Review Article **www.ijcps.com**

International Journal of
Chemical and Pharmaceutical Sciences
2015, Mar., Vol. 6 (1)

ISSN: 0976-9390
IJCPS

Transdermal Drug delivery system: Preparation, aspects: *in-vivo* and *in-vitro* evaluation

Prem Kumar P*, Balamurugan K and Azeez SA.

Department of Pharmacy, Annamalaiuniversity, Annamalainagar, Tamilnadu, India.

***Corresponding Author:** E-Mail: prempharma222@gmail.com

Received: 16 Mar 2015, Revised and Accepted: 18 Mar 2015

ABSTRACT

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. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. A wide variety of pharmaceuticals are now available in transdermal patch form.

Keywords: Transdermal drug delivery system, Iontophoresis, Electroporation, Ultrasound.

1. INTRODUCTION

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 [1]. Currently, transdermal drug delivery is one of the most promising methods for drug application. Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications [2]. 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. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first pass metabolism respectively [3]. 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.

1.1. Mechanism of absorption

1.1.1. Drug delivery routes across human skin [1, 2]

Drug molecules in contact with the skin surface can penetrate by three potential pathways:

- Through the sweat ducts,
- Directly across the stratum corneum (Figure 1).

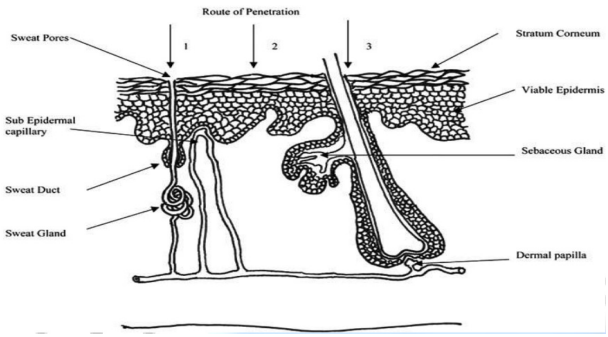

Figure - 1: Simplified representation of skin showing routes of penetration: (1. through the sweat ducts; 2. directly across the stratum corneum; 3.Via the hair follicles).

- Via the hair follicles and sebaceous glands (Collectively called the shunt or appendageal route)

1.2. Factors affecting transdermal permeation

1.2.1. Physicochemical properties of the penetrant molecules [2, 7, 8]

Partition coefficient

- A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.
- It maybe altered by chemical modification without affecting the pharmacological activity of the drug.

pH conditions

- Applications of solutions whose pH values are very high or very low can be destructive to the skin.
- With moderatepH values, the flux of ionisable drugs can be affected by changes inpH that alter the ratio of charged and uncharged species and their transdermal permeability.

Penetrant concentration

- Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.
- At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

1.3. Physicochemical properties of the drug delivery system [1, 2]

Release characteristics

Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:

- Whether the drug molecules are dissolved or suspended in the delivery systems.
- The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
- pH of the vehicle

Composition of the drug delivery systems

- The composition of the drug delivery systems e.g., boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight.

Enhancement of transdermal permeation

Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the drug delivery systems.

1.4. Formulation aspects of TDDS

Basic components of TDDS [1,7]:

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

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 released of a drug throughout the device with safe status. 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, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butyl rubber etc.

Synthetic polymers

e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc. The polymers like polyethylene glycol, eudragits, ethylcellulose, polyvinylpyrrolidone and hydroxy propyl methylcellulose are used as matrix type TDDS. The

polymers like EVA, silicon rubber and polyurethane are used as rate controlling TDDS.

Selection of drugs

The selection of drug for TDDS is based on physicochemical properties of drug [9,10]. Transdermal drug delivery system is much suitable for drug having:

- Extensive first pass metabolism.
- Narrow therapeutic window.
- Short half-life which causes non-compliance due to frequent dosing.
- Dose should be less (mg/day).
- 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).

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. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability.

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 andexert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Adhesives must be skin-compatible, causing minimal irritation or sensitization, and removable without in flicting physical trauma or leaving residue. In addition, they must be able to dissolve drug and excipients 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. Polyacrylate, 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. Polyisobutylene *(PIBs)*, in contrast, are characterized by alow 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 flow less state. They are thermoplastic in nature. Compounded HMPSA are ethylene vinyl acetate copolymers, paraffin waxes, low density polypropylene, styrene-butadiene copolymers, and ethylene-ethacrylate copolymers. Uncompounded HMPSA are polyesters, polyamides and polyurethanes [12, 13].

Backing laminate

Protects patch from outer environment. Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in 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 [14].

Examples of some backing materials are vinyl, polyester films, polyester-polypropylene films, polypropylene resin, polyurethylene, Co Tran 9722 film, ethylene-vinyl acetate, aluminized plastic laminate clear.

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 apart 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. 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 metallised laminates [15].

Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

1.5. Types of transdermal drug delivery system

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 [16, 17].

Multi-layer drug in adhesive

This type is also similar to the single layer but it contains an 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 [16, 17].

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 [16, 17].

1.6. 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 3). 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 [6, 18]. Transderm Scop (Scopolamine) for 3 days protection of motion sickness and Transderm Nitro (Nitro-glycerine) for once a day medication of angina pectoris.

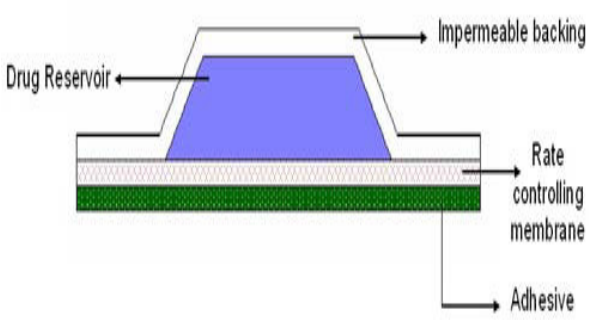

Figure - 3: Polymer membrane permeation-controlled TDDS.

1.7. 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) on to an impervious backing layer (Figure-4). 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 [6, 18].

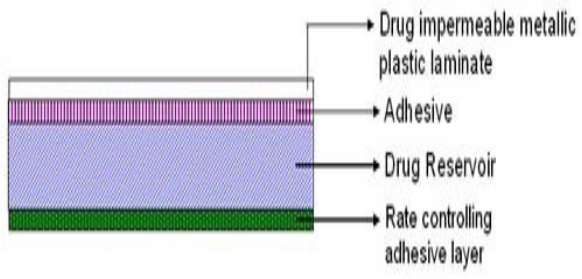

Figure - 4: Adhesive diffusion controlled TDDS.

Deponit (Nitro-glycerine) for once a day medication of angina pectoris.

1.8. 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 5). 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 [6, 18].

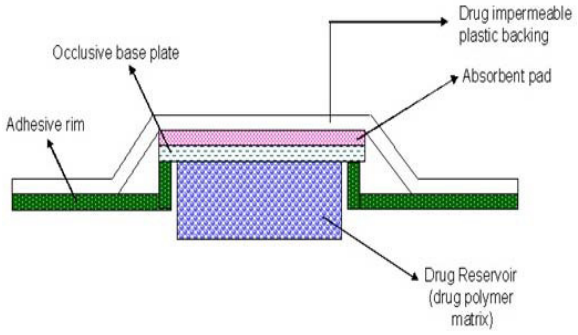

Figure - 5: Matrix diffusion controlled TDDS.

Nitro Dur (Nitro-glycerine) used for once a day medication of angina pectoris.

1.9. 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 6). 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 centre and surrounded by an adhesive film [6, 18].

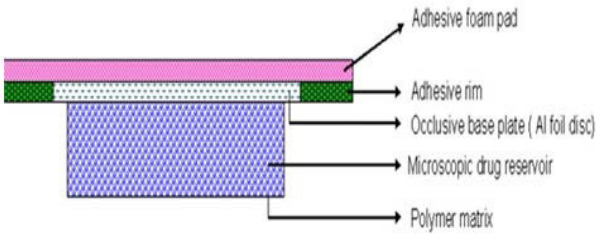

Figure - 6: Micro-reservoir controlled TDDS.

Nitro-dur® System (Nitro-glycerine) for once a day treatment of angina pectoris

1.10. Methods for preparation of TDDS

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 [19].

1.11. Asymmetric TPX membrane preparation method

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 Gardner 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.

1.12. 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. Enhancer's indifferent 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 [20].

1.13. 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.

1.14. By using "IPM membranes" method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers 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 [21].

1.15. 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 canbe 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 propyleneglycol; 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 [22].

1.16. Aluminium backed adhesive film method

Transdermal drug delivery system may produce unstable atrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable 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 custam made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks [23].

1.17. 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 [20].

1.18. 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 petridish. 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 [24].

1.19. Evaluation of TDDS

Interaction studies

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 stable product, 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 [25].

Thickness of the patch

The thickness of the drug loaded patch is measured at three different points by using a digital micrometer screw gauge (Mitutoyo, Japan) and the average thickness and standard deviation for the same to ensure the thickness of the prepared patch was calculated [24, 25].

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 [25].

Folding endurance

Folding endurance of patches should be determined by repeatedly folding a small strip of film (2 cm x 2 cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value [4].

Tensile strength

The tensile strength should be determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke. The force required to break the film was considered as a tensile strength and it was calculated as kg/cm^2 [4].

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 [1].

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

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 [2].

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

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.

WVP=W/A

Where, WVP is expressed in gm/m^2 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^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 analyse the drug contain with the suitable method (UV or HPLC technique).Then take the average of three different samples [1].

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 analyzed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated [25].

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 [1].

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 [25].

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 cross linking 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 [1].

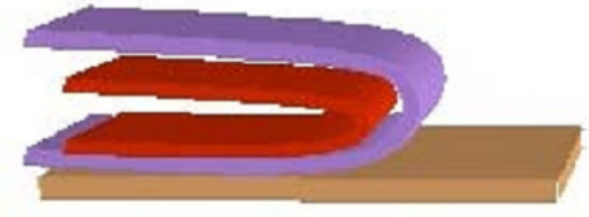

Figure - 7: Peel adhesion test.

Peel adhesion test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion (Figure 7). 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°C angle, and the force required for tape removed is measured.

Tack properties

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

Thumb tack test

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.

Flatness test

Three longitudinal strips are to be cut from each film at different portion like one from the centre, 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 [25].

$$\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100$$

Where, L1 is the final length of each strip and L2 is the initial length of each strip.

Rolling ball tack test

This test measures the softness of a polymer. 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 8). The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch [25].

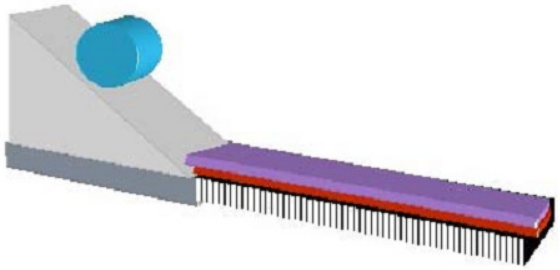

Figure - 8: Rolling ball tack test.

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 (Figure 9) and recorded as tack value, which is expressed in ounces or grams per inch width [25].

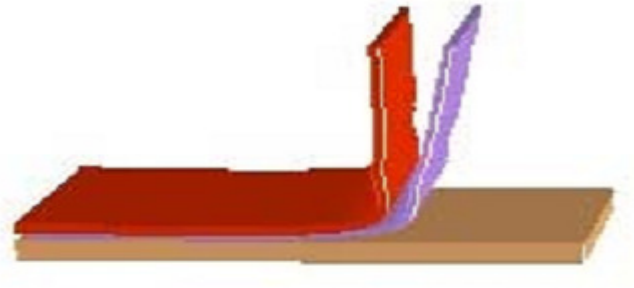

Figure - 9: Quick stick (peel-tack) test.

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

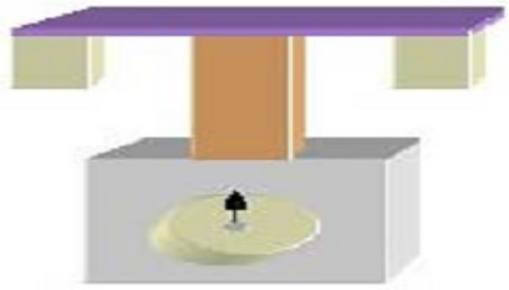

Figure - 10: Probe Tack test.

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.

1.20. *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 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± 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 is to be performed in triplicate and the mean value can be calculated.

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±0.5°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 by 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) [25].

1.21. Advance devices

To achieve and to maintain a plasma drug concentration above the minimum therapeutic level, the barrier properties of the skin must be overcome before the effective transdermal controlled delivery of drugs can be successfully accomplished. Modification of the conventional device is done to achieve the goal of reducing skin's barrier properties and enhancing transdermal permeation of drugs.

Microblades

This is a device used for percutaneous drug delivery by overcoming the skin's natural barrier made use of micro projections. The need for such a device existed because it was hypothesized that once a drug penetrated through stratum corneum with the aid of the device, permeation through the remaining layers could proceed readily. The apparatus basically consists of a cutter having a plurality of micro protrusions having a height chosen with respect to the layer of skin that is to be disrupted and a 'stop' for preventing the apparatus from penetrating the skin beyond a predetermined distance. Godshall (2002) designed a bed of micro protrusions attached to a drug reservoir from where the drug can move to adjacent disruptions. An area between micro protrusions acted as a penetration 'stop' that prevented the permeation of skin by micro protrusions to a depth greater than the height of micro protrusions. A silicon substrate was used for fabrication of micro protrusions, on which silicone dioxide was deposited over which photo resist (to mask chlorine reactive ion that penetrates silicon substrate) was deposited. It was found that blade lengths of less than 50 µm did not produce micro cuts sufficient to provide required degree of diffusion and blade lengths of more than 175 µm were painful to the patient [26].

Microneedles

A gel filled compartment fitted with micro needles was found to be capable of opening the skin permeation pathways up to a depth of 150 µ when applied with pressure [28]. The microneedle drug delivery device included plunger/syringe/pump forcom pressing the reservoir to drive the drug from reservoir through the microneedles. A sealing mechanism was also incorporated to contain the drug in one or more reservoirs until it was ready to be delivered. It further included a rate control mechanism to regulate rate and extent of drug delivery and an adhesive thus, immobilizing the microneedles during its insertion into the skin [27]. A device for enhancing the delivery of drug through a braded skin utilized iontophoresis. The micro needles had a blunt, flat tip and a length sufficient to penetrate the stratum corneum without piercing the stratum corneum. Microneedles produce pores proportional to the needle diameter, typically in the N104nm range that increases with the needle length employed (Figure 11).

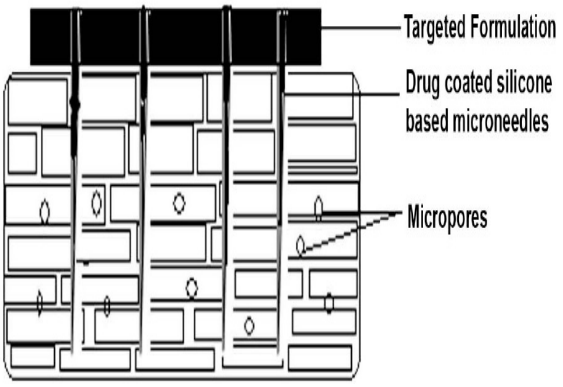

Figure – 11: Microneedle array.

In vivo studies have demonstrated delivery of oligonucleotides, desmopressin, and

human growth hormone, reduction of blood glucose levels from insulin delivery, increase of skin transfection with DNA, and elicitation of immune response from delivery of DNA and protein antigens [28, 29].

Needleless syringe

This device features an elongate, tubular duct having alumen for delivering the particles towards the target tissue. The device has a membrane which is ruptured by gas pressure to generate a supersonic gas flow in which therapeutic agent is injected [29] as depicted in Figure 12.

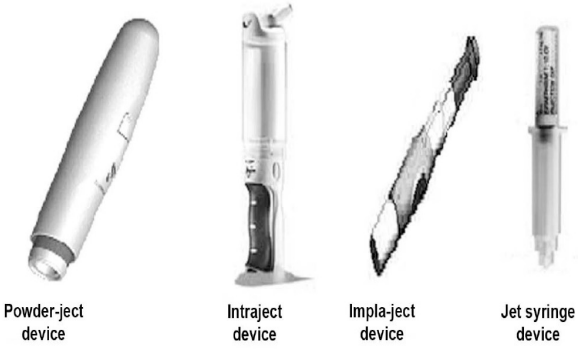

Figure - 12: Needle less syringe devices.

1.21. Increase in local temperature

Local increase in temperature increases blood flow and in turn, rate of permeation/transport of active substance into the skin increases. This technique has the advantage of not employing a chemical, is non-invasive and hence, does not require activation of self-repair mechanism by the skin. Stanley *et al*. (2002) developed a transdermal device that employed an oxidation reaction for controlled heating of skin. Heat generating component comprised of a mixture of activated carbon, iron powder, saw dust, sodium chloride and water. Application of heat (42-44ºC) for 4 hr was found to be sufficient to decrease the time required for the patch to deliver steady state serum concentration of fentanyl from 14-18 hr to 3-4 hr [30]. Koch *et al*. (2004) used an effective component Opraflex to increase the local skin temperature and observed an increase in the transdermal absorption rate of morphine base from 5.7 to 26.4%. Controlled heat could take care of both baseline pain and episodes of break through pain by employing one single Duragesic RTM patch. Similarly, faster delivery of nitro-glycerine, sufentanil, nicotine, insulin, dexamethasone or testosterone was achievable by using controlled heating patch.

1.22. Electroporation

This method involves the application of high voltage pulses to the skin that induces the formation of transient pores. High voltages (100 V) and short treatment durations (milliseconds) are most frequently employed as depicted in Fig: 13. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. Small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater that 7kDA [31].

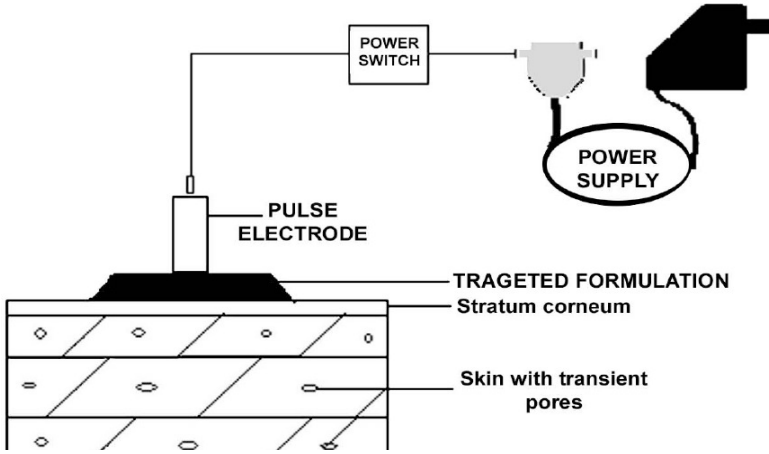

Figure – 13: Electroporation technique.

1.23. Ultrasound

This technique involves the application of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment. It uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability. Ultrasound devices deliver low frequency energy, in the 20 kHz region compared to the higher 1MHz energy used in physiotherapy, across the skin. The ultrasound energy pulses have the capability of producing both a physical increase in air pressure above the topical application site and the tissue effects utilized in medical therapy applications. However, ultrasound-facilitated transdermal delivery has not yet been tried and tested in the clinical field as depicted in Fig: 14. Therefore, it's acceptance as a routine mechanism for topical delivery of macromolecules is still hypothetical [31].

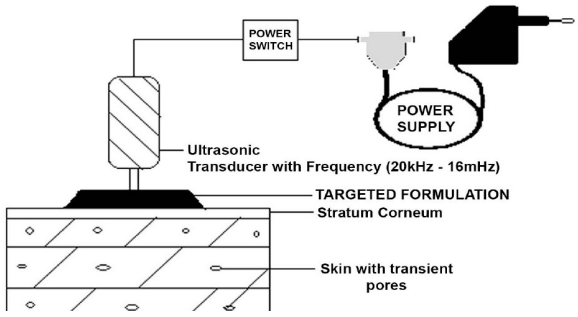

Figure – 14: Ultrasound device.

1.24. Iontophoresis

Iontophoresis involves the application of a small electrical current (usually, 500 microamperes cm^2) to facilitate the transfer of drugs through the dermal layers into the area to be treated, either into the surrounding tissues for localized treatment or into the circulatory system for systemic treatment (Figure 15). Positively charged ions are driven into skin at the anode while negatively charged ions are driven into skin at the cathode. Studies have shown increased skin permeation of drugs at anodic/cathodic electrodes regardless of predominant molecular ionic charge [26].

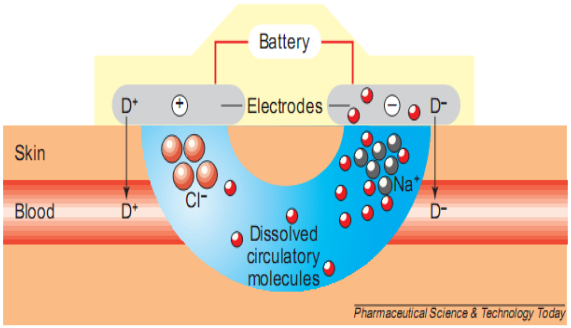

Figure - 15: Schematic of an iontophoretic device.

1.25. Regulation strategy for TDDS

There are currently 19 drugs and drug combinations administered by various delivery methods that are approved in the United States (Tables 1 and 2). Data were obtained from the FDA Orange Book [32].

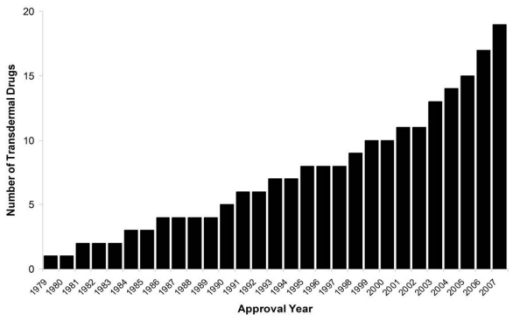

Figure - 16: Cumulative number of transdermal drugs approved by the FDA since 1979.

1.26. Clinical safety study of TDDS

More severe skin irritation may affect the efficacy or safety of the product. Transdermal products have properties that may lead to skin irritation and/or sensitization. The delivery system, in conjunction with the drug substance, may cause these reactions. In the development of transdermal products, dermatologic adverse effects are evaluated. Separate skin irritation and sensitization studies also are used for this purpose. These studies are designed to detect irritation and sensitization under condition of maximal stress and may be used during the assessment of transdermal products [6].

Table - 1: List of drug flux ratios with or without permeation enhancers.

Drug name	Permeation enhancers	Ratio of drug flux with enhancer to drug flux without enhancer
Progesterone	EVA 40	1.00
Progesterone	GML/EP/EVA 40	5.67
Progesterone	Polysiloxane	1.00
Progesterone	GML/EP/PVP/Polysiloxane	1.70
Buspirone	EVA 40	1.00
Buspirone	GML/EVA 40	9.19
Buspirone	GML/EP/EVA 40	10.03
Buspirone	GML/EP/PVP/ Polysiloxane	3.53
Buspirone	EP/EVA 40	1.28
Buspirone	Polysiloxane	1.00
Estradiol	EVA 40	1.00
Estradiol	GML/EP/EVA 40	2.11
Estradiol	Polysiloxane	1.00
Estradiol	GML/EP/PVP/ Polysiloxane	1.38
Oxybutynin base	Polysiloxane	1.00
Oxybutynin base	GML/EP/PVP/ Polysiloxane	1.46

Table - 2: Summary of patents utilizing hydroxide-releasing agents as permeation enhancers in TDDS.

Patent number	Drug	Hydroxide releasing agent(g)	PH	Flux
US20036562368B2	Oxybutynin	NaOH		
		0.15	-	1747.7[a]
		0.25	-	2853.5[a]
		0.35	-	2322.8[a]
US20036562370B2	Estradiol	NaOH		
		0	7.22	0.22[a]
		0.0155	8.75	4.55[a]
		0.025	8.90	7.01[a]
US20036562370B2	Estradiol	Potassium Phosphate tribasic	-	-
		0	6.4	0.6[b]
		0.1	8.89	5.6[b]
		0.3	10.83	10.2[b]
		0.48	9.87	5.3[b]
US20036565879B1	Oxytocin	NaOH	-	236.8[a]
US20046719997B2	Phenylpropanolamine HCl	NaOH	-	-

a: µg/cm^2/24 h, b :mg/cm^2/24 h

Study designs

Recommended designs for skin irritation and skin sensitization studies for the comparative evaluation of transdermal drug products are described below.

Sample size

30 subjects.

Exclusive criteria

Dermatologic disease that might interfere with the evaluation of test site reaction.

Duration of study

22 days.

Study design

A randomized, controlled, repeat patch study that compares the test patch to the innovator patch. Placebo patches (transdermal patch without the active drug substance) and/or high- and low-irritancy controls (eg. Sodium lauryl sulphate 0.1% and 0.9% saline) can be included as additional test arms.

Patch application

Each subject applies one of each of the patches to be tested. Test sites should be randomized among patients. Patches should be applied for 23 ± 1 hr daily for 21 days to the same skin site. At each patch removal, the site should be evaluated reaction and then patch is reapplied. Application of a test patch should be discontinued at a site if predefined serious reactions occur at the site repeated applications. Application at a different site may subsequently be initiated.

Evaluations

Scoring of skin reactions and patch adherence should be performed by an observer at each patch removal, using an appropriate scale.

Dermal response

0 = no evidence of irritation

1 = minimal erythema,

2=definite erythema, readily visible; minimal edema or minimal popular response.

3 = erythema and papules

4 = definite edema

5 = erythema, edema and papules

6 = vesicular eruption

7 = strong reaction spreading beyond test site

Other effects

A = slight glazed appearance

B = marked glazing

C = glazing with peeling and cracking

F = glazing ad fissures

G = film of dried serous exudates covering all or part of the patch site

H = small petechial erosions and/or scabs.

Dermal reactions should be scored on a scale that describes the amount of erythema, edema and other features defining irritations.

Data presentation and analysis

Individual daily observations should be provided, as well as a tabulation that presents the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score, and the number of days until sufficient irritation occurs to preclude patch application for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed [6].

Skin sensitization study

Sample size

200 subjects.

Exclusion criteria

a. Dermatologic disease that might interfere with the evaluation of the test site reactions.

b. Use of systemic or topological analgesics or antihistaminicwithin 72 hr of study or systemic or topical corticosteroids within 3 weeks of study enrolment.

Duration of study

6 weeks

Study design

A randomized, controlled study on the three test products: the test transdermal patch, the innovator patch, and the placebo patch (transdermal patch without the active drug substance).

Patch application

Test sites should be randomized among patients. The study is divided into three sequential periods:

Induction Phase

Applications of the test materials should be made to the same skin sites 3 times weekly for 3 weeks, for a total of 9 applications. The patches should remain in place for 48 hrs on weekdays and for 72 hrs on weekends. Scoring of skin reactions and patch adherence should be performed by a trained observer at each patch removal, using an appropriate scale. Dermal reactions should be scored on a scale that describes the amount of erythema, edema and other features relating to irritation.

Rest Phase

The induction phase is followed by a rest phase of two weeks, during which no applications are made.

Challenge Phase

The patches should be applied to new skin sites for 48 hrs. Evaluation of skin reactions should be made by a trained blinded observer at 30 min and at 24, 48 and 72 hrs after patch removal.

Data representation and analysis

The individual daily observations should be made, as well as a tabulation of the percentage of the subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all subjects should be calculated for each test product and a statistical analysis of the comparative results should are performed.

Combined studies

Alternatively, the cumulative skin irritation study and the skin sensitization study can be combined into a single study. The study design would be identical to the described for the skin sensitization study, except that patch application during the induction during the induction phase should be daily for 23±1 hr each day over 21 days [6].

2. CONCLUSION

This article provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance intopromising 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.

3. REFERENCES

1. Dipen MP and Kavitha K. Formulation and evaluation aspects of transdermal drug delivery system. **Int. J. Ph. Sci.** 2011; 6(2): 83-90.

2. Divyesh P, Nirav P, Meghal P and Navpreet K. Transdermal drug delivery system. **Int. J. Ph.Sci.,** 2011; 1(1): 62-80.

3. Anisha S, Promod K, Vipin K and Garima G. Approaches used for penetration enhancementin transdermal drug delivery system. **Int. J. Ph. Sci.** 2010; 2(3): 708-716.

4. Eseldin K, Rakesh KS, Esmaeil BM, Abd-alkadar ZA. Transdermal Drug Delivery System: Design and Evaluation. **Int. J. Adv. Ph. Sci.** 2010; 201-211.
5. Tyagi RKA., Chandra D. Singh Md and Rahman A. Transdermal drug delivery system. **IJPSR.** 2011; 2(6):748-757.
6. Vyas SP and Khar RK. **Controlled drug delivery: Concepts and advances: Transdermal drug delivery,** Vallah Prakashan, First edition, 2008; 411-476.
7. Franz TJ. **Transdermal delivery. In: Kydonieus A, ed. Treatise on controlled drug delivery: Fundamentals, optimization, applications.** Marcel D: 1991; 341-421.
8. Pfister WR and Hsieh DS. Permeation enhancers compatible with transdermal drug delivery systems. Part I: Selection and formulation considerations. Med. Device, 1990; 1: 48-55.
9. Chung SJ. Future drug delivery research in South Korea. **J. Controlled Release.** 1999; 62(1-2):73-9.
10. Izumoto T, Aioi A, Uenoyana S, Kariyama K and Azuma M. Relationship between the transference of drug from a transdermal patch and physicochemical properties. **Chem. Pharm. Bull.** 1992; 40(2): 456-8.
11. Karande P, Jain A, Ergun K, Kispersky V and Mitragotri S. Design principles of chemical penetration enhancers for transdermal drug delivery. **Nat. Acad. Sci.** 2005; 102: 4688-93.
12. Pocius AV. Adhesives In: Howe- Grants M, Ed. Kirk-OthmerEncyclopedia of Chemical Technology. Wiley-Interscience, 1991; 445-466.
13. Walters KA. Transdermal drug delivery systems In: Swarbick K., Boylan J.C, eds. **Encyclopedia of Pharmaceutical Technology,** Marcel D: 1997; 253-293.
14. Keith AD. Polymer matrix considerations for transdermal devices, **Drug. Dev. Ind. Pharm.** 1983; 9: 605-625.
15. Sinha VR and Pal KM. Permeation enhancers for transdermal drug delivery. **Drug Dev. Ind. Pharm.** 2000; 26: 1131-1140.
16. Foco A, Hadziabdic J and Becic F. **Transdermal drug delivery systems.** Med. Arch. 2004, 58: 230-4.
17. Willams AC and Barry BW. Penetration Enhancers. **Adv. Drug Del. Rev.** 2004; 56: 603-618.
18. Pellet M, Raghavan SL, Hadgraft J and Davis AF. The application of supersaturated systems to percutaneous drug delivery In: Guy R.H and Hadgraft. **J. Transdermal drug delivery,** 2003; 305-326.
19. Swarbrick J and Boylan J. Transdermal drug delivery devices: System design and composition. **Encyclopedia of Pharmaceutical Technology,** 309-37.
20. Baker W and Heller J. Material selection for transdermal delivery systems", In Transdermal Drug Delivery: Developmental Issues and Research Initiatives, J. Hadgraft and R.H. Guys, Eds. Marcel D, 1989; 293-311.
21. Deo MR, Sant VP, Parekh SR, Khopade AJ and Banakar UV. Proliposome-based transdermal delivery of levonorgestrel. **Jour. Biomat. Appl.** 1997; 12: 77-88.
22. Al-Khamis K, Davis SS and Hadgraft J. Microviscosity and drug release from topical gel formulations.Int. **J. Pharm. Sci.** 1986; 3: 214-217.
23. Anon. Transdermal delivery systems-general drug release standards. **Pharmacopeial Forum**. 1980; 14: 3860-3865.
24. Mayorga P, Puisieux F and Couarraze G. Formulation study of a Transdermal delivery system of primaquine. **Int. J. Ph. Sci.** 1996; 132: 71-79.
25. Crawford RR and Esmerian OK. Effect of plasticizers on some physical properties of cellulose acetate phthalate films. **J. Pharm. Sci.** 1997; 60: 312-314.
26. Ashok KJ, Nikhila P, Lakshmanaprabu S and Gopal V. Transdermal drug delivery system: an overview. **Int. J. Pharm. Sci.** 2010; 3(2): 49-54.
27. Ashok KT, Bharti S and Subheet J. **Innovations in Transdermal Drug Delivery: Formulations and Techniques,** Department of Pharmaceutical Sciences, Drug Research, Punjabi University, 2007; 1:23-36.
28. Park JH. Biodegradable polymers microneedles. **J. Controlled Release,** 2005, 104(1): 51-66.
29. Gregor C and Ulrich V. Nanotechnology and the transdermal route. **J. Controlled Release.** 2010; 141: 277-280.
30. Gaur PK, Mishra S, Purohit S and Dave K. Transdermal drug delivery system. Ameri. **J. Pharm. Sci. Res.** 2009; 2(1): 14-20.
31. Mark R, Prausnitz L and Robert L. **Transdermal drug delivery,** NIH Public

Access Author Manuscript; 2008; 26(11):1-18.

32. Nat AS, Hendry SP and Sheldrake C. 2006; US20067060048B1.