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FORMULATION AND EVALUATION ASPECTS OF TRANSDERMAL DRUG DELIVERY SYSTEM

1.Tandale Adesh Manmohan, 2. Dr.L.D.Hingane

1. Student, 2. Professor

1. Dr.Babasaheb Ambedkar Marathwada University, Aurangabad

Aditya Pharmacy College,Beed-431122

2.Dr.Babasaheb Ambedkar Marathwada University, Aurangabad

Aditya Pharmacy College, Beed-431122

ABSTRACT

The conventional oral dosage forms has significant drawbacks of poor bioavailability due to hepatic first pass metabolism and 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. To improve such characters transdermal drug delivery system (TDDS) was emerged which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body thereby reducing both the size and number of doses. TDDS is such a mode of delivery which has been explored extensively over the last 25 years, with therapeutic success. TDDS is ideally suited for diseases that demand chronic treatment. Topical administration of drugs offers many advantages over conventional oral dosage form. Important advantages of TDDS are limitation of hepatic metabolism, enhancement of therapeuticefficiency and maintenance of steady plasma level of the drug.

Keywords: Transdermal drug delivery system (TDDS), Bioavailability, Hepatic first pass metabolism, therapeutic efficacy.

INTRODUCTION

Transdermal therapeutic system are defined as self contained, discrete dosage form which when applied to intact skin deliver the drug through the intact skin at a control rate to the systemic circulation and maintain the

drug concentration within the therapeutic window for prolonged period of time. Recently, the use of transdermal patches for pharmaceuticals is limited because only a few drugs has proven to be effectively delivered through skin. In order to achieve the objective of systemic medication through topical application to the intact skin surface. They wereexemplifies first with the development of a Scopolamine-releasing TDD system (Transderm- Scop) for 72 hrs for prophylaxis or treatment of Motion-induced nausea, then by the successful marketing of nitroglycrine-releasing TDD system (Deponit, Nitrodisc, nitro-dur,transderm- nitro).

Transdermal patch uses a special membrane to control the release rate at which the liquid drug contained patch reservoir can pass through the skin and itno the blood stream. Transdermal delivery not only provide controlled,constant administration of the drug, but also allows continuous input of drugs with short biological half lives, and eliminates pulsed delivery into systemic circulation which is responsible for undesirable side effects.

ADVANTAGES

- Transdermal medication delivers a steady infusion of the drug over prolonged period of time therefore avoiding adverse side effects and therapeutic failure frequently associated with intermittent dosing can also be avoided.
- Alternative route of administration for the patients who cannot tolerate oral dosage forms such as vomiting patient.
- Increases therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption and drug interaction with food,drink and other administered drugs.
- Avoidance of first pass metabolism because it bypasses the liver.
- Simplified regimen leads to improved patient compliance and reduced inter and intra-patientvariability.
- Self administration is possible and they are non invasive, avoiding the inconvenience ofparenteral therapy.
- Drug input can be terminated at any point of time by removing the transdermal patch.
- They are easily and rapidly identified in emergencies (for example,unresponsive,unconscios orcomatose patient) because of their physical presence, features and identifying markings.

At the same time transdermal drug delivery has Few disadvantages that are limiting the usetransdermal delivery.

DISADVANTAGES

- Only relatively potent drugs are suitable candidates for transdermal delivery because of thenatural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application from one or more of thesystem

components, necessitating discontinuation.

• The delivery system cannot be used for drugs requiring high blood levels.

• The use of transdermal delivery may be uneconomical.

Marketed Products of Transdermal Patches

Brand Name	Drug	Manufacturer	Indications
Nicotinell®	Nicotine	Novartis	Pharmacological smoking cessation
NuPatch 100	Diclofenac diethylamine	Zydus Cadila	Anti Inflammatory
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in males
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Catapres TTS®	Clonidine	Alza	Hypertension
Oxytrol®	oxybutynin	Watson Pharma	Overactive bladder

For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

Anatomy and physiology of skin

Skin is one of the most extensive organ of the body covering an area of about 2msq on in an average human adult. This multi-layered organ receives approximately one third of all blood circulating through the body. With thickness of only a millimeter, the skin separates the underlying blood circulation network from outside environment.

Human skin comprises of three distinct but mutually dependent tissues:

A) The stratified, vascular, cellular epidermis,
B) Underlying dermis of connective tissues and
C) Hypodermis.

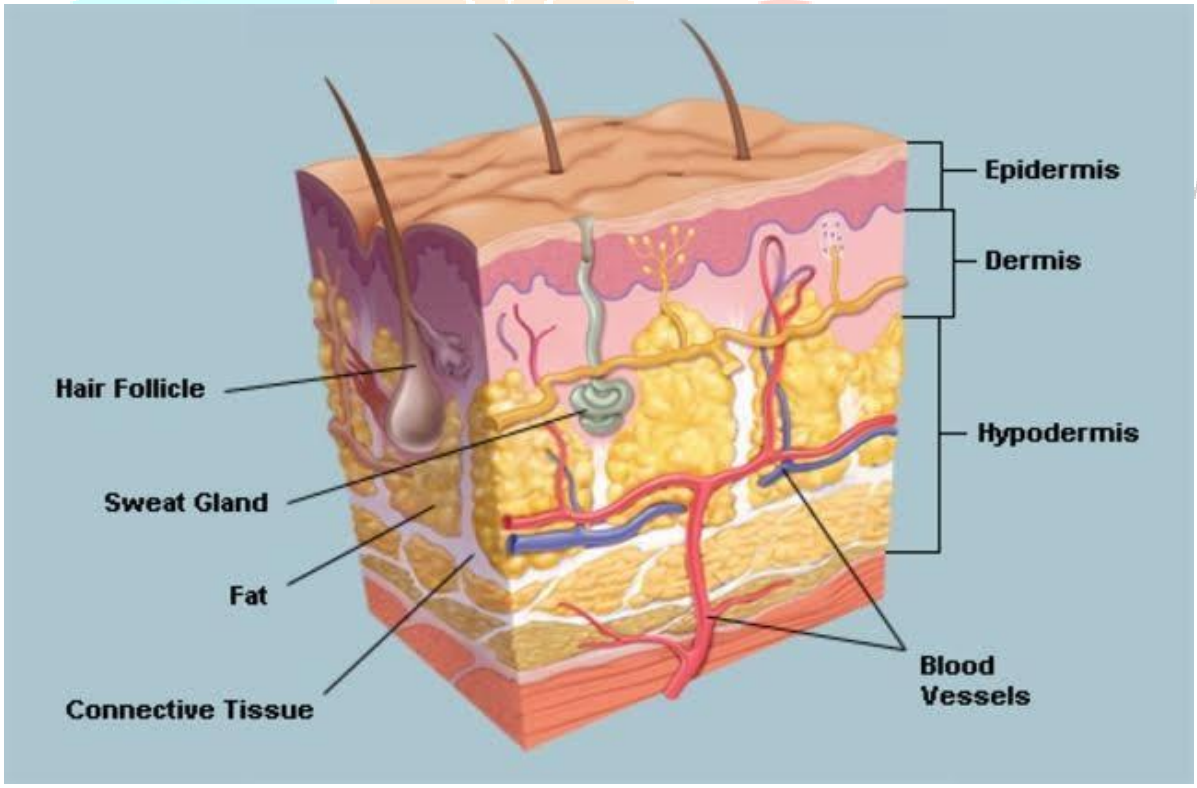


Figure: Structure of skin Epidermis

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, 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 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.

Route of Permeation of skin.

The diffusant (drug) has two potential entry routes to the blood vasculature; through theepidermis itself or diffusion through shunt pathway, mainly hair follicles with their associated sebaceous glands and the sweat ducts. Therefore, there are

Two major routes of penetration.

Transcorneal penetration

Intra cellular pepenetrations

Drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. as stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

Intercellular penetration.

Non-polar substances follow the route of intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments.

Transappendegeal penetration

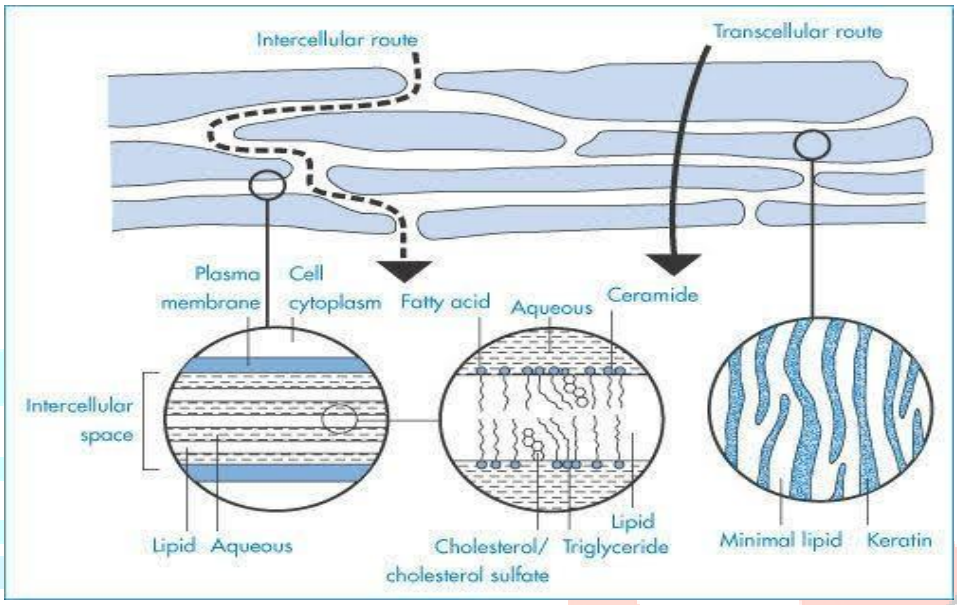
This is also called as the shunt pathway. In this route, the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands. The Transappendegeal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). however this route may be of some importance for large polar compounds. The route through which permeation occurs is largely

Dependent on physico-chemical characteristics of penetrant, most importantantly being the relative ability to partition into each skin phase.the transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through Viable epidermis.
3. Finally through the papillary dermis into the Microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step. The

stratum corneum acts like a passive diffusion medium. So for transdermal drug diffusion, the various skin tissue layers can be represented by a simple multilayer model as shown in fig.



Kinetics of transdermal permeation

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic system. Transdermal permeation involves following steps:

- Sorption by stratum corneum,
- Penetration of drug through viable epidermis,
- Uptake of the drug by capillary network in dermal papillary layer.

This permeation is possible only if drug posses certain physicochemical properties. The rate of permeation across the skin(dQ/dt) is given by

dQ/dt = P(Cd – Cr)

Where Cd and Cr are the concentrations of the skin penetrant in the donor compartment(e.g, on the surface of stratum corneum) and in the receptor compartment(e.g, body) respectively Ps Is the overall permeability coefficient of the skin tissue to the penetrant and is given by

$$P_s = \frac{K_s}{h_s} \times D_{ss}$$

Where Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule form a transdermal therapeutic system on to the stratum corneum, Dss is the apparent diffusivity for the steady state diffusion of the molecule through a thickness hs of the skin tissue. As the ks, Dss, hs are constant under given condition, the permeability coefficient(ps) for a skin penetrant can be considered to be a constant.

Now it is clear that a constant rate of drug permeation can be obtained only when Cd>>Cr i.e, the drug concentration at the stratum corneum(Cd) is consistently greater than the concentration in the body(Cr) , then equation one becomes

The rate of skin permeation(dQ/dt) 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) that is either constant or greater than the rate of skin uptake(Ra) i.e., Rr>> Ra

Since ., Rr is greater than Ra, the drug Concentrations on the skin surface(Cd) is maintained at a level equal to or greater than the equilibrium (or saturation) solubility of the drug in Stratum corneum(Cs) i.e., Cd>>Cs .therefore maximum rate of skin permeation[(dQ/dt)m] is Given by equation:

$$(dO/dt) = P_s \times C_s$$

From the above equation, it can be seen that the maximum rate of skin permeation depends on the skin permeability coefficient(Ps) and its equilibrium solubility in the stratum corneum(Cs). Thus skin permeation appears to be stratum corneum limited.

2. FORMULATION ASPECTS OF TDDS

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 solvents

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. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc. The polymers like polyethylene glycol, eudragits, ethyl cellulose,polyvinylpyrrolidone and hydroxypropyl methylcellulose are used as matrix type TDDS. The polymers like EVA , silicon rubber and polyurethane 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 .

- Extensive first pass metabolism.
- Narrow therapeutic window.
- Short half-life which causes non-compliance due To frequent dosing.
- Dose should be less (mg/day) .
- Low molecular weight (less than 500 Daltons).

- Adequate solubility in oil and water (log P in the Range of 1-3).
- Low melting point (less than 200°).

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 toAttain higher therapeutic levels of the drug 26. They alter the protein and lipid packaging of stratum corneum, thus Chemically modifying the barrier functions leading to increasedpermeability .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, d-Limonene, Linoleic acid.

$Formula: \quad l = D \times \frac{dc}{dx}$

Where D is the diffusion coefficient

c is the concentration of the diffusing moleculex is is the spatial coordinate

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 beRemovable from the smooth surface without leaving a residue .

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 desiredpharmacological effect without losing their adhesive properties and skin tolerability. PSAs used in commercially available Transdermal systems Include polyacrylate, polyisobutylene, and polysiloxane. 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, 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 allowfluid-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.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 Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the applications of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a Part of dosage form fordelivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding Chemical inertness and permeationto 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.

7. Other excipients

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

Methods of Preparation of TDpatc

- Polymer membrane permeation-controlled TDDS

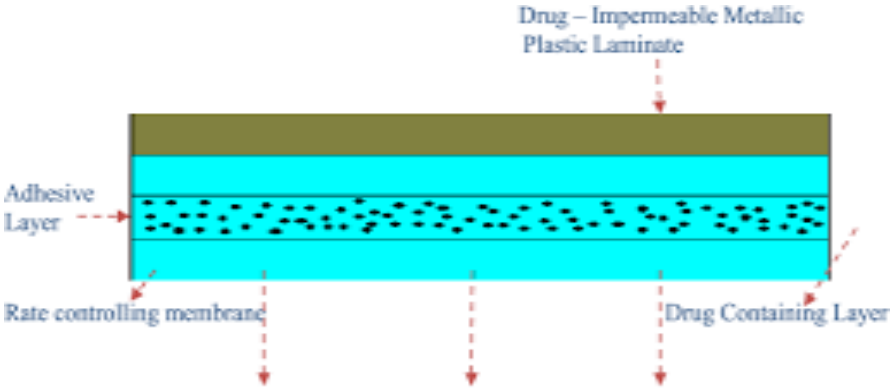
is system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, 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 . 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 controllingmembrane.

Fig – polymer membrane permeation controlled system

Transderm Scop (Scopolamine) for 3 days protection of motion sickness and Transderm Nitro (Nitroglycerine) for Once a day medication of angina pectoris.

- **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 a 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 a adhesive diffusion controlling drug delivery system .Deponit (Nitroglycerine) for once a day medication of angina pectoris.



- **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 .lnstead of applying the adhesive On the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim . Nitro Dur (Nitroglycerine) used for once a day medication of angina pectoris

- **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 solutionof 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 cross-linking the polymer in situ. A Transdermal system therapeutic system thus formed as a medicated disc positioned at the center and surrounded by an adhesive rim.

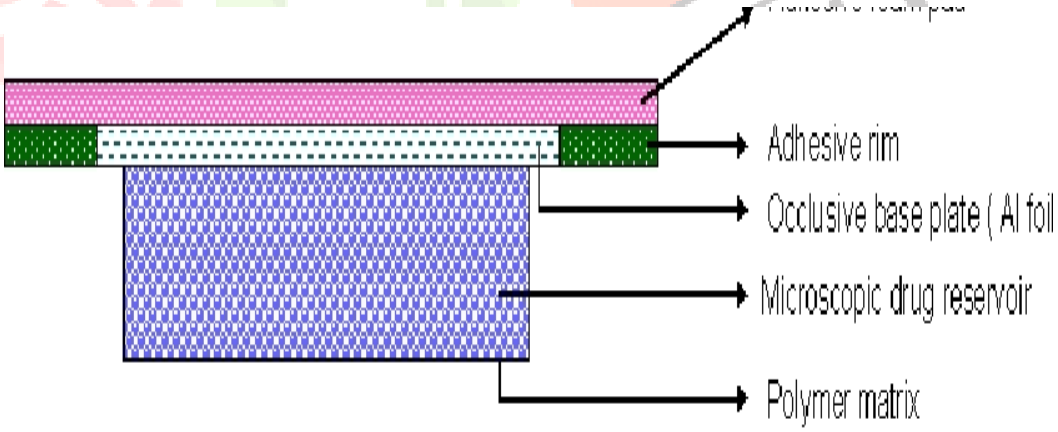


FIGURE 6: MICRORESERVOIR SYSTEM

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

3. EVALUATION ME

The evaluation methods for transdermal dosage form can be classified into followingtypes:

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

1. Physicochemical Evaluation

- Interaction studies

The drug and the excipients must be compatible with one another to produce aproduct 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 development. Interaction studies are taken out by Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical properties like assay, melting point, Waves numbers, absorption maxima .

1. **Thickness of the patch**

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

2. **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 .

3. **Folding endurance**

A specific area of strip is cut and repeatedly folded at the same place till it broke. Thenumber of times the film could be folded without breaking gave the value of Folding endurance.

4. **Percentage moisture content**

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

5. **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.

6. **Water vapour permeability (WVP) evaluation**

Water vapour permeability can be determined by a natural air circulation oven. The WVP can be determined By the following formula .

WVP=W/A

Where, WVP is expressed in gm/m2 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 m2.

7. **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.

8. **Content uniformity test**

10 patches are selected and content is determined for individual patches. If 9 out of 10patches have content Between 85% to 115% of the specified value and one hascontent not less than 75% to 125% of the specified value, Then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test .

9. **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 asCrystalline form or amorphous form in the patch .

10. **Shear Adhesion test**

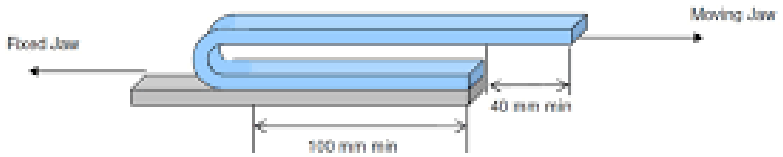
This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel 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 .

11. **Adhesive studied Peel Adhesion test:**

In this test, the force required to remove an adhesive coating form a test substrateis 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 .

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 polymeras well as on the use of tackifying resins in Polymer .



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

12. 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 .

$$\% \, constriction = \frac{I_1 - I_2}{I_1} \times 100$$

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

13. 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.

$$Elongation\, percentages = \frac{L_1 - L_2}{L_2} \times 100$$

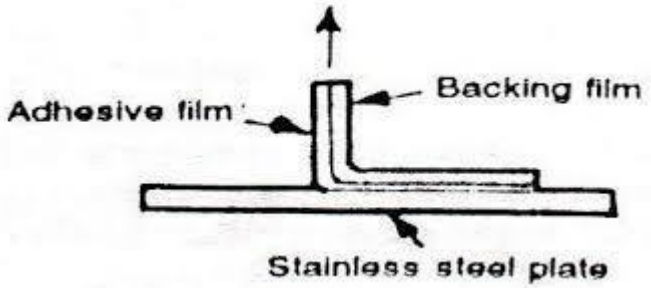
Where, L_1= is the final length of each strip. L_2= is the initial length of each strip.

14. 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). Thedistance the ball travels along the adhesive provides the measurement of tack, Which is expressed in inch .

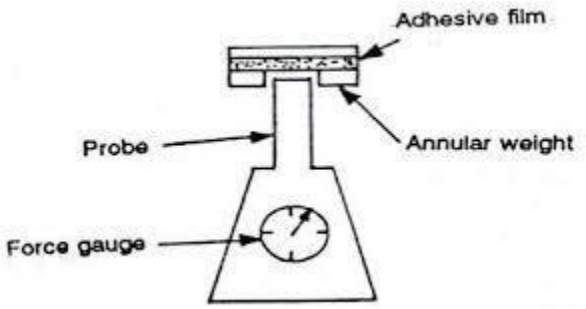
15. Quick stick (peel-tack) test

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 and recorded as tack value, which is expressed in ounces or grams per inch width .



16. 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 .



17. Shear strength properties or creep resistance

Shear strength is the measurement of the cohesiveuStrength of an adhesive polymer i.e., device should not ship on application determined by measuring the time it takesto pull an adhesive coated tape off a stainless plate. Minghetti et al., (2003) performedthe test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.

18. 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.

2. In vitro Evaluation of TDDS

In vitro drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by U spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be Calculated.

In vitro skin permeation studies

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wister rats weighing 200 to 250 gm. Hair from the abdominal region isto 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 thediffusant. 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 ofDrug permeated (mg cm2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm2).

3. In vivo Evaluation

3.1 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 . Human volunteers.

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 evaluatingtransdermal drug delivery system are mouse, hairless rat, hairless dog, hairlessrhesus 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.

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.

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 cm2) 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. he patch is to be removed after 24hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury .

CONCLUSION

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 provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems as a ready reference for the research scientists who are involved in TDDS. The foregoing shows that 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, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

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