

REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system (TDDS) specialist are ongoing to explore for new method that can efficiently and painlessly transmit better molecules in therapeutic quantity to overcome the Difficulties allied with oral route, namely poor bioavailability due to first pass metabolism and receptiveness to produce rapid blood level. Transdermal drug delivery get improved the therapeutic effectiveness and security of drugs by more site specific way but spatial and temporal placement within body is necessary to reduce both the size and number of doses essential to achieve the objective of systemic medication through topical application to the intact skin surface. Transdermal patches deliver the drugs for systemic effects at a predetermined and controlled rate. Through a diffusion process, the drug enter the bloodstream directly though the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood, the drug will keep diffusing into the blood for a long period of time, maintain the constant concentration of drug in the blood flow. TDDS is act as micro emulsion, Transdermal patches, Niosomes, Ethosome and liposomal drug delivery system is act as Novel approach of carrier mediated drug delivery system. The success of all the TDDS depends on the skill of the drug to permeate skin in sufficient quantities to achieve its desired therapeutic effect. This review article provides a detailed study of transdermal that is benefit, disadvantages, mechanism, factors affecting skin permeation and types. Characterization of transdermal patch is use to check its quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity & cutaneous toxicological studies.

KEYWORDS: TDDS, first pass metabolism, Niosomes, Ethosome, bioavailability.

INTRODUCTION

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks -- namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.^[1]

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. New drug delivery system are also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e. peptides, proteins) to their site of action, without incurring significant immunogenicity or biological inactivation.

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate

to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.^[2]

Advantages of transdermal drug delivery system

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

1. Avoidance of first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. Predictable and extended duration of activity.
4. Minimizing undesirable side effect.
5. Provides utilization of drug with short biological half life, narrow therapeutic window.
6. Avoiding the fluctuation in drug level.
7. Maintain plasma concentration of potent drug.
8. Termination of therapy is easy at any point of time.
9. Greater patient compliances due to elimination of multiple dosing profile.
10. Ability to deliver the drug more selectively to a specific site.
11. Provide suitability for self administration.
12. Enhance therapeutic efficacy.

Disadvantages of transdermal drug delivery system

1. The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
2. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.^[3]

Skin As A Site For Drug Infusion^[5,6,7,8]

The skin is the largest organ of the body. The skin an average adult body is about 20 square feet and it received about one third of total available blood. The skin is multilayered organ composed of three histological tissue.

The outermost layer of skin, epidermis is which provides a waterproof barrier and creates our skin tone. Dermis, beneath epidermis, contains tough connective tissue, hair follicles, and sweat glands and Deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.

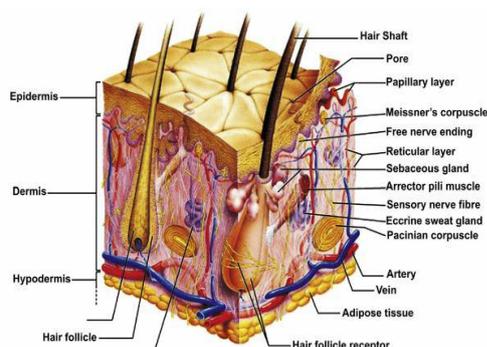


Fig 1: Anatomy of skin represents different parts.

There are main three pathways through which foreign particles diffused or penetrate in to skin^[9,10,11]

1. Transcellular/Intracellular permeation through the stratum corneum.
2. Intercellular permeation through the stratum corneum.
3. Transappendageal permeation via the hair follicles, sweat and sebaceous gland.

Mechanism of transdermal permeation^[10,11]

Transdermal permeation of a drug moiety involves the following steps:

- i. Sorption by stratum corneum.
- ii. Permeation of drug through viable epidermis.
- iii. Uptake of the drug moiety by the capillary network in the dermal papillary layer.

- iv. The drug must possess some physicochemical properties to reach target site via systemically through stratum corneum. The rate of permeation of drug moiety across the skin is governed by following equation:

$$dQ/dT = Ps(C_d - C_r)$$

Where, C_d = concentration of penetrate in the donor phase (on the surface of skin);

C_r = concentration of penetrate in the receptor phase (body); and P_s is the overall permeability coefficient of the skin which is defined as:

$$P_s = K_s D_{ss}/h_s$$

Where, K = Partition coefficient of the penetrant;

D_{ss} = Apparent diffusivity of penetrant

h_s = Thickness of skin.

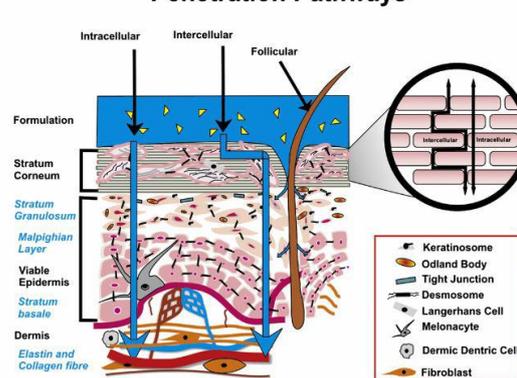
Penetration Pathways

Fig. 2: Different route of skin penetration.

A constant rate of drug permeation achieved, if $C_d > C_r$ then the equation reduced as:

$$dQ/dT = P_s \cdot C_d$$

The rate of skin permeation (dQ/dt) becomes a constant, if the C_d value remains fairly constant throughout the course of skin permeation. To maintain the C_d at a constant value, it is critical to make the drug to be released at a rate (R_r) which is always greater than the rate of skin uptake (R_a), i. e., $R_r \gg R_a$ as shown in figure.8.

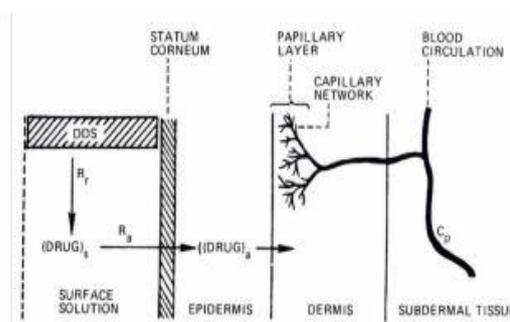


Fig. 8: Schematic representation of the relationship between the rate of drug release (R_r) from a transdermal system and the rate of release of absorption (R_a) by the skin.^[5]

By doing so, the drug concentration on the skin surface (C_d) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum (C_s), i.e., $C_d \gg C_s$; and maximum rate of skin permeation (dQ/dt)_m as expressed by equation.

$$[dQ/dT]_m = P_s C_s^e$$

Apparently, the magnitude of (dQ/dt)_m is determined by the skin permeability coefficient (P_s) of the drug and its equilibrium solubility in the stratum corneum (C_s^e).

A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. Today the most common transdermal system present in the market mainly based on semipermeable membranes which were called as patches.

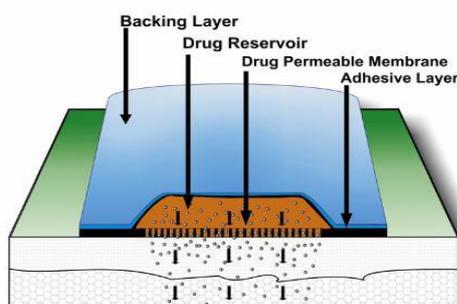


Fig. 3: Transdermal patch showing its different components.

Types Of Transdermal Patches^[12,5]

Single-layer drug-in-adhesive

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



Fig. 4: Single layer drug in adhesive patch and its different component.^[12,5]

The rate of release of drug is expressed as:

$$dQ/dT = Cr/1/P_m + 1/P_a$$

Where C_r = drug concentration in reservoir compartment;

P_a = Permeability coefficient of adhesive layer;

P_m = Permeability coefficient of rate controlling membrane.

Multi-layer drug-in-adhesive

In this system drug and excipients incorporated with adhesive but both layer of adhesive separated by single

layer membrane. The released of drug occurred through diffusion phenomenon.



Fig. 5: Multi-layer drug in adhesive patch and its different component.^[12,5]

The rate of release of drug is governed by following equation:

$$dQ/dT = K_a/r \cdot D_a/h_a \cdot C_r$$

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

Drug reservoir-in-adhesive

In the reservoir system, inclusion of liquid compartment containing drug solution/suspension between baking layer and semipermeable membrane followed by adhesive layer and release liner.



Fig. 6: Drug reservoir in adhesive patch and its different component^[12,5]

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

$$dQ/dT = K_a/r \cdot D_a/h_a(t) \cdot A(h_a)$$

Where h_a = thickness of adhesive layer; A = thickness of diffusional path.

Drug matrix-in-adhesive

This system is designed by inclusion of semisolid matrix having drug in solution or suspension form which is in direct contact with the release liner.



Fig. 7: Single layer drug in adhesive patch with its different component.^[12,5]

The rate of release of drug is governed by following equation:

$$dQ/dT = A C_p D_p^{1/2} / 2t$$

Where A = the initial drug loading dose dispersed in the polymer matrix;

C_p = solubility of the drug;

D = diffusivity of the drug in the polymer

Basic components of TDDS

- Polymer matrix/drug reservoir
- Drug
- Permeation enhancer
- Adhesive
- Backing film
- Liner
- Plasticizer

Polymer matrix/Drug Reservoir^[13,14,15]

It is the very important component in TDDS and control the release of drug from patch. The polymers used in

TDDS should be stable. They should not produce any toxic effect either alone (or) with other excipients in TDDS formulation. They shouldn't expensive one and it should be easily manufactured. They should have good stability and more compatibility with drugs and other components of System. The cross linked poly ethylene glycol, eudragit, ethyl cellulose, poly vinyl pyrrolidone and hydroxyl propyl methyl cellulose are used as matrix formers in TDDS.

The polymers like EVA, poly urethane and silicone rubber are used as rate controlling membrane.

Table 1: List of Polymers Used In TDDS.

Polymers used in TDDS		
Natural polymers	Synthetic polymer	Synthetic elastomer
Cellulose derivative	PVA	Poly butadiene
Gelatin	Poly vinyl chloride	Hydrin rubber
Shellac	Polyethylene	Poly iso butylenes
Starch	PVP	Silicon Rubber
Waxes	Poly acrylate etc	Nitrile
Gums		Acronitrile
Natural rubber		Neoprene
Chitosan etc.		Butyl rubber etc

Drug^[16,17]

The selection of drug is based on its properties like physicochemical as well as biological properties. Drug should have higher first pass metabolism. Drugs having narrow therapeutic window. Drugs with short half-life. Drugs with frequent dosing. Low molecular weight moieties (<1000 Dalton) Drugs with low dose (mg/day). Low melting point substances (<200°C) Drugs having affinity with both lipophilic and hydrophilic phases. Drugs without any dermatological effect are suitable for formulation as transdermal

Permeation Enhancers

These are the substances which reversibly change the structure of stratum corneum and increase the permeation of drug from skin to blood stream. They are two types

1) Chemical enhancers [accelerants, absorption promoters (or) permeation enhancers]^[18,19]

They act by increasing drug permeability by reversible damage to stratum corneum.

To consider the stratum corneum.

To increase partition coefficient of drug.

Table 2: List of Chemical Enhancers Used In TDDS.

Chemical Enhancers	Examples		
Solvents	Water, Methanol, Ethanol, Propylene Glycol, Di-Methyl Acetamide	Fatty Acids & Esters	Oleic Acid, Linoleic Acid, Lauric Acid, Capric Acid
Terpenes	Menthol, Cardamom Oil, Cinnamon Oil, 18-Cineol, Carvone	Surfactants	Anionic: SLS, Decyl Methyl Sulfonate Non-Ionic: Pluronic F127, Pluronic F68 Bile Salts: Sodium Taurocholate, Sodium Deoxycholate
Pyrolidone	N-Methyl 2-Pyrrolidone, Axone	Amides	Dimethyl Acetamide, Dimethyl Formamide
Sulfoxides	DMS, Didecyl Sulfoxides	Miscellaneous	Phosphor Lipids, Amino Acid Derivatives, Enzymes, Urea

2) Physical Enhancers^[18]

The following physical techniques have been used for enhancing the permeability of drug through skin.

- Ionotophoresis
- Electrophoresis
- Sonophoresis
- By using micro needles
- Magnetophoresis
- By using laser radiation

The combination of chemical enhancer and the magnetophoresis having greater enhancing power which is recently detected in lidocaine hydrochloride patch.

Adhesive^[20]

It is used to affix the patch on the skin. It should be adhere on the skin with light pressure applied by finger. It should be easily removed from the skin surface without leaving any residue. It should not produce any irritation. It should have excellent contact with the skin. Should compatible with other components in formulation. It should be allow permeating the drug freely from the patch.

E.g. polyacrylates, poly iso butylenes, silicone derivatives.

Backing Laminate^[21,22]

It is used to protect the patch from outer environment. They must be chemically resistant. They won't allow to permeation of components in the patches. They have optimal elasticity, flexibility and tensile strength. It should have low water vapour transition rate. If a drug incorporated into a liquid (or) gel in the formulation, the backing material should be heat stable to allow fluid tight packing of drug reservoir (form-fill seal process). E.g. vinyl, poly ethylene and poly ester film

Liner^[22]

It is used to protect the patch during the storage. It is removed during application of patch on skin. It should be chemically inert. It consists of two layers, one is base layer and other is release coating layer. The base layer may be occlusive (E.g. poly ethylene, poly vinyl chloride).

The release coat layer made up of silicon (or) Teflon. The polyester foil and metallized laminate are also used as release liner.

Plasticizer^[23]

They are used to provide plasticity to transdermal patch. This also chemically inert and compatible will all other ingredients in the formulation.

E.g. PEG, PG, tri-ethyl citrate, di-butyl phthalate.

Some of the plasticizer also act as a permeation enhancer
E.g. propylene glycol.

Table 3: Ideal properties of drugs for TDDS.^[23-25]

Parameters	Properties
Dose	Should be low (low than 20 mg/day)
Half-life	10 or less (h)
Molecular weight	<400 Da
Partition	Log P (octanol-water) between 1.0 and
Coefficient	4.0
Skin permeability	>0.5 x 10 ⁻³ cm/h
Coefficient	
Liophilicity	10 < Ko/w < 1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<2000C
pH	Between 5.0 and -9.0

Various methods for preparation TDDS

a. Asymmetric TPX membrane method

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. [(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent 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].^[27]

b. Circular teflon mould method

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate 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 leveled 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 24 hrs 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.^[28]

c. Mercury substrate method

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10- 15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.^[29]

d. By using "IPM membranes" method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.^[30]

e. By using "EVAC membranes" method

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.^[31]

f. Aluminium backed adhesive film method

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custommade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.^[32]

g. Preparation of TDDS by using Proliposomes

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

desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.^[33,34]

h. By using free film method

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.^[35]

Evaluation

1) Physical Appearance^[39]

All the formulated patches were visually inspected for colour, clarity, opaque, transparency, flexibility & smoothness.

2) Interaction Studies^[39,40]

Not only in TDDS almost all the dosage forms contain the excipients. These excipients must be compatible with the drug to avoid a loss of stability and reduce in bioavailability. The interaction studies are commonly carried out in thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical properties of drug excipients.

3) Thickness of Patch^[41]

The thickness of patch is measured in a different points of the formulated patches by different points of formulated patches by using digital micrometer/micrometer screw gauge/ travelling microscope/vernier callipers. Determine the average thickness and standard deviation for the same ensure the thickness of the formulated patch.

4) Weight Uniformity^[41]

Before done the weight uniformity test the formulated patches were dried at 60°C for 4 hours. A specified area of the patch is to be cut in different parts of patch and it is weighed in digital balance. The average weight and standard deviation values are to be calculated from individual weights.

5) Folding Endurance^[41]

A specific area of the patch is cut evenly and folds it repeatedly at the same place till it broke. The number of folding is noted before the breaking of patch. It will give the folding endurance.

6) Percentage Moisture Loss^[41]

The formulated patches are weighed individually and kept in a desiccators containing anhydrous calcium chloride at room temperature for 24 hours. After the 24 hours the patches are weighed at a specific time interval until the constant weight is obtained. The percentage moisture loss is calculated by using following formulae:

Percentage moisture loss = (Initial wt - final wt)/initial wt) X 100

7) Percentage Moisture Uptake^[41]

Formulated patches are weighed individually and kept in a desiccators containing saturated potassium chloride or ammonium chloride. The RH is maintained as 84%. After 24 hours the patches are reweighed at a specific time intervals till the constant weight is attained.

Percentage moisture uptake = (final wt - initial wt)/initial wt) X 100

8) Water Vapour Permeability Evaluation (WVP)^[42]

It is determined by natural air circulation over. It can be determined by following formulae;

WVP=W/A

WVP is expressed in g/m² per 24 hours.

Where, W = amount of vapour permeated through the patch (gm/24 hour)

A = surface area of the exposure samples (m²)

9) Drug Content Analysis^[42]

An accurately weighed portion of formulated patches is dissolved in a suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 hours by using shaker incubator. Then the solution is sonicated and it is filtered. Then the filtrate is analysed by using suitable techniques such as UV (or) HPLC etc., with proper dilution.

10) Uniformity Of Dosage Unit^[43]

An accurately weighed portion of formulated patches are cut in small pieces which are transferred in to a specific volume in volumetric flask. Dissolve it in a suitable solvent and sonicate for complete extraction of drug from patch and volume make up with solvent. The solution is allowed to settle down for an hour and the supernatant liquid was collected and performs a proper dilution to give desired concentration. It is filtered using 0.2 µm membrane filter and analysed by using suitable analytical techniques like UV, HPLC etc.

11) Percentage Elongation Break Test^[45]

It is determined by calculating the length of the patch just before the break point.

Percentage elongation = (Final length-initial length)/initial lengthx100

12) Flatness^[44]

A transdermal patch should possess a smooth surface which not constrict with time. It can be studied by flatness test. In this test, one strip is cut from centre and two strips are cut from right and left sides. The length of each strip is measured. The variation in length is measured by percentage constriction. If the percentage constriction is 0%, it indicates 100% flatness.

% construction = (initial length -final length)/initial length x100

13) Thumb Tack Test^[43]

It is one of the qualitative test applied for the determination of tack property of adhesives. Simply the thumb is pressed over the adhesive layer and the relative tack property is determined.

14) Rolling Ball Tack Test^[46]

In this evaluation, the distance that stainless steel ball travels along an upward facing adhesive is measured. If the further travelling of ball, it indicates the adhesive is less tacky.

15) Quick Stick (Or) Peel Tack Test^[46]

It is used for the measurement of the peel force required to break the bond between the adhesive and the substrate by pulling the tape (adhesive layer) away from substrate (stainless steel plate) at the speed of 12 inch/minute.

16) Probe Tack Test^[46]

The measurement of the force which is required to pull the probe away from the adhesive lower at fixed rate. It is expressed in grams.

17) Polariscope Examination^[43]

The specific surface area of pieces from the patch is cutted and placed on the objective slide to observe the drugs crystals. It is used to find out the drug whether in crystal form (or) amorphous form in the patch.

18) Shear Adhesion Test^[43]

It is used to measure the cohesive strength of the adhesive polymer. Adhesive film is placed over a stainless steel and a specified amount is hung from the tape to affect it pulling in direction parallel to the plate. Shear adhesion strength is measured by calculating the it takes to pull the tape of the plate. If the longer time take for removed, the shear strength is greater.

19) Peel Adhesion Properties^[43]

The peel adhesion is known the force required to remove the adhesive film from the substrate. The force required to pull a single coated tape is measured in this test. The coat is must applied to a substrate at 180⁰C.

20) In-vitro Drug Release Studies^[39]

The paddle over disc method (USP apparatus-V) can be utilised for the assessment of the drug release from the prepared patches. The dry film is cutted with specific

size and the shape and it is weighed accurately. Then the piece of cutted patch is affixed in a glass plate by using adhesive. Then the plates are immersed in a 500ml of dissolution medium placed in the cylindrical vessel. The temperature is maintained at $30^{\circ} + 5^{\circ}$ C and the paddle was set at a distance of 2.5cm from the glass plate at the bottom. RPM is fixed as 50. The samples are withdrawn at appropriate time intervals up to 24 hours, fresh medium is replaced during each sampling. Then the samples are analysed by UV (or) HPLC to detect the drug release.

21) In-Vitro Drug Permeation Studies^[39]

It is done by using Franz diffusion cell. Abdominal skin with full thickness of male wistar rats (200-250 gm weight) is act as a semi permeable membrane. The membrane (abdominal skin) was isolated from rat abdomen and it is cleared properly, the tissues and the blood vessels present over the skin also removed. Then the skin is equilibrated in medium for 1 hour before starting the experiments and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of diffustant. The temperature of the cell was maintained at $32^{\circ} + 5^{\circ}$ C using thermostatically controlled heater. The isolated rate spin is mounted between the donor receptor compartments of the cell, with the epidermis facing upward in to the compartment. The specified volume is taken out from the receptor compartment and it is repeated with fresh medium. Then the samples are filtered and analysed by UV (or) HPLC.

22) Skin Irritation Test^[43]

Skin permeation and sensitization testing is performed by using healthy rabbits. The formulated patches are applied on the dorsal surface of the skin rabbits. Before affixing the patch the hair is removed from the skin of the rabbits. After 24 hours the skin is to be observed.

23) Stability Studies^[39]

It is carried out according to ICH guidelines. The formulated transdermal patches are stored at $40^{\circ} + 0.5^{\circ}$ C and 75 + 5% RH for six months. The samples were withdrawn at 0,30, 60, 90 and 180 days and it analyse suitably for drug content.

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