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AN OVERVIEW OF TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. An advantage of a transdermal drug delivery route over other types of delivery systems such as oral, topical, intravenous, intramuscular, etc. is that the patch may essentially can provide a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Basic components of TDDS include polymer matrix, membrane, drug, penetration enhancers, pressure sensitive adhesives, backing laminates, release liner, etc. Transdermal patches can be divided into various systems like reservoirsystem, matrix system and micro-reservoir system, which are used to incorporate the active ingredients into the circulatory system via the skin.

KEYWORDS: TDDS, Basic components, types of transdermal patches.

INTRODUCTION

TDDS is an integral part of noval drug delivery system. Since the beginning of life on the earth human applied a lot of substances to their skin as cosmetics and therapeutic agents. The trans dermal drug delivery route has become one of the most successful and innovative drug delivery systems.

Drugs with very short half-life, narrow therapeutic window, and poor bioavailability-transdermal drug system are convenient. Skin serves as site of drug application for local as

well as systemic effects. There are wide varieties of drugs for which topical or transdermal is viable options.

Transdermal drug delivery systems (TDDS), also known as "patches", are dosage forms designed to deliver a therapeutically effective amount of drug across a patient'sskin .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 overinjectables and oral routes by increasing patientcompliance and avoiding first-pass metabolism, respectively.

DEFINITION

Transdermal drug delivery system is defined as topically administered dosage form in the form of patches which deliver drugs for systemic effects at a predetermined and controlled rate.

Advantages

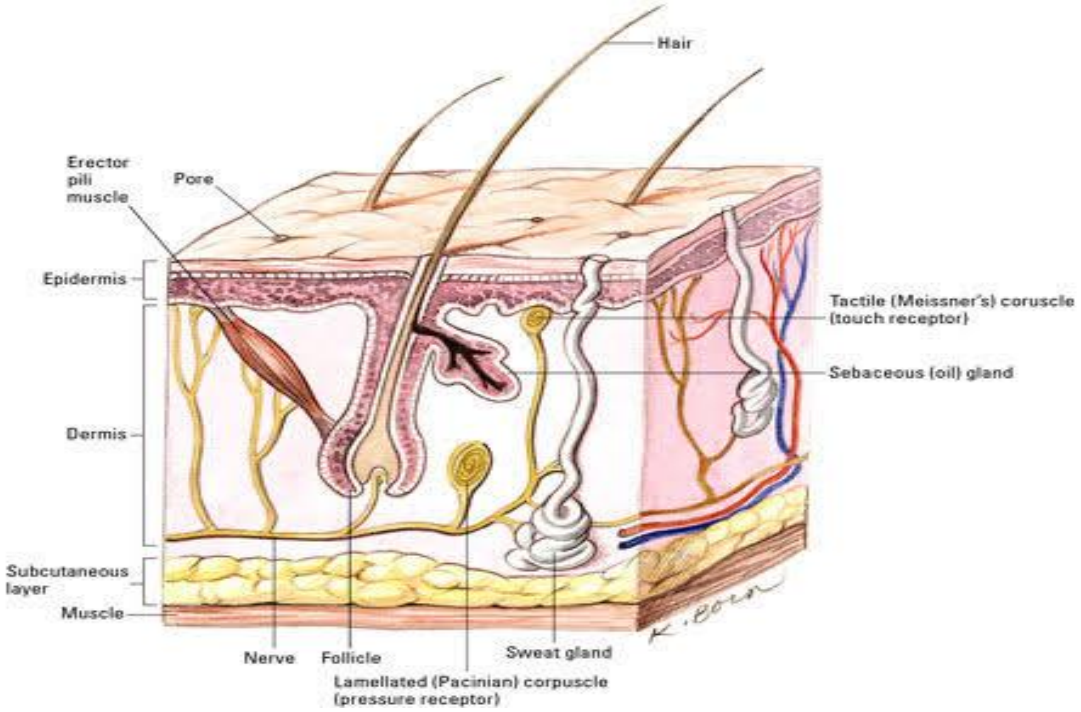
- Self-administration is possible and continuous, sustained release of drug.
- Dose delivery unaffected by vomiting or diarrhoea.
- Drug administration stops with patch removal.
- Prolonged duration of action.
- Avoidance of first pass metabolism
- Minimizing undesirable side effect
- Maintain plasma concentration of potent drug.
- Termination of therapy is easy at any point of time.
- Greater patient compliances due to elimination of multiple dosing profile

Disadvantages

- Not suitable for high drug doses.
- Adhesion may vary with patch type and environmentalConditions.
- Skin irritation and hypersensitivity reactions may occur.
- Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.

ANATOMY OF SKIN

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. Skin consists of two main parts, the superficial, thinner portion, which is composed, of epithelial tissue is the epidermis and dipper thicker layer Dermis.



Epidermis

It results from an active epithelial basal cell population and is approximately 150 micrometer thick. It is the outermost layer of skin and process of differentiation results in migration of cells from basal layer towards the skin surface. The end result of this process is the formation of a thin, stratified and extremely resilient layer(the stratum corneum) at the skin surface.

Stratum Corneum: This is the outermost layer of skin, also called horny layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral

lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.

Viable epidermis: This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms.

Dermis: electron microscopic examination shows that the dermis is made up of a network of robust collagen fibers of fairly uniform thickness with regularly spaced cross striations. It is about 3 to 5 mm and contains the blood vessels, lymph vessels, and nerves. It also provide oxygen and nutrients to the skin while removing toxins and waste products.

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 mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

EVALUATION PARAMETERS

1. Interaction studies

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characterssuch as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.,

2. Thickness of the patch

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

3. Weight uniformity

The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4. Folding endurance

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

5. Percentage Moisture content

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

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

6. Percentage Moisture uptake

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

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

7. Water vapour permeability (WVP) evaluation

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

WVP=W/A Where, WVP is expressed in gm/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 m2.

8. Drug content

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

9. Uniformity of dosage unit test

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2□m membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated

10. Polariscope examination

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

11. Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

12. Peel Adhesion test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a

stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured.

13. Thumb tack test

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

14. Flatness test

Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

15. Percentage Elongation break test

The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

$$\text{Elongation percentage at break} = 100(L1-L2)/L2$$

Where, L1is the final length of each strip and L2 is the initial length of each strip.

16. Rolling ball tack test

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

17. Quick Stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required 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

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

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

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 donorcompartment. 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

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) 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

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.

The components of transdermal devices include

1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Other excipients

1. Polymer Matrix

The Polymer controls the release of the drug from the device.

Possible useful polymers for transdermal devices are:

a) Natural Polymers

e.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers

e.g. Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c) Synthetic Polymers

e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

2. Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 daltons.

2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.

3. The drug should have low melting point.

Along with these propertiesthe drug should be potent, having short half life and be non irritating.

3. Permeation Enhancers

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

These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, N- methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

b) Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethylsulphoxide etc.

Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.

Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Biary system: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways.e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

c) miscellaneous chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents.

Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß- cyclodextrin and soyabean casein.[8]

4. Other Excipients

a) Adhesives

The fastening of all transdermal devices to the skin has so far been done by usinga pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria

(i) Should adhere to the skin aggressively, should be easily removed.

(ii) Should not leave an unwashable residue on the skin.

(iii) Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria.

(i) Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.

(ii) Permeation of drug should not be affected.

(iii) The delivery of simple or blended permeation enhancers should not be affected.

b) Backing membrane

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminiumfoil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc)

Desirable features for transdermal patches

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is (typically) zero orde

FACTORS AFFECTING DRUG PENETRATION

Two types of factors affect the drug penetration such as biological and physiochemical factors these factors are listed below

- Biological factors
- Skin age
- Skin condition
- Species difference
- Blood supply
- Skin metabolism
- Regional skin site.
- Physiochemical factors
- Temperature and pH
- Skin hydration
- Diffusion coefficient
- Drug content
- Molecular size and shape
- Partition Coefficient

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