N, Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotine suitable for use in smoking cessation, Ind. J. Pharm. Sci., 2006; 68: 179-184.
30. Aarti N, Louk ARMP, Russsel OP, Richard HG, Mechanism of oleic acid induced skin permeation enhancement *in vivo* in humans, J Contr. Rel., 1995; 37: 299-306.
31. Vyas SP, Khar RK, "Targetted and controlled Drug Delivery Novel carrier system", 1st Edition, CBS Publishers and distributors, New Delhi, 2002; 411-447.
32. *www.pubmed.com*, 2009, Available on: NIH Public Access on July 2009.
33. Tanner T. and Marks R., "Review Delivering drugs by the transdermal route: review and comment", *Skin Research and Technology* 2008; 14: 249–260.
34. Baynes RE, Monteiro-Riviere NA, Qiao GL, Riviere JE, Toxicol Lett, 1997; 93: 159-169.
35. Benson HA, Transdermal drug delivery: Penetration enhancement techniques, Curr. Drug Deliv., 2005; 2: 23-33.
36. Jasti BR, Abraham W, Ghosh TK, Transdermal and Topical drug delivery systems, In: Ghosh TK, Jasti BR, (eds) Theory and Practice of Contemporary Pharmaceutics 1st ed Florida: CRC Press; 2005, 423-53.
37. Kenji S, Yasunori M, Polymers for transdermal drug delivery systems, J. Contr. Rel., 29; 1994: 173-185.
38. Chein YW, Transdermal drug delivery and delivery system, In, Novel drug delivery system, Volume 50, Marcel Dekker Inc, New york, 1992; 301-381.
39. Lec ST, Yac SH, Kim SW, Berner B, One way membrane for Transdermal drug delivery systems / system optimization, Int. J. Pharm., 1991; 77: 231 -237.
40. Morganti P, Ruocco E, Wolf R, Ruocco V, Percutaneous absorption and delivery systems, Clinical Dermatol., 2001; 19: 489-501.
41. Panchagnula R, Transdermal delivery of drugs, Ind. J Pharmacol. 1997; 29: 140-56.
42. Tsai JC, Guy RH, Thornfeldt CR, Gao WN, Feingold KR, Elias PM, Metabolic Approaches to Enhance Transdermal drug delivery, J. Pharm Sci., 1998; 85: 643-648.