IJPSR (2012), Vol. 3, Issue 08 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 April, 2012; received in revised form 08 May, 2012; accepted 11 July, 2012

DESIGN, EVALUATION AND RECENT TRENDS IN TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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Keywords:
TDDS,
Topical Drug Delivery,
Types of TDDS,
Recent trends

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ABSTRACT

Transdermal drug delivery system (TDDS) is topically administered dosage form in the form of patches which deliver drugs for systemic effects at a predetermined and controlled rate. It works very simply in which drug is applied inside the patch and it is worn on skin for long period of time. By this constant concentration of drug remain in blood for long time. Polymer matrix, drug, permeation enhancers are the main components of TDDS; Polymers include gelatine, gum Arabic, methyl cellulose, starch, shellac, etc. (as a natural) to synthetic ones (polyethylene, polystyrene, acetyl co-polymer, polyvinyl chloride, polyamide, polyvinyl acetate, etc.) TDDS are of many types varying from single layer drug in adhesive to multi layer drug in adhesive and others are reservoir and the matrix systems. The market value of TDDS products are increasing with rapid rate, more than 35 products have now been approved for sale in US, and approximately 16 active ingredients are approved globally for use as a TDDS. Transdermal drug delivery is a recent technology which promises a great future it has a potential to limit the use of needles for administering wide variety of drugs but cost factor is a important thing to consider since developing nations like INDIA have second highest population, but due to higher cost TDDS are the hidden part of therapy used in general population. This review article provides an overview of TDDS, its advantageous and disadvantageous, basic components, types, evaluation and recent trends.

INTRODUCTION: In recent years, Transdermal drug delivery has become an increasingly important field. Due to the ability to provide sustained release therapies and ease of application and delivery, the field is experiencing a high growth rate [1]. The market value for transdermal delivery products was $12.7 billion in 2005 and it is expected to increase to $21.5 billion in 2010 and $32 billion by 2015 [2, 3].

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate [4]. A transdermal therapeutic system is a device which release drug to the skin at a controlled rate well below the maximum that the tissue can accept. Thus the device, not the stratum corneum, control the rate at which a drug diffuses through the skin [5].

In theory, transdermal patches work very simply. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since, there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow [6].

Advantages of TDDS over controlled release formulations [7]:

1. Avoidance of first pass metabolism.
2. Stable and controlled blood level.
3. Comparable characteristics with intravenous infusions.
4. Ease of termination of drug action, if necessary.
5. Long duration of actions (ranging from a few hours to a week).
6. No interference with gastric and intestinal fluid.
7. Suitable for administrations of drugs having
    a. Very short half life. E.g. nitroglycerine
    b. Narrow therapeutic window.
    c. Poor oral bioavailability.

Disadvantages of TDDS [7]: The route is unsuitable when;

1. Drug dose is large.
2. Drug has larger molecular size (makes absorption difficult; should be ideally be below 800-1000daltons)
3. Drug is sensitising and irritating.
4. Drug is metabolised in skin.
5. Drug undergoes protein binding in skin.
6. Drug is highly lipophilic or hydrophilic (should be moderately soluble in both oil and water)

Properties that influence Transdermal Delivery:

- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response [8].

Kinetics of Transdermal Permeation: Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.
2. Penetration of drug through epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physiochemical properties. The rate of permeation across the skin is given by:

$$dQ/dt = Ps (Cd - Cr) \quad \ldots\ldots 1$$

Where Cd and Cr are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. Ps is the overall permeability coefficient the skin tissue to the penetrant. This permeability coefficient is given by the relationship:

$$Ps = Dss\ Ks/\ hs \quad \ldots\ldots 2$$

Where Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and hs is the overall thickness of skin tissues. As Ks, Dss and hs are constant under given conditions the permeability coefficient Ps for a skin penetrant can be considered to be constant. From equation (1) it is clear that a constant rate of drug permeation can be obtained only when Cd >> Cr i.e. the drug concentration at the surface of the stratum corneum Cd is consistently and substantially greater than the drug concentration in the body Cr. The equation becomes:

$$dQ/dt = Ps\ Cd \quad \ldots\ldots 3$$

The rate of skin permeation is constant provided the magnitude of Cd remains fairly constant throughout the course of skin permeation. For keeping Cd constant the drug should be released from the device at a rate Rr i.e. either constant or greater than the rate of skin uptake Ra i.e. Rr >> Ra. Since Rr >> Ra , the drug concentration on the skin surface Cd is maintained at a

level equal to or greater than the equilibrium solubility of the drug in the stratum corneum Cs .i.e. Cd>>Cs. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

(dQ/dt)m = Ps Cs…… 4

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient Ps and is equilibrium solubility in the stratum corneum Cs. Thus skin permeation appears to be stratum corneum limited [9].

Types of Transdermal Patches: There are four major transdermal Systems.

1. **Single-layer Drug-in-Adhesive**

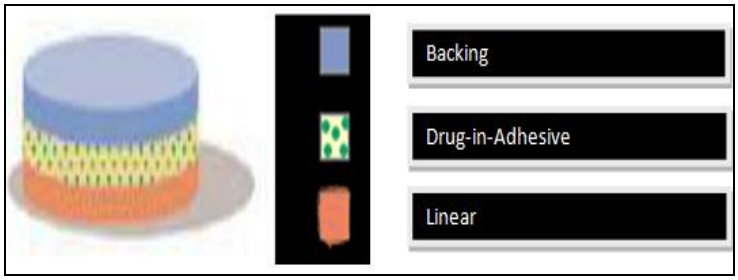


FIG. 1: SINGLE-LAYER DRUG-IN-ADHESIVE

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin [10].

The intrinsic rate of drug release from this type of drug delivery system is defined by

$$dQ/dT = Cr/1/Pm + 1/Pa$$

Where Cr is the drug concentration in the reservoir compartment and Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane, Pm is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. Pm and Pa, respectively, are defined as follows.

$$Pm = Km/r.\ Dm/\ hm.$$

$$Pa = Ka/m\ Da/\ ha$$

where Km/r and Ka/m are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively; Dm and Da are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and hm and ha are the thicknesses of the rate controlling membrane and adhesive layer, respectively [9, 11].

2. **Multi-layer Drug-in-Adhesive:**

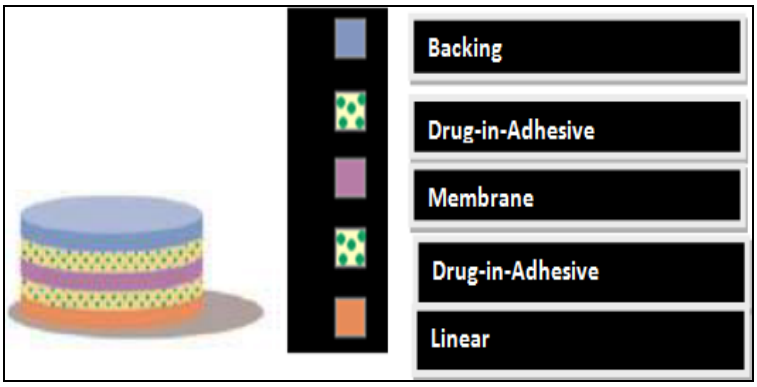


FIG. 2: MULTI-LAYER DRUG-IN-ADHESIVE

The multi-layer drug-in-adhesive is similar to the single-layer drug-in-adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film [10].

The rate of drug release in this system is defined by:

$$dQ/dt = Ka/r\ .\ Da\ Cr/\ ha$$

Where, Ka/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer [4, 11].

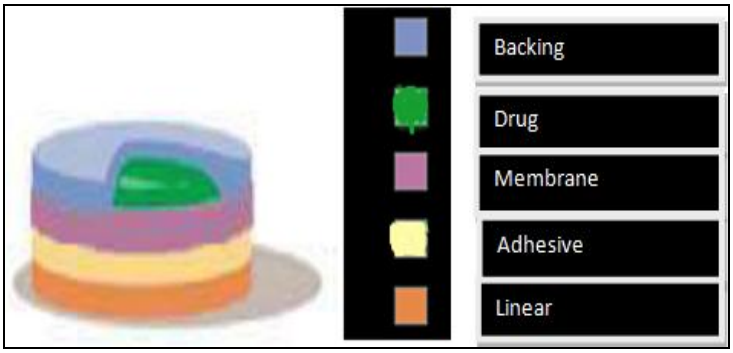


FIG. 3: DRUG RESERVOIR-IN-ADHESIVE

The reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane [10].

The rate of drug release from this drug reservoir gradient controlled system is given by:

$$dQ/dt = Ka/r.\ DaA(ha)/ha(t)$$

In the above equation, the thickness of the adhesive layer for drug molecule to diffuse through increases with time ha (t). To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusional path A (ha) [8, 9].

3. **Drug Matrix-in-Adhesive:**

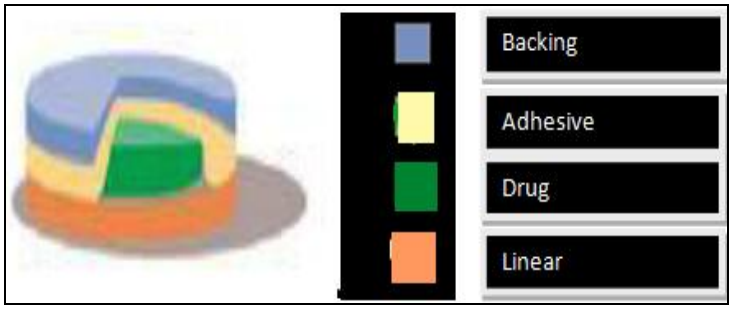


FIG. 4: DRUG MATRIX-IN-ADHESIVE

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix [10].

The rate of drug release from this type of system is defined as:

$$dQ/\ dt = ACp\ Dp\ ½\ /2t$$

Where A is the initial drug loading dose dispersed in the polymer matrix and Cp and Dp are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, Cp is essentially equal to CR, where CR is the drug concentration in the reservoir compartment [8, 9].

Methods of Preparation of TDDS:

1. **Polymer membrane permeation-controlled TDDS:** In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied (**Figure 1**). The rate of drug release from this type of transdermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate controlling membrane [12, 13].

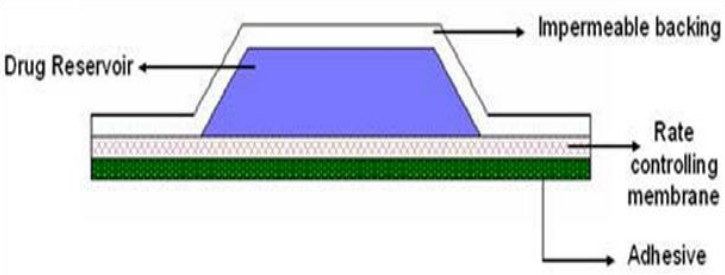


FIG. 1: POLYMER MEMBRANE PERMEATION-CONTROLLED TDDS

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

2. **Adhesive diffusion controlled TDDS:** The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in case of hot-melt adhesives) onto an impervious backing layer (**Figure 2**). The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlling drug delivery system [12, 13].

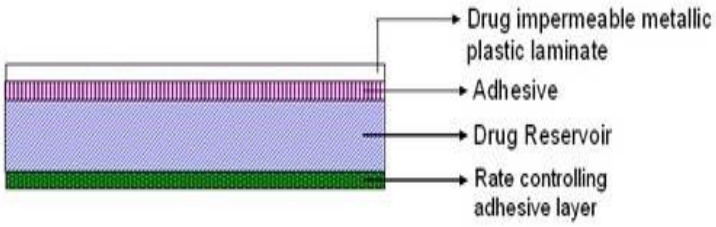


FIGURE: 2 ADHESIVE DIFFUSION CONTROLLED TDDS

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

3. **Matrix diffusion controlled TDDS:** The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer (**Figure 3**). Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim [12, 13].

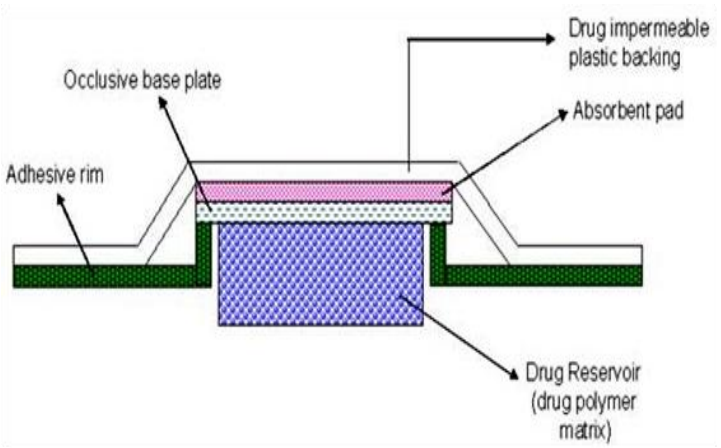


FIGURE: 3 MATRIX DIFFUSION CONTROLLED TDDS

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

4. **Micro-reservoir controlled TDDS:** This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs (**Figure 4**). The thermodynamically unstable dispersion is stabilized quickly by immediately crosslinking the polymer in situ. A transdermal system, therapeutic system thus formed as a medicated disc positioned at the center and surrounded by an adhesiverim[12, 13].

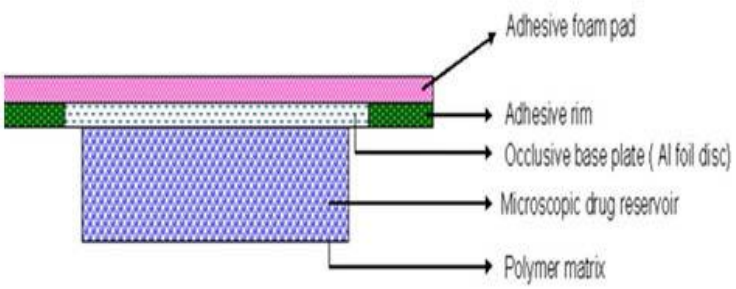


FIGURE 4: MICRORESERVOIR CONTROLLED TDDS

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

Basic Components of TDDS:

1. Polymer matrix / Drug reservoir.
2. Drug.
3. Permeation enhancers.
4. Pressure sensitive adhesive (PSA).
5. Backing laminates.
6. Release liner.
7. Other excipients like plasticizers and solvent.

1. **Polymer matrix / Drug reservoir:** Polymers are the heart of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have good stability and compatibility with the drug and other components of the system and they should provide effective 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, butylrubber *etc*.

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

The polymer like polyethylene glycol [14], eudragits [15], ethylcellulose, polyvinylpyrrolidone [16] and hydroxy-propylmethylcellulose [17] are used as matrix type TDDS. The polymers like EVA [18], silicon rubber and polyurethane [19] are used as rate controlling TDDS.

2. **Selection of drugs:** The selection of drug for TDDS is based on physicochemical properties of drug. Transdermal drug delivery system is much suitable for drug having [20, 21].

   - Extensive first pass metabolism.
   - Narrow therapeutic window.
   - Short half-life which causes non-compliance due to frequent dosing.
   - Dose should be less (mg/day) [22].
   - 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).

3. **Permeation enhancers:** These compounds are useful to increase permeability of stratum corneum by interacting with structural components of stratum corneum *i.e.,* proteins or lipids to attain higher therapeutic levels of the drug [23]. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability [24]. Some example are Dimethyl sulfoxide, Propylene glycol,2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Pluronic, Cardamom oil, Caraway oil, Lemon oil, Menthol, dlimonene, Linoleic acid [25].

4. **Pressure sensitive adhesives:** The pressure-sensitive adhesive (PSA) affixes the transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue [26, 27]. Adhesives must be skin-compatible, causing minimal irritation or sensitization, and removable without inflicting physical trauma or leaving residue. In addition, they must be able to dissolve drug and excipient in quantities sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability.

PSAs used in commercially available transdermal systems include polyacrylate, polyisobutylene and polysiloxane [28]. Polyacrylates are most widely used. In general, all acrylic adhesives are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of polyacrylate matrices.

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

Silicone, adhesives are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicones, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups. To address this problem, special silicones have been developed that are rendered resistant to amine-catalyzed condensation through end-capping of silanol functional groups. Hot Melt Pressure Sensitive Adhesives (HMPSA), HMPSA melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flowless state. They are

thermoplastic in nature. Compounded HMPSA are Ethylene vinyl acetate copolymers, Paraffin waxes, Low density polypropylene, Styrene-butadiene copolymers, and Ethylene-ethacrylate copolymers. Uncompounded HMPSA are Polyesters, Polyamides and Polyurethanes.

5. **Backing laminate:** Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefin's, polyesters, and elastomers in clear, pigmented, or metallized form. Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability. In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate [29, 30].

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

6. **Release Liners:** During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug.

   However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (*e.g*. paper fabric) or occlusive (*e.g*. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon.

   Other materials used for TDDS release liner include polyester foil and metalised laminates[27, 31].

7. **Other excipients:** Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir [18, 32]. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch [32, 33].

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

1. Physicochemical evaluation.
2. *In vitro* evaluation.
3. *In vivo* evaluation.

1. **Physicochemical Evaluation:**

a. **Interaction studies:** The drug and the excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation and development. Interaction studies are taken out by Thermal analysis, FTIR, UV and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, absorption maxima [34, 35, 36].

b. **Thickness of the patch:** The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch [37].

c. **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 [37].

d. **Folding endurance:** A specific area of strip is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of endurance [37].

e. **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 [37];

Percentage moisture content =

[(Initial weight- Final weight) / Final weight] ×100.

f. **Percentage moisture uptake:** The prepared patches are to be weighed individually and to be kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake by below formula;

Percentage moisture uptake=

[(Final weight- Initial weight)/ Initial weight] ×100.

g. **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 [38];

$$WVP=W/A$$

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.

h. **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 [38].

i. **Content uniformity test:** 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85 - 115% of the specified value and one has content not less than 75 - 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 - 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% - 115%, then the transdermal patches pass the test [39].

j. **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 analytical technique (UV or HPLC) and the drug content per piece will be calculated [40].

k. **Polariscopic examination:** A specific surface area of the piece is to be kept on the object slide of polariscopic and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch [40].

l. **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 [40].

m. **Adhesive studied:**

i. **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 5**). Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single

tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180°C angle, and the force required for tape removed is measured [40].

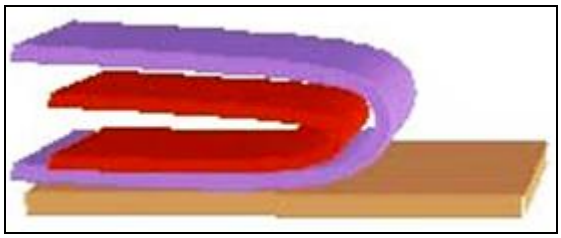


FIGURE: 5 PEEL ADHESION TEST

ii. **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 [40].

iii. **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 [40].

n. **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 [36].

$$\% \text{ constriction} = I_1 - I_2 / I_1 \times 100$$

Where, I_1 = Initial length of each strip. I_2 = final length of each strip.

o. **Percentage elongation break test:** The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below formula [41].

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

Where, L1= is the final length of each strip.

L2= is the initial length of each strip.

p. **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 (**Figure 6**). The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch[12]**.**

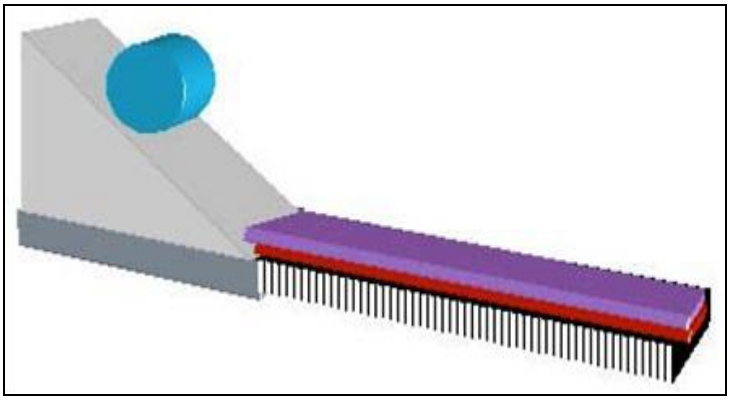


FIGURE 6: ROLLING BALL TACK TEST

q. **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 7**) and recorded as tack value, which is expressed in ounces or grams per inch width [12].

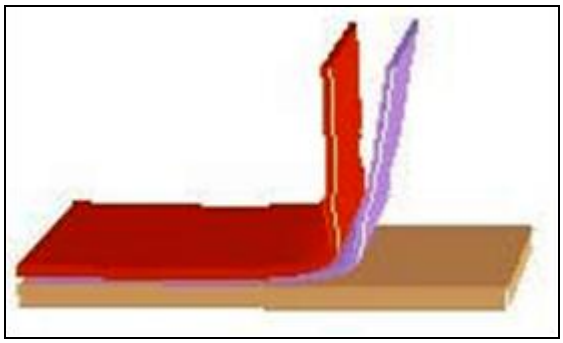


FIGURE: 7 QUICK STICK (PEEL-TACK) TEST

r. **Probe Tack test:** In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it (**Figure 8**). The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams [12].

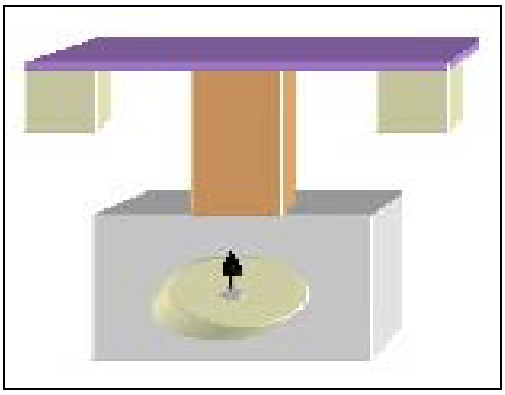


FIGURE: 8 PROBE TACK TEST

s. **Shear strength properties or creep resistance:** Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti *et al.,* (2003) performed the test with an apparatus (**Figure 9**) which was fabricated according to PSTC-7 (pressure sensitive tape council) specification [39].

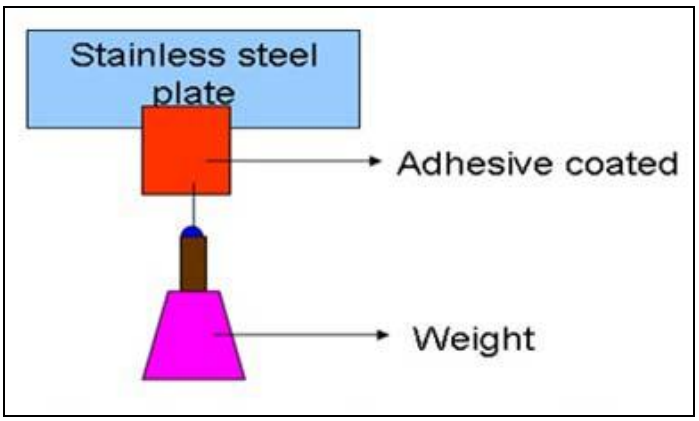


FIGURE: 9 SHEAR STRENGTH PROPERTIES OR CREEP RESISTANCE

t. **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 [42].

2. ***In vitro* Evaluation of TDDS:**

a. ***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 [42].

b. ***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 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 cm2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^2) [42].

c. ***In vivo* Evaluation:** *In vivo* evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using: Animal models and Human volunteers.

i. **Animal models:** Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both *in vitro* and *in vivo* experiments. Rhesus monkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man [12].

ii. **Human models:** The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug [12].

d. **Skin Irritation study:** Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50 cm^2) of the rabbit is to be cleaned and 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 [40].

Applications of Transdermal Patches [4, 9]:

1. The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking.

2. Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).

3. Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).

4. Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.

5. The anti-hypertensive drug Clonidine is available in transdermal patch form.

6. Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.

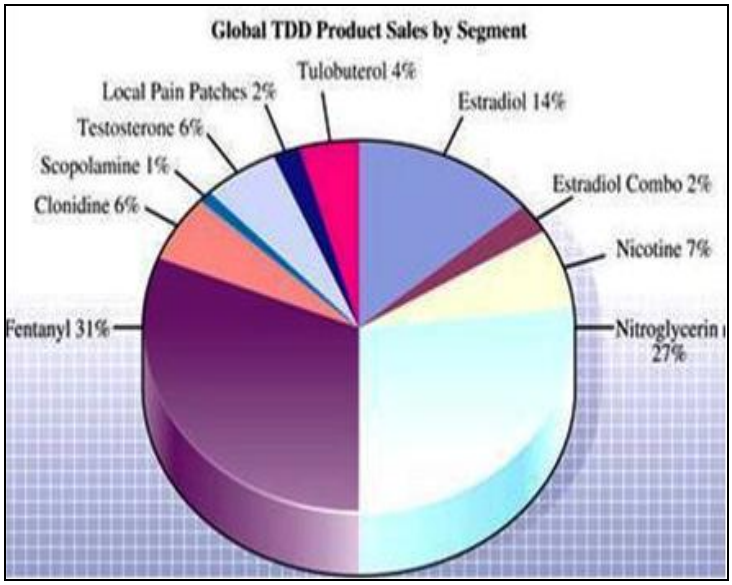
7. Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

Transdermal Market: The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally [43]. **Table 1** gives detail information of the different drugs which are administered by this route and the common names by which they are marketed it also gives the conditions for which the individual system is used [44].

TABLE 1: TRANSDERMAL MARKET

PRODUCT NAME	DRUG	MANUFACTURE	INDICATION
Alora	Estradiol	TheraTech/proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	Theratech/GalxosmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	ALZA/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	EthicalHoldings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/Norethindrone	Noven,Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerine	Schwarz pharma	Angina pectoris
Duragesic	Fentanyl	Alza/ Jansscn pharmaceutical	Moderate /severe pain
Estraderm	Estradiol	Alza/Novartis	Post menstrual syndrome
Fematrix	Estrogen	Ethical holdings/solvay healthcare LTD	Post menstrual syndrome
Fempatch	Estradiol	Parke-davis	Post menstrual syndrome
Habitraol	Nicotin	Novartis	Smoking cessation
Minitrann	Nitroglycerine	3M pharmaceuticals	Angina pectoris
Nicoderm	Nicotin	Alza/glaxo smithkline	Smoking cessation
Nicotrol	Nicotin	Cygnus inc./Mc Neil Consumer products Ltd.	Smoking cessation
Nitrodisc	Nitroglycerine	Roberts pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerine	Key pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/progesterone	Ethical holding/schering	Hormone replacement therapy
Ortho-Evara	Norelgestromin/estradiol	Ortho/Mc Neil pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Transderm Scop	Scopolamine	Alza/Novartis	Motion sickness
Transderm nitro	Nitroglycerine	Alza/Novartis	Angina pectoris

Recent trends in TDDS [45, 46]**:** The pie diagram given below shows that fentanyl and nitroglycerine are the drugs most popularly marketed using transdermal patches.



Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called “active” transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create

transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

TABLE 2: CURRENTLY APPROVED USFDA DRUGS FOR TDDS

YEAR	GENERIC (BRAND) NAMES	INDICATION
1979	Scopolamine (Transderm Scop®)	Motion sickness
1984	Clonidine (Catapress TTS®)	Hypertension
1986	Estradiol (Estraderm®)	Menopausal symptoms
1990	Fentanyl (Duragesic®)	Chronic pain
1991	Nicotine (Nicoderm®, Habitrol®, Prostep®)	Smoking cessation
1993	Testosterone (Androderm®)	Testosterone deficiency
1995	*Lidocaine/epinephrine (Iontocaine®)*	Local dermal analgesia
1998	Estradiol/norethindrone (Combipatch®)	Menopausal symptoms
1999	Lidocaine (Lidoderm®)	Post-herpetic neuralgia pain
2001	Ethinyl estradiol/norelgestromin (OrthoEvra®)	Contraception
2003	Estradiol/levonorgestrel (Climara Pro®)	Menopause
2003	Oxybutynin (Oxytrol®)	Overactive bladder
2004	*Lidocaine/ultrasound (SonoPrep®)*	Local dermal anesthesia
2005	Lidocaine/tetracaine (Synera®)	Local dermal analgesia
2006	*Fentanyl/iontophoresis (Ionsys®)*	Acute postoperative pain
2006	Methylphenidate (Daytrana®)	ADHD
2006	Selegiline (Emsam®)	Depression
2007	Rotigotine (Neupro®)	Parkinson's disease
2007	Rivastigmine (Exelon®)	Dementia
2008	Granisetron (Sancuso®)	Chemo-induced emesis
2009	*Oxybutynin (Gelnique®)*	Overactive bladder
2010	Buprenorphine (Butrans®)	Chronic pain

Future Scope:

The future scope of the TDDS includes:

- An insulin patch
- Sufentanil patch for chronic cancer pain
- Varenicline patch for smoking cessation and a high-dose nicotine patch for fast metabolizers
- Estrogen and testosterone patches for post-menopausal women
- Selegiline patch for depression in the elderly and cocaine addiction
- Clonidine transdermal for the treatment of delerium in trauma patients
- Dexamethasone iontophoretic delivery for the treatment of tennis elbow
- An iontophoretic sumatriptan patch for migraine treatment, and
- Transdermal glyceryl trinitrate for acute stroke therapy, to name a few

CONCULSION: Transdermal drug delivery system is useful for topical and local action of the drug. The drug which shows hepatic first pass effect and unstable in GI conditions, are suitable candidate for TDDS. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration and many new researches are going on in the present day to incorporate newer drugs via the system.

Future developments of TDDS will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use.

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How to cite this article:
Hanumanaik M, Patil U, Kumar G, Patel SK, Singh I and Jadatkar J: Design, Evaluation and Recent Trends in Transdermal Drug Delivery System: A Review. *Int J Pharm Sci Res*, 2012; Vol. 3(8): 2393-2406.