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Research Article

Transdermal Drug Delivery System

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ABSTRACT

Conventional dosage forms which require multidose therapy have many problems and complications. Design of a conventional dosage forms should be such that it delivers right amount of drug in right manner to the target site. The encouragement in development of novel drug delivery system is apart from therapeutic efficacy is its cause. Redesigning the unit and means is a difficult task and profitable task so a controlled released drug delivery system, a novel drug delivery system evolves which facilitates the release of drug at predetermined rate. Controlled drug delivery can be achieved by transdermal drug delivery system which can deliver the drug through skin to the systemic circulation at a predetermine rate over a prolonged period of time.

Keywords: Transdermal, drug delivery.

INTRODUCTION

Transdermal drug delivery has gained lot of interest over last decade as it offers many advantages over conventional and oral dosage forms. For transdermal products the goal is to maximize the flux of drug through the skin in to the systemic circulation and minimize its retention and metabolism in skin. Conventional dosage forms usually requires multi dose therapy which results in fluctuations in peak plasma concentration so increasing in oral dose to get effective plasma concentration may result in over dosing so close monitoring is required. Continues intravenous infusion is recognized as a superior mean of drug administration as its delivers drug for a prolong period of time but it has certain risks and need hospitalization of patient. The benefits of intravenous infusion can be duplicated without harmful effects using skin as port of drug administration by means of transdermal drug delivery system. This is known as transdermal administration and drug delivery system are known as transdermal therapeutic system or transdermal patches. Development of scopolamine releasing TDDS (transderm) for 72 hours for prophylaxis or treatment of motion induced nausea, then by successful marketing of nitroglycerine-releasing TDDS (Deponit, nitrodisc, nitro-dur,transderm-nitro) transderm-Scop was approved by FDA in 1979 for preventing nausea and vomiting during travel particularly by sea.

Definition[1,2,6,8,9,11,18,20]

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.

Advantages[11-14,16,20]

Transdermal medication provides safe, convenient and pain-free self administration for patients. Transdermal delivery may be useful in those patients who are polymedicated. Transdermal drug delivery provide a constant rate of release of medicine to maintain concentration level of drug for a longer period of time as to avoid peak and drop associated with oral dosing and parenteral administration. Transdermal patches improved therapeutic effects of various drugs by avoiding specific problems associated with drugs such as presystemic metabolism, formation of toxic metabolites, low absorption, gastro intestinal irritation etc. Useful in drugs possesses short half-life as to avoid frequent dosing administration.

Disadvantages[4,7,11-14,16]

The drug moiety must possess some physicochemical properties for penetration through skin and if dose of drug is large i.e. more than 10- 25mg/day transdermal delivery is very difficult. Daily dose of drug preffered less than 5mg/day. Local irritation at the site of administration such as itching, erythema and local edema may be caused by drug or the excipients used in the formulations. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product. Some patients develop contact dermatitis at the site of application due to components. The barrier function of the skin changes from one site to another, from person to person and with age.

Skin[3,8,9,12-14,16]

Anatomy and physiology of skin

Skin is one of the most extensive organ of the body covering an area of about 2 m or 20 square feet on in an average human adult. This multilayerd 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

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outside environment. Human skin comprises of three clear but mutually dependent tissues: The stratified, vascular, cellular epidermis, Underlying dermis of connective tissues and Hypodermis

Route of permeation of skin[21,22]

There are two major routes of penetration.

Transcorneal penetration

Intra cellular penetration[22]

Intercellular penetration[22]

Transappendegeal penetration

Mechanism of transdermal permeation[17,20]

Transdermal permeation of a drug moiety involves the following steps: Sorption by stratum corneum. Permeation of drug through viable epidermis. Uptake of the drug moiety by the capillary network in the dermal papillary layer. 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(Cd –Cr)` Where, Cd= concentration of penetrate in the donor phase (on the surface of skin); Cr= concentration of penetrate in the receptor phase(body); and Psis the overall permeability-coefficient of the skin which is defined as Ps=KsDss/hs Where, K = Partition coefficient of the penetrant; Dss= Apparent diffusivity of penetrant; hs= Thickness of skin.

Mechanism of action of transdermal patch

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

I. Iontophoresis:

II. Electroporation

III. Application by ultrasound

IV. Use of microscopic projection

Types of transdermal patches[12,15]

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: dQ/dT=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

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: dQ/dT=[(Ka/r.Da)/ha]Cr, Where Ka/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, assimilation of liquid compartment containing drug solution /suspension between backing layer and semipermeable membrane followed by adhesive layer and release liner. The rate of drug release from this drug reservoir system is given by dQ/dT=[(Ka/r.Da)/ha(t)]A(ha), Where ha = thickness of adhesive layer; A = thickness of diffusional path.

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 goverened by following equation: $dQ/dT=AC_PD_P^{1/2}/2t$, 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.

Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available in the market.

Basic component of transdermal system[5,8,10-12,16,19,20]

Polymer Matrix or matrices

Polymers are the foundation of transdermal system. The selection of polymer and design are of prime importance. Considerations for polymer selection in transdermal delivery system: Should be stable and non-reactive with the drug moiety. Easily available, fabricated and manufactured in to desired formulations. The properties of polymer e.g. molecular weight glass transtition temp. melting point and chemical functionality etc. should be such that drug can easily diffuse through it and with other components of system. Mechanical properties should not change if large amount of drug incorporate. Should provide consistent release of drug throughout the life of system.

Drug

For successfully developement of a TDDS, the drug should be chosen with great care. Transdermal patches offer many advantages to drugs that undergo extensive first-pass metabolism, drugs with narrow therapeutic window or drugs with a short half-life, which cause noncompliance due to frequent dosing. There are some examples of drugs that are suitable for TDDS, like Nicardipine hydrochloride, Captopril, Atenolol, Metoprolol tartarate, Clonidine, Indapamide, Propranolol hydrochloride, Carvedilol, Verapamil hydrochloride and Niterdipine, etc.

Release liners

The patch is covered by protective liner during storage until it is used. The release liner is removed and discarded just before the application of patch over the skin since release liner is in intimate contact with the transdermal system hence it should be physically as well as chemically inert. The 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 as release liner in transdermal patches include polyester foil and metalized laminate.

Backing laminate

While designing the backing layer following points must be in consideration: Must be flexible. Having low water vapour transmission rate so as to promote skin hydration

and thus greater skin permeability of drug. Should be compatible with transdermal system as in use while applying. Should be chemical resistant. Having good tensile strength. Non irritant. Examples of backing laminate are polyethylene film, polyester film, and polyolefin film, and aluminum vapour coated layer.

Penetration enhancers

Compounds which promote the penetration of topically applied drugs are commonly referred as absorption promoters, accelerants, or penetration enhancers. Penetration enhancers are incorporated into a formulation to increase the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin. Thus allow the drug to penetrate to the viable tissues and enter the systemic circulation.

Permeation enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Permeation enhancers are hypothesized to affect one or more of these layers of skin to achieve penetration enhancement of drugs. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability. These may be conveniently classified under the following main headings.

Solvents
Surfactants
Bile salts
Binary systems
Miscellaneous chemicals

PSAs (pressure sensitive adhesives)

PSAs are the material that adhere to a substrate, here skin, by application of light force and leave no residue when removed. They form interatomic and intermolecular attractive forces at the interface, provided that the intimate contact is formed. To obtain this degree of contact, the material must be able to deform under slight pressure, giving rise to the term "pressure sensitive." A PSA wets the surface and spreads onto the skin when its surface energy is less than that of the skin. After the initial adhesion, the PSA/skin bond can be built by stronger interactions (e.g., hydrogen bonding), which will depend on skin characteristics and other parameters. Widely used PSA polymers in TDDS are polyisobutylene-based adhesives, acrylics and silicone-based PSAs, hydrocarbon resin, etc

Adhesive layer

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. Adhesion is understood to be the net effect of three phenomenon's namely; Peel:The resistance against the breakage of the adhesive bond; Track:The ability of a polymer to adhere to a substrate in this case skin with little contact Pressure and; Creep: The viscous relaxation of the adhesive bond upon shear.

Other excipients

Plasticizers.
Solvents.

Approaches in the development of transdermal therapeutic system[5,10-14,16]

Recent technology used in transdermal drug delivery system

I. Iontophoresis.
II. Electroporation.
III.Microneedle-based Devices.
IV.Abrasion
V.Needle-less Injection
VI.Laser Radiation
VII.Microporation
VIII.Needleless injection

Evaluation of transdermal system[8,10-16,20]

Interaction studies

The drug and polymer compatibility was characterized by means of FTIR spectroscopy. The compatibility was checked by making physical mixture of drug and polymer (1:1) and then the FTIR analysis of the mixture was done. The peaks should not be changed in FTIR spectra of mixtures, and it should be similar to the pure drug and polymer FTIR spectra. Evaluation is of three types: Physicochemical evaluation, Invitro studies and Invivo studies.

Physical or physicochemical evaluation of transdermal system

Film thickness

This is measured by using micro meter, electronic vernier callipers, with a least count of 0.01mm, dial gauge, or screw gauge. Thickness is measured at five different points on the film and average of five readings is taken.

Percentage flatness

strips are selected as the average per cent of length calculated from the 7 cm strips. Zero percent constriction is equivalent to 100 percent flatness. % Constriction =(initial length-final length)/initial length *100

Folding endurance

It is determined by repeatedly folding a small strip of film (2 x 2 cm) at the same place till it breaks.The number of time the film could be folded at the same place without breaking is the folding endurance value.

Tensile strength

It is determined by using a modified pulley system. The force required to break the film is considered as tensile strength and it is measured as kg/cm^2.

Patch thickness

It is measured by using digital micrometer screw gauge at three different points and calculation of mean value is done.

Elongation break test

It is determined by noting the length just before the break point. The elongation break can be calculated by the formula: Elongation break =(final length-initial length)/initial length

Weight uniformity

weight uniformity is studied by randomly selecting patches 10 in number. A specified area of patch is to be cut in different parts of the patch and weighed in a digital balance. Calculate average weight and standard deviation value from the individual weights. It is performed for each formulation.

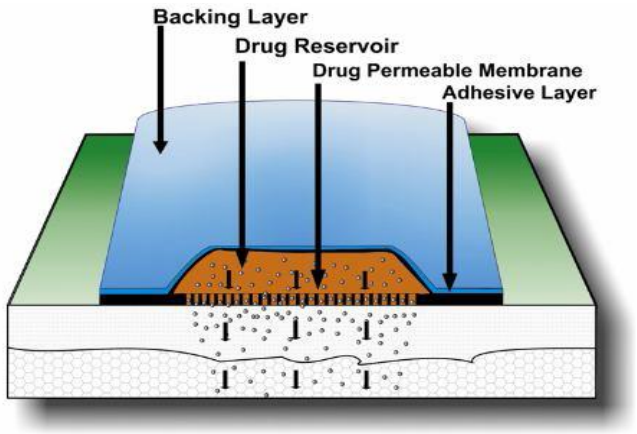

Figure 1: Structure of skin.

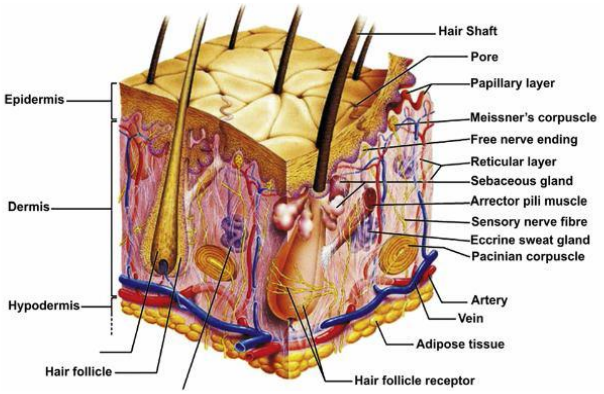

Figure 2: Structure of Skin.

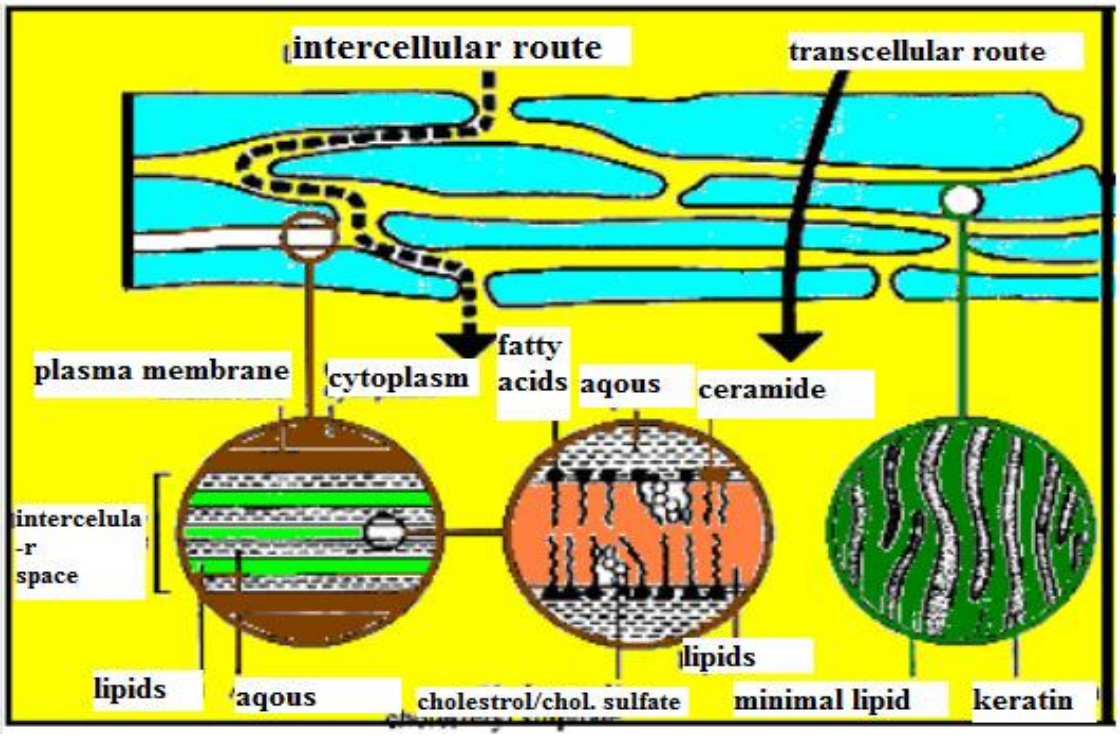

Figure 3: Different route of skin penetration.

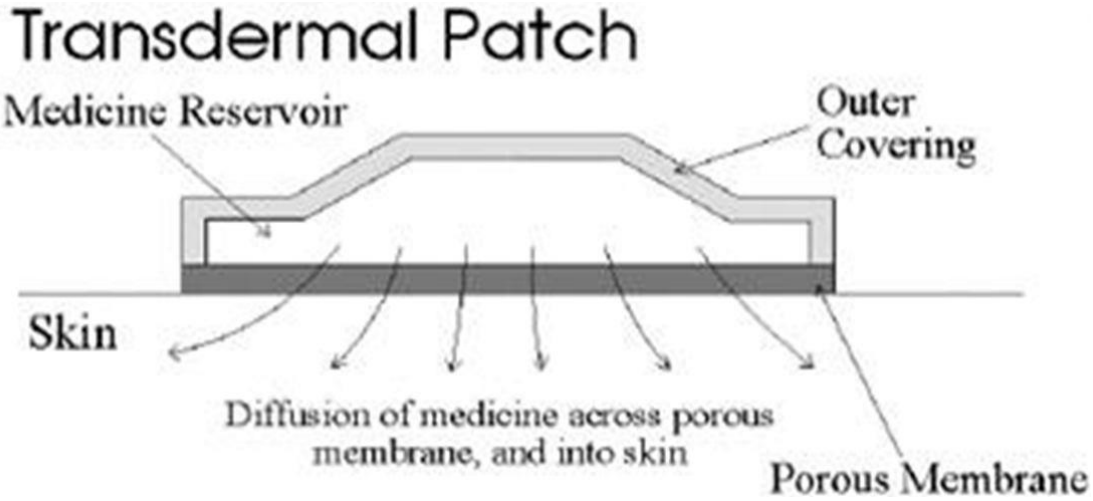

Figure 4: Transdermal patch.

Table 1: Polymer useful for transdermal patches.

Polymer	Category	Role
Gelatin	Natural polymer	Base, adhesive
Na-alginate		Base, adhesive
Gum Arabic		Base with adhesive
Gum tragacanth		Adhesive
Natural rubber		Base with adhesive
Carmellose	Semi synthetic polymer	Base, adhesive
Methyl and ethyl cellulose		Base, adhesive
Hydroxyl propyl cellulose		Base, adhesive
Styrene-butadiene rubber	Synthetic elastomers	Base with adhesive
Silicone rubber		Base with adhesive
Polyvinyl alcohol	Synthetic polymer	Base, adhesive
polyethylene		Linear, backing
polypropylene		Membrane, linear
polystyrene		Co-adhesive
Polyhydroxyethyl methacrylate (PHMA)		Linear, backing
Polyvinyl chloride (PVC)		Base, adhesive
Ethylene vinyl acetate		Membrane

Drug content

A film of required area (1 x1 cm / 2 x 2 cm etc.) is cut, place small piece of film in to 100 ml buffer (pH 7.4 or 6.8 or as prescribed) and shake continuously for 24 hours. Then the whole solution is ultrasonicated for 15 minute. And filteration is done, then the drug is estimated spectrophotometrically and the drug content is determined.

Percentage of moisture content

Individually films are weighed and left in a dessicator containing anhydrous calcium chloride or activated silica at room temperature for 24 hours. They are weighed individually until they show constant weight. Calculation of % of moisture content is done as the difference between initial and final weight by the final weight. % moisture Content=[initial weight-final weight]/final weight *100

Percentage of moisture uptake

A weighed film is a kept in dessicator at room temperature for 24 hours and taken out and 84% relative humidity (a saturated solution of potassium chloride) in a dessicator and the films are exposed to it until a constant weight is obtained. The percentage of moisture uptake is calculated as the difference between the final and initial weight by initial weight. % moisture uptake=[final weight-initial weight]/initial weight *100

Water vapour transmission rate

Glass vials approx. 5 ml capacity of equal diameter are taken for transmission study. All vials are washed thoroughly and dried in an oven completely. Weigh about 1 gm of anhydrous/ fused calcium chloride and kept in all the taken vials. Films are fixed on the brim of vials and weighed individually then keep in closed dessicator containing saturated solution of potassium chloride to maintain humidity approx. 84%. The vials were weighed at 6, 12, 24, 36, 48 and 72 hours respectively. WVP is calculated in gm/m2 per 24hrs Transmission rate=[(final weight-initial weght)/area*time]*100

Content uniformity test

Select 10 patches but content is determined for individual patches. If 9 out of 10 showed content between 85-115%

Table 2: 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 Coefficient	Log P (octanol-water) between 1.0 and 4.0
Skin permeability Coefficient	>0.5 x 10^{-3} cm/h
Liophilicity	10 < Ko/w < 1000
Oral bioavailability	Low
Therapeutic index	Low
Melting point	<200^{0}C
pH	Between 5.0 and -9.0

having specified valueand no one has shown 75-125% of the specified value,it means the test has been passed. If 3 patches show the content between 75-125% then take 20 additional patches and further test performed. If these 20 patches show content between 85- 115 %of specified value, then the patches pass the test.

Uniformity of dosage unit test

Accurate weighed patch is cut into small pieces and transferred to volumetric flash having specific volume of suitable solvent for dissolution of drug and then sonicate for a limited period of time to completely extract the drug from pieces and then mark the volume with the same solvent. The solution obtained is kept untouched for 1 hour to settle down then supernatant is diluted as per the requirement. Now the diluted solution was filtered with the help of membrane having pore size 0.2µm and analyzed with suitable analytical (HPLC / UV) technique and the drug content was calculated.

Polariscope examination

Polariscope is the instrument used to study the crystal structure of drug in a patch. Cut the specific area of patch

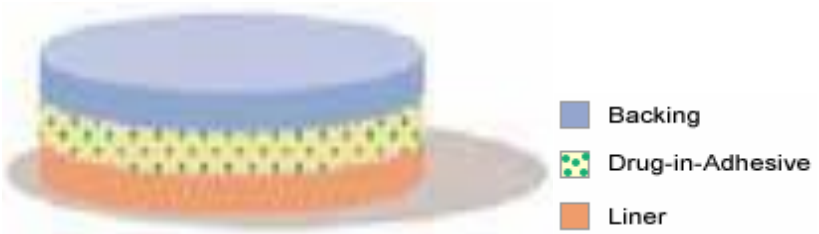

Figure 5: Single layer drug in adhesive patch and its different Component.

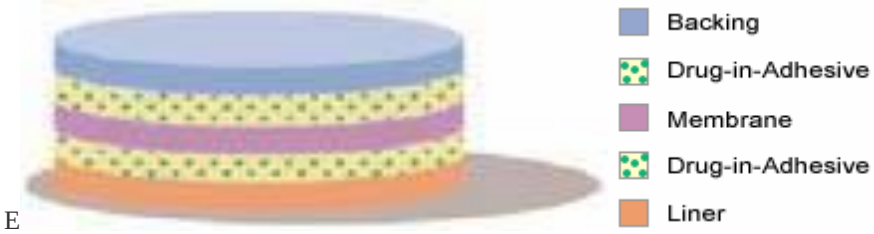

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Figure 6: Multilayer drug in adhesive patch and its different Component.

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Figure 7: Drug reservoir in adhesive patch and its different Component.

Figure 8: Single layer drug in adhesive patch with its different Component.

and now keep on the slide to observe whether the drug is in crystalline form or amorphous form.

Adhesive studies

Shear adhesion test

This test is used to determine the cohesive strength of an adhesive polymer. The strength value is affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers used. An adhesive coated patch is stacked between the plate made of stainless steel and specified weight hung from the patch parallel to this plat. The time taken to pull off this patch is the cohesive strength. Greater the strength more is the shear strength

Peel adhesion test

The measurement of patch strength between an adhesive and a substrate is defined as adhesion. The force required for removing adhesive coating from the steel used as test substrate. The type and amount of polymer, the molecular weight and the composition of polymers determine the adhesive properties. The single patch is pasted to test substrate (Steel) and it pulled from the substrate at 180^{o} angle. Failure of adhesive is indicated with no residue on substrate.

Tack properties

Tack is the ability of polymer to adhere to a substrate with little contact pressure. Application with little finger pressure is important in transdermal systems. Tack is dependent on molecular weight as well as composition of polymer and tackifying resins used in the polymer.

Tests for tack include

Thumb tack test

Rolling ball tack test

Peel tack or quick stick test

Probe tack test

Skin irritancy studies

The skin irritancy can be performed on healthy rabbits / mice albino / rats and potential of transdermal system can be evaluated by modified Draize test. Clean and remove the hair from the dorsal surface of test animal and clean surface then apply rectified spirit. Apply the transdermal formulation over the clean surface for 24 hour.Now remove the formulation and observe the status of skin.The

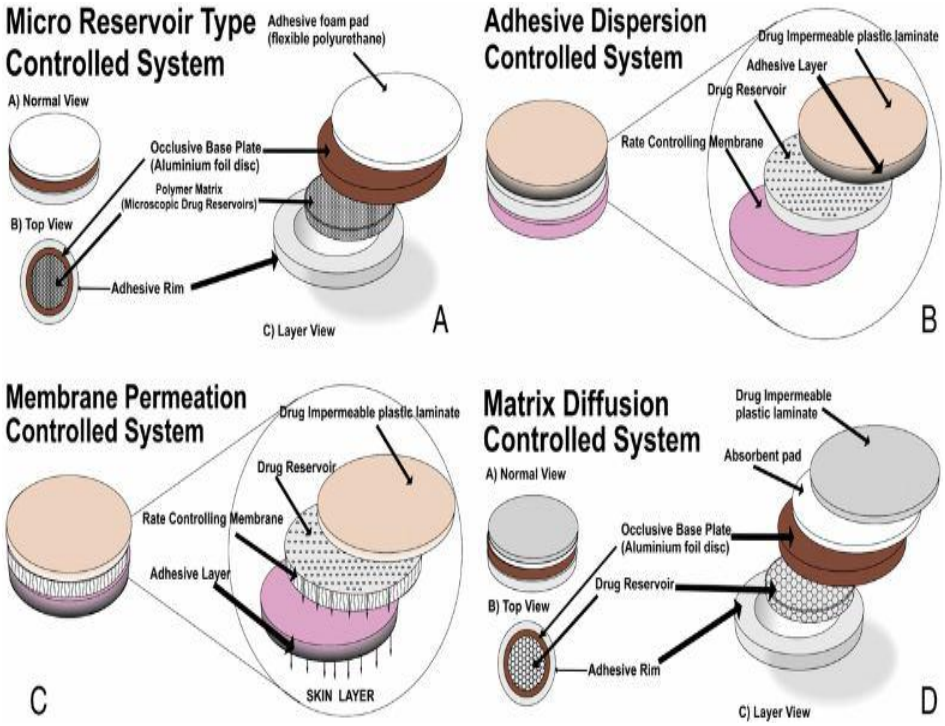

Figure 9: (A): Showing the presence of microscopic spheres of drug reservoir, (B) Development of adhesive dispersion controlled therapeutic system (C) Diagrammatic representation of membrane permeation controlled system, (D): Representation of matrix type transdermal system[5].

score are given from 0 to 4 depending the degree of erythema as follows : zero point given for no erythema , 1 point for slight erythema-(barely perceptible-light pink), 2 point for moderate erythema(dark pink),3 points for moderate to severe erythema(dark pink) and 4 points for severe erythema (extreme redness).

Confocal laser scanning microscopy (clsm)

Penetration of drug from the patch can be assessed using CLSM.Non-occulsive application of transdermal formulation for 8 hours to the dorsal skin. Sacrifice the mice by heart puncture, dorsal skin is excised and washed with distill water. Place the excised skin on aluminium foil and the dermal side of the skin is generally teased off any adhering fat and/ or subcutaneous tissue. Now cut in to pieces of $1mm^2$ and tested for probe penetration. The full skin thickness is optically scanned at different increments through the z-axis of a CLS microscope.

Stability studies

The stability of active component is a major criterion in determining acceptance or rejection of transdermal system. The stability studies were performed as according to ICH guidelines at different temperature and relative humidity 25-30^{0}c (60% relative humidity) and 45- 50^{0}c (75% relative humidity) over a period of 60 days. Withdraw the samples at 0,3,6, and 9 weeks respectively and were analyazed for their physical appearance, drug content and in-vitro diffusion studies.

Invitro evaluation

in-vitro release studies

The best available tool today which can at least quantitatively assure about the biological availability of a drug from its formulation is its in vitro dissolution test.this can be performed by the following: Paddle over disc apparatus (USP apparatus 5). Cylindrical apparatus (USP apparatus 6). Reciprocating disc.

In-vitro skin permeation and release kinetics studies

The design and development of transdermal patch is greatly influenced by in vitro studies. In-vitro studies greatly help in investigating the route of skin permeation and the rate of transfer through skin by which drug entered in to systemic circulation. These studies can easily performed and methodology used allowed flexibility in adapting the model in addressing different aspects involved in preliminary or feasibility studies in the development of transdermal patch.

Franz Diffusion Cell

The in-vitro skin permeation of transdermal patches can be studied using Franz diffusion cell (most commonly used) with an effective permeation area of $1.0cm^2$ and receptor cell volume of 10 ml. The temperature is maintained at 32^{0}C +-0^{0}c. The lower is receptor compartment filled with 10 ml PBS and is constantly stirred in a magnetic stirrer at 100rpm. The skin is mounted on a receptor compartment with the stratum corneum side facing upward in to the upper donor compartment. Samples are withdrawn through the sampling port of the diffusion cell at predetermined time interval over 24 hours and are analysed. The receptor phase is immediately filled with equal volume of fresh diffusion buffer.

Horizontal-type skin permeation system

Flow Diffusion Cell.

In-Vivo Studies

These studies are the true depiction of formulation performance. The variables which were not considered during in-vitro study taken in to account. In-vivo studies of

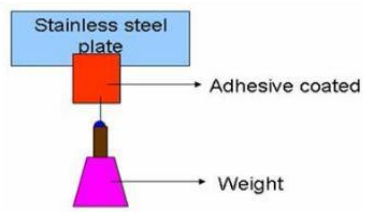

Figure 10: Shear strength test.

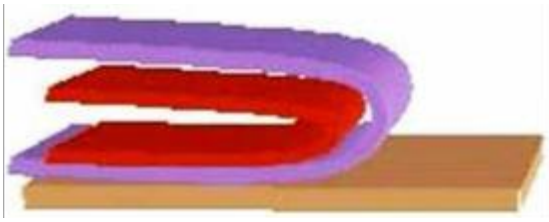

Figure 11: Peel adhesion test.

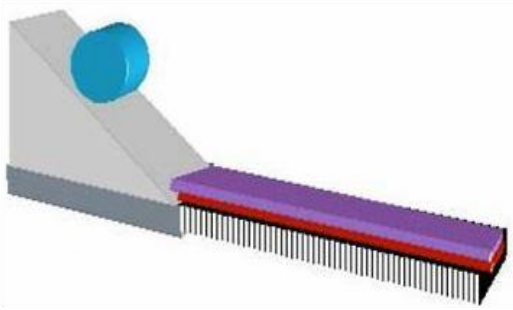

Figure 12: Rolling Ball Tack Test.

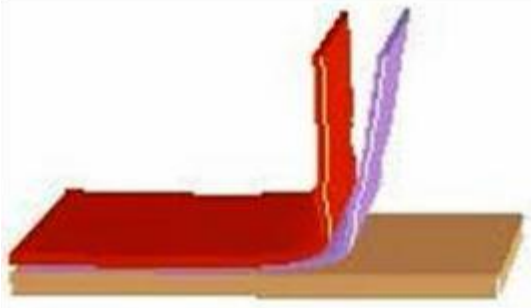

Figure13: Peel tack test.

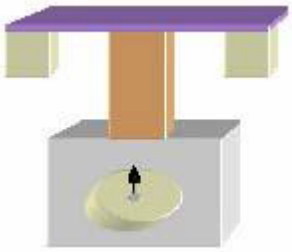

Figure 14: Probe tack test.

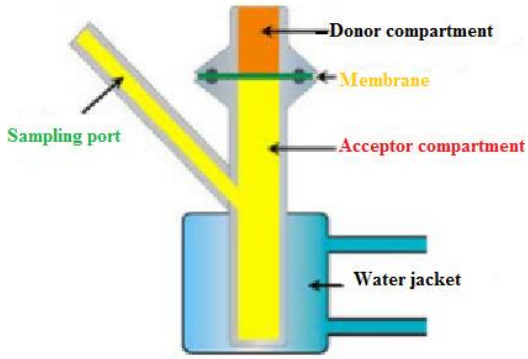

Figure15: Franz diffusion cell.

transdermal system can be done by using following model:
Animal Models,
Human volunteers, Biophysical Model.

CONCLUSION

The transdermal drug delivery system has gain importance in recent year as the transdermal route is an extremely attractive option for the drug with appropriate Pharmacology and physical chemistry. The transdermal drug delivery has capable advantage of avoiding hepatic first pass metabolism, improve to bioavailability, decrees gastro intestinal irritation due to local contact with gastric mucosa, maintaining constant blood level for a longer period of time resulting in decrees of dosing frequency and improved patient compliance. In recent years it has proved that benefits of intravenous drug infusion can be closely duplicated without harmful effects by using skin as part of drug administration to provide continuous transdermal drug infusion through intact skin

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