World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 8, Issue 5, 2019 ISSN: 2319-5622 USA CODEN: JPROK3

Review Article

RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS): AN OVERVIEW

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Received on: 11-04-2019; Revised and Accepted on: 21-05-2019

ABSTRACT

Conventional dosage form has significant setbacks of poor bioavailability and frequent dosing due to hepatic first pass metabolism. Transdermal drug delivery systems (TDDS), dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. It is (TDDS) also known as "patches," are. 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. 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. The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS.

KEYWORDS: *Transdermal drug delivery systems (TDDS), Topical drug delivery, Hepatic first pass metabolism, therapeutic efficacy, Patches.*

INTRODUCTION

The word Transdermal has been derived from the root 'trans' meaning through, across or beyond and 'derma' meaning skin. Transdermal drug delivery system was introduced to overcome the difficulties of drug delivery through oral route. Transdermal systems are a desirable form of drug delivery because of the obvious advantages over other routes of delivery. Transdermal delivery provides convenient and pain-free self-administration for patients [1]. Transdermal drug delivery system is self-contained, discrete dosage form which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation [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. Transdermal delivery provides a leading edge over injectables and oral route by increasing patient compliance and avoiding first pass metabolism. During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent [3]. Transdermal Drug Delivery System (TDDS) are defined as self contained, discrete dosage forms which are also known as "patches" [4, 5] when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation [6]. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin [7]. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. Currently transdermal delivery is one of the most promising methods for drug application [8]. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application [9]. That wills improves bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms [10]. Transdermal delivery not only provides controlled, constant administration of drugs, 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. Several important advantages of transdermal drug delivery are limitations of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintenance of steady plasma level of drug [3]. The

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DOI: https://doi.org/10.5281/zenodo.3236719

developments of TDDS is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important economy [7]. The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a zero order rate for a period of several hours to days following application to the skin. This is especially advantageous for prophylactic therapy in chronic conditions [11]. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy [12].

Anatomy of skin:

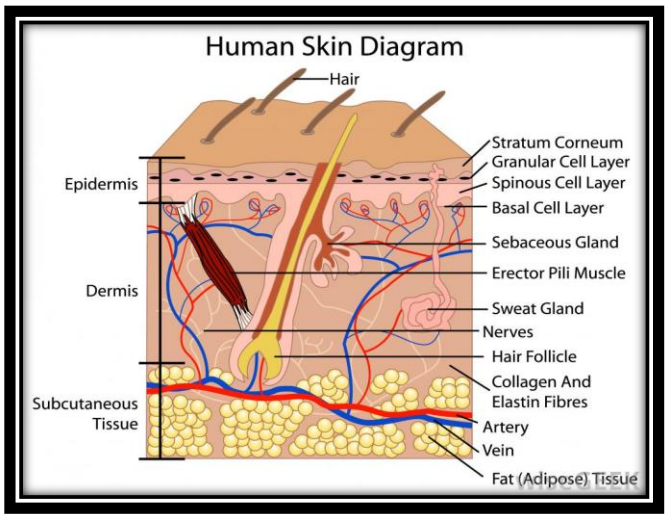


Fig. 1: Anatomy of Skin

The structure of human skin (fig.1) can be categorized into four main layers

- The epidermis
- The viable epidermis
- A non-viable epidermis (*Stratum corneum)*
- The overlying dermis
- The innermost subcutaneous fat layer (Hypodermis)

The Epidermis:

The epidermis is a continually self-renewing, stratified squamous epithelium covering the entire outer surface of the body and primarily composed of two parts: the living or viable cells of the Malpighian layer (viable epidermis) and the dead cells of the *stratum corneum* commonly referred to as the horny layer [5]. Viable epidermis is further classified into four distinct layers as shown in [14]

- *Stratum lucidum*
- *Stratum granulosum*
- *Stratum spinosum*
- *Stratum basale*

Stratum corneum:

This is the outermost layer of skin also called as horny layer. It is the rate limiting barrier that restricts the inward and outward movement of chemical substances. The barrier nature of the horny layer depends critically on its constituents: 75-80% proteins, 5-15% lipids, and 5-10% ondansetron material on a dry weight basis.

Stratum corneum is approximately 10 mm thick when dry but swells to several times when fully hydrated. It is flexible but relatively impermeable. The architecture of horny layer (figure 3) may be modelled as a wall-like structure with protein bricks and lipid mortar. It consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocytes are embedded in a lipid matrix which plays a significant role in determining the permeability of substance across the skin [13].

Viable epidermis:

This is situated beneath the *stratum corneum* and varies in thickness from 0.06 mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as *stratum lucidum*, *stratum granulosum, stratum spinosum,* and the *stratum basale*. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basale layer move outward, they itself alter morphologically and histochemically, undergoing keratinization to form the outermost layer of *stratum corneum* [14].

Dermis:

Dermis is the layer of skin just beneath the epidermis which is 3 to 5 mm thick layer and is composed of a matrix of connective tissues, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water, and thus provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophillic molecules [15].

Hypodermis:

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all three layers and reach in systemic circulation [16].

Advantages of transdermal drug delivery systems: [17]

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are:

- Avoidance of first pass metabolism
- Avoidance of gastro intestinal incompatibility

- Predictable and extended duration of activity
- Minimizing undesirable side effects
- Provides utilization of drugs with short biological half lives, narrow therapeutic window
- Improving physiological and pharmacological response
- Avoiding the fluctuation in drug levels
- Inter and intra patient variations
- Maintain plasma concentration of potent drugs
- Termination of therapy is easy at any point of time
- Greater patient compliance due to elimination of multiple dosing profile
- Ability to deliver drug more selectively to a specific site

Limitations of transdermal drug delivery systems: [18-20]

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin
- Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitization
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

Types of transdermal patches: [10, 21]

1. Single-layer drug-in-adhesive:

In this system drug and excipients is included with skin adhesive which serve as formulation foundation as a single breaking layer. The rate of release of drug is through diffusion phenomenon. The rate of release of drug is expressed as:

$$d_Q/d_T = Cr/(1/Pm + 1/Fa)$$

Where, Cr = drug concentration in reservoir compartment; Pa = Permeability coefficient of adhesive layer; Pm = Permeability coefficient of rate controlling membrane.

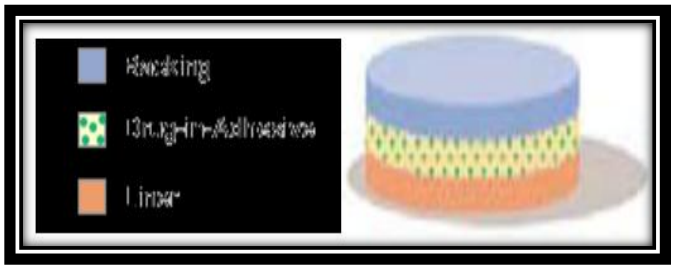


Fig. 2: Single-layer drug-in-adhesive

2. Multi-layer drug-in-adhesive:

In this system drug and excipients mixed with adhesive but both layer of adhesive separated by single layer membrane. The released of drug occurred through diffusion phenomenon. The rate of release of drug is governed by following equation:

$$d_Q/d_T = [(Ka/r.Da)/ha]Cr$$

Where Ka/r = partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

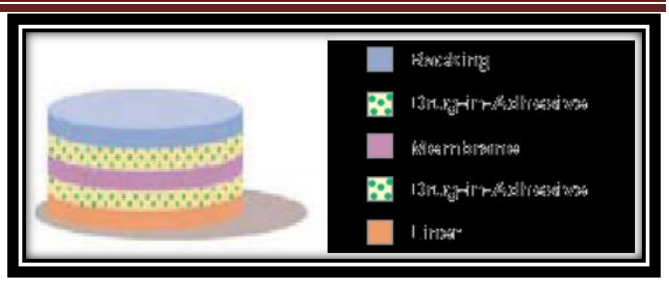


Fig. 3: Multi-layer drug-in-adhesive

3. Drug reservoir-in-adhesive:

In the reservoir system, assimilation of liquid compartment containing drug solution /suspension between backing layer and semi permeable membrane followed by adhesive layer and release liner. The rate of drug release from this drug reservoir system is given by

$$d_Q/d_T = [(Ka/r.Da)/ha(t)]A(ha)$$

Where, ha = thickness of adhesive layer; A = thickness of diffusional path.

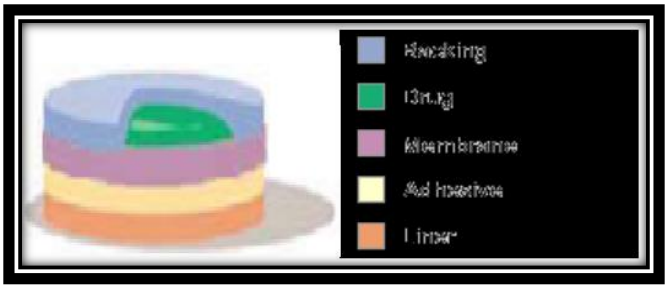


Fig. 4: Drug Reservoir-in-Adhesive

4. Drug matrix-in-adhesive:

This system is designed by mixing of semisolid matrix having drug in solution or suspension form which is in direct contact with the release liner. The rate of release of drug is governed by following equation:

$$d_Q/d_T = ACPDP\ 1/2/2t$$

Where, A = the initial drug loading dose dispersed in the polymer matrix; Cp = solubility of the drug; D = diffusivity of the drug in the polymer.

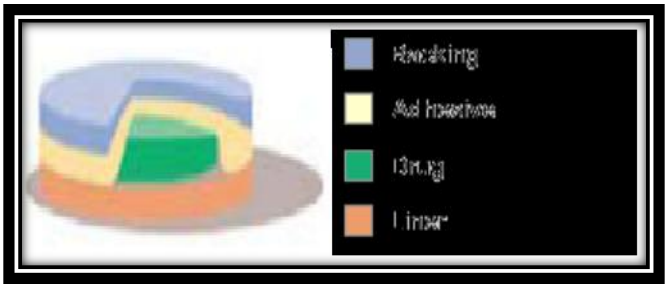


Fig. 5: Drug Matrix-in-Adhesive

Table No. 1: Drugs used in the Transdermal Patch [22]

Brand Name	Drug	Manufacturer	Indication s
Nicotin ell	Nicotine	Novartis Pharmacological	smoking cessation
Matrife n	Fentanyl	Nycomed	Pain relief patch
Ortho EvraTM	Norelgostromin / Ethinyl Estradiol	ORTHO-McNEIL	Postmenstrual syndrome
NuPatc h 100	Diclofenac diethylamine	Zydus Cadila	Anti-inflammatory
Neupro R	Rigotine	Rigotine	early-stage idiopathic Parkinson' s disease
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
NicodermR	Nicotine	Alza/GlaxoSmithK line	Smoking cessation

Components of transdermal patches:

1-Polymer Matrix
2-Drug
3-Permeation Enhancer
4-Other excipients

1) Polymer Matrix:

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

a) Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
b) The polymer should be stable.
c) The polymer should be nontoxic
d) The polymer should be easily of manufactured
e) The polymer should be inexpensive
f) The polymer and its deagration product must be non toxic or non-antagonistic to the host.
g) Large amounts of the active agent are incorporated into it.

Types of polymer:

a) Natural polymers: Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.
b) Synthetic Elastomers: Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.
c) Synthetic polymers: Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamiode, polyurea, epoxy.

2) Drug: Drug solution in direct contact with release liner.

Physiochemical properties:

a) The drug should have a molecular weight less than 1000 Daltons.
b) The drug should have affinity for both lipophilic and hydrophilic phases.
c) The drug should have a low melting point.

Biological properties:

a) The drug should be potent with a daily dose of the order of a few mg/day.
b) The half life (t½) of the drug should be short.
c) The drug must not produce allergic response.
d) Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.

Permeation enhancers: [13]

These are the compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrate.

J = D dc/dx J = the Flux

D = diffusion coefficient; C = Concentration of the diffusing specters; X = Spatial coordinate

Where D is the diffusion coefficient and is a function of size, shape and felxibilty of the diffusing molecule as well as the membrane resistance, c is the concentration of the diffusing molecule and x is the spatial coordinate. Thus enhancement of flux across membranes reduces to considerations of:

- Thermodynamics(lattice energies, distribution coefficient)
- Molecular size and shape.
- Reducing the energy required to make a molecular hole in the membrane

Permeation enhancer is hypothesized to affect structure of proteins and lipids therefore altering the barrier energy to whole formation.

Chemical approach: [25, 26]

This includes:
(a) Synthesis of lipophilic analogs;
(b) Delipidization of stratum corneum;
(c) Co-administration of skin permeation enhancers. This chemical approach can further be classified according to their chemical class

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

Biochemical approach this includes:
(a) Synthesis of bio-convertible pro-drugs.
(b) Co-administration of skin metabolism inhibitors.

Physical approach includes:

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

Adhesive layer: [26-28]

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

1. Peel: The resistance against the breakage of the adhesive bond.

2. Track: The ability of a polymer to adhere to a substrate with little contact Pressure

3. Creep: The viscous relaxation of the adhesive bond upon shear

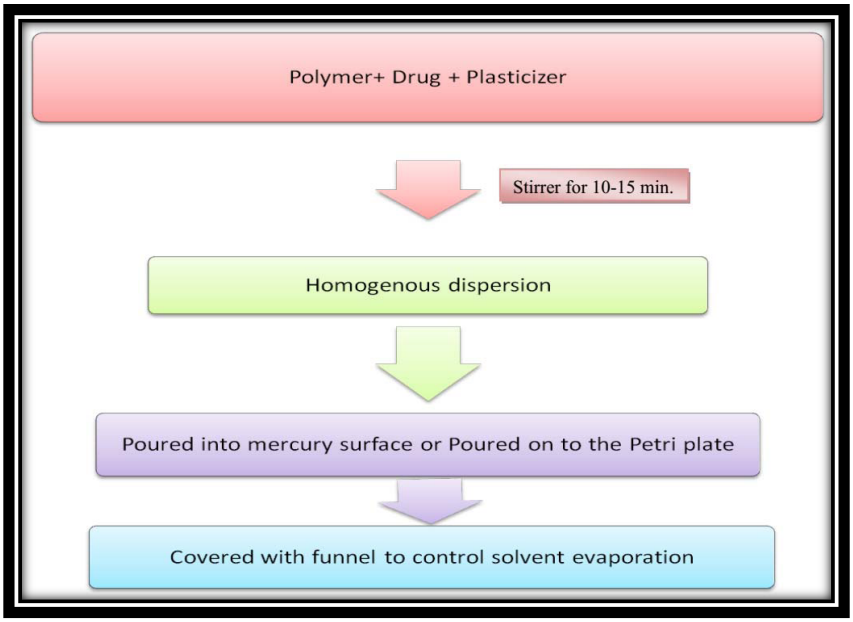
- The ideal characters of adhesive materials are,
  1. High biocompatibility (low irritancy, toxicity, allergic reaction etc.);
  2. Good adhesive to oily, wet, wrinkled and hairy skin;
  3. Good environment resistance against water and humidity;
  4. Easy to remove from the skin;
  5. High permeability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

Backing layer: [27]

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

Method of Preparing Transdermal Patches: [28]

Method of preparation of TDDS was summarized by modifying the earlier reported methods. The patches were prepared by solvent casting method. The polymer (for example PVP/HPMC) was taken in a beaker with a minimum quantity of the solvent. Then 2/3rd of the solvent was mixed with the other polymers (for example PVA) and was added firstly with stirring at lower rpm and later at a higher speed. The plasticizer was added and homogeneously mixed and the drug was included with enduring agitation and the volume was made up. The films were cast onto a suitably designed and fabricated glass mould and then dried in oven at 40^{oC}. The films were removed by using sharp blade by inserting along the edges of the film. The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place.



Factors Affecting Transdermal Bioavailability: [30-33]

Two major factors affect the bioavailability of the drug through transdermal routes:

(1) Physiologicalfactors (2) Formulation factors

Physiological factors include:

i. Stratum corneum layer of the skin
ii. Anatomic site of application on the body
iii. Skin condition and disease
iv. Skin metabolism
v. Skin irritation and sensitization

Formulation factors include:

(i) Penetration enhancers used
(ii) Vehicles and membrane used
(iii) Physical chemistry of transport
(iv) Method of application
(v) Device used

Evaluation Parameters:

1. Interaction studies: [30, 34]

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in

formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.,

2. Thickness of the patch: [32]

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

3. Weight uniformity: [32]

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.

4. Folding endurance: [32]

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

5. Percentage Moisture content: [32]

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula. Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.

6. Percentage Moisture uptake: [32]

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

7. Water vapour permeability (WVP) evaluation: [30]

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula WVP=W/A Where, WVP is expressed in gm/m2 per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m^2.

8. Drug content: [30]

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. Uniformity of dosage unit test: [33]

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 m membrane filter and analysed byμfiltered using 0.2 suitable analytical techniques (UV or HPLC) and the drug content per piece will be calculated.

10. Polariscope examination: [33]

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

11. Shear Adhesion test: [33]

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.

12. Peel Adhesion test: [33]

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured.

13. Thumb tack test: [33]

It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected. 14. Flatness test:23 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.

14. Flatness test: [35]

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.

15. Percentage Elongation break test: [33]

The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.Elongation percentage = L1-L2/ L2 ×100 Where, L1is the final length of each strip and L2 is the initial length of each strip.

16. Rolling ball tack test: [35]

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive.

The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

17. Quick Stick (peel-tack) test: [35]

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

18. Probe Tack test: [35]

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

19. In vitro drug release studies: [34]

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.

20. In vitro skin permeation studies: [34]

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a 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 cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

21. Skin Irritation study: [33]

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm^2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

22. Stability studies: [34]

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.

CONCLUSION

Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive patches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. This article 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. It promises to eliminate needles for administration of a wide variety of drugs in the future. TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

REFERENCES:

1. Reddy YK, Reddy DM, Kumar MA. *Ind* J Res Pharm Biotech **2014**;2(2):1094-1103.
2. Shingade GM, Quazi1 A**,** Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, Gaikwad DD. Recent trend on transdermal drug delivery system. Drug Deliv & Therapeu **2012**;2(1):66-75.
3. Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. A review on transdermal patches. Pharm Res J **2010**;3(1): 139-149.
4. Bhowmik D, Chiranjib, Chandira M, Jayakar B, Sampath KP. Recent advances in transdermal drug delivery system. Int J Pharm Tech Res **2010**;2(1):68-77.
5. Kumar A, Pullankandam N, Prabhu SL, Gopal V. Transdermal drug delivery system: an overview. Int J Pharm Sci Rev Res **2010**;3(2):49-54.
6. Divya A, Rao MK, Gnanprakash K, Sowjanya A, Vidyasagar N, Gobinath M. A review on current scenario of transdermal drug delivery system. Int J Res Pharm Sci **2012**;3(4):494-502.
7. Jain NK, Controlled and novel drug delivery. 1st, CBS Publisher and Distributors, New Delhi. **2001**:100-129.
8. Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system. Plegia Res Lib **2011**;2(5):17-29.
9. Dhawan S, Aggarwal G. Development, fabrication and evaluation of transdermal drug delivery system- a review. Pharm info.net. **2009**;1(1):1-25.
10. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The Pharm Innovat **2012**;1(4):66-75.
11. Mehta R. Topical and transdermal drug delivery: what a pharmacist needs to know. InetCE. 1st, Arizona **2004**;1(1):1-10.
12. Loyd V, Allen Jr, Nicholas G, Popovich, Howard C, Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th, Wolter Kluwer Publishers, New Delhi. **2005**;298-299.
13. Jain NK. Pharmaceutical product development. 1st CBS Publisher and Distributors. New Delhi. **2002**;221-228.

14. Robinson JR, Lee VH. Controlled drug delivery fundamentals and applications. 2nd New York. **2005**;523-536.
15. Wilson R, Waugh A, Grant A. Anatomy and physiology in health and illness. 9th edition **2001**;363-366.
16. Kumar D, Sharma N, Rana AC, Agarwal G, Bhat ZA. A review: transdermal drug delivery system: a tool for novel drug delivery system. Int J Drug Dev Res **2011**; 3(3):70-84.
17. Hadgraft J, Guy R. In Transdermal Drug Delivery, Marcel Dekker, Inc., New York and Basel, Vol. 35, 296.
18. Govil SK, Tyle P, Eds. Drug Delivery: Fundamentals and Application, Marcel Dekker, Inc., New York, **1998**;385-406.
19. Misra AN, Jain NK. Controlled and Novel Drug Delivery, 1st Edition, CBS Publishers and Distributors, New Delhi, **2002**;101-107.
20. Monkhouse D.C, Huq A.S. Drug Delivery. Ind Pharm **1988**;14(2-3):183.
21. Arunachalam A, Karthikeyan M, Kumar V. Prathap M, Sethuraman S, Ashutoshkumar, S, Manidipa S. Transdermal Drug Delivery System: A Review. Curr Pharm Res **2010**;1(1):70-81.
22. Barry B. Transdermal drug delivery.Aulton M.E, Pharmaceutics: the science of dosage form design, churhcill Livingston. **2002**;499-533.
23. Barry BW. Mode of action of penetration enhancers on the kinetics of percutaneous absorption. J Contr Rel **1987**;43-51.
24. Hock S Tan, William R Pfister. Pressure sensitive adhesives for transdermal drug delivery system. **1999**;2:60-69.
25. Govil SK, Radnic EM, Sterner DG. U.S patent **1993**;5: 262,165.
26. Govil SK. In. Drug Delivery devices, P. Tyle(Ed), Marcel Dekker, NewYork. **1988**;338.
27. Wade A and wellar PJ. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical publishing Association **1994**;362-366.
28. Kandavalli S, Nair v, Panchagnula R. Polymers in Transdermal drug delivery systems. Pharm Tech **2002**;62-78. Available from: www.pharmatech.com Accessed on 15 Jan, 2008.
29. Aarti N, Louk AR, Russel O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement in vivo in humans. J contr Rel **1995**;37:299-306.
30. Lec ST, Yac SH, Kim SW, Berner B. One way membrane for Transdermal drug delivery system optimization. Int J Pharm **1991**;77:231-237.
31. Singh J, Tripathi KT and Sakia TR. Effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev Ind Pharm **1993**;19:1623-1628.
32. Vyas SP and Khar RK. Targeted and controlled Drug Delivery Novel carrier system. 1st Ed., CBS Publishers and distributors, New Delhi, **2002**;411- 447.

How to cite this article:

Swapnil More et al. RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS): AN OVERVIEW. J Pharm Res 2019;8(5):346-353. **DOI: https://doi.org/10.5281/zenodo.3236719**

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil