TRANSDERMAL DRUG DELIVERY SYSTEM: A PUBLIC REVIEW

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ABSTRACT: Today about 74% of drug are taken orally and are found not be as effective as desired. to improve such character's transdermal drug delivery system was emerged. TDDS are topically applied ''patches'' designed to deliver a therapeuticall effective amount of drug across a patient's skin at controlled by the skin or membrane in the delivery system The main goal of TDDS is to deliver drug into systemic circulation through skin at predetermined rate with minimal inter &interpatient variation The human skin is a reality accessible surface for drug delivery . skin of an average adult body covers a surface of approximately 2m2 and receives about one – third of the blood circulation through the body over the past decodes developing controlled drug delivery has become increasingly important in the pharmaceutical industry The human skin surface is known to containing on an average 10-70 hair follicles & 200 – 250 sweat ducts on every square cm of the skin area. its interesting benefit such as less absorption more uniform plasma level improved bioavailability decrease side effect efficacy & quality of the product . The advantage of transdermal drug delivery system that is painless technique of administration of drugs . His article provides an overview of types of TDDS methods of preparation & its physicochemical of evaluation.

Keywords: Systemic blood circulation, First pass metabolism, Skin permeation, Transdermal drugdelivery system.

INTRODUCTION:

Transdermal drug delivery systems (TDDS) are the topically applied "patches" designed to deliver a therapeutically effective dose of a drug across the patient's skin at a controlled rate for the systemic effect (Mishra, 1997; Patel et al., 2011). With the introduction of the first transdermal patch of scopolamine in 1979, the transdermal drug delivery has made an important contribution to the medical practice in the past three decades but is yet to be recognized as a major alternative to the oral delivery and hypodermic injections (Langer, 2004; Prausnitz et al., 2008). The major obstacle for the topical drug delivery is the low diffusion rate of drugs across the relatively impermeable, outermost skin layer, the stratum corneum (Bouwstra et al., 2002). Besides, the intercellular lipid region, the major pathway for lipophilic drugs, has a diffusion path length of about 500mm which is much longer than the thickness of stratum corneum (20 mm) (Gaur et al., 2009; Phillips et al., 1995).

ADVANTAGES:

a) Can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.
b) Can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhoea.
c) To avoid the first pass effect e.g., Transdermal Nitro-glycerine. It is rapidly metabolized by the liner when taken orally.
d)Non-invasive, avoiding the inconvenience of parenteral therapy.
e) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine 7 day.
f) The activity of drugs having a start half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
g) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

DISADVANTAGES:

a) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
b) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's permeability.
c) Some drugs e.g., scopolamine transdermal patch placed behind the ear, it is uncomfortable.
d) Long time adhere is difficult.

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-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].

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-butyl phthalate 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 levelled 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.

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 levelled mercury surface, covered with inverted funnel to control solvent evaporation.

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.

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.

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 custom-made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

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 overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

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 is 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.

APPLICATION OF TRANSDERMAL THERAPY:
Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitro-glycerine for angina, clonidine for hypertension, scopolamine for motion sickness, and oestradiol for oestrogen deficiency, all through patches.

At that time, biotech Medicinals was still being developed. During the past decade biotech products have come into their own, buttransdermal have essentially remained static. The number and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used . One reason forthis undoubtedly is the fact that only certain specialized firms can manufacture transdermal patches. Companies prefer to have full control of their projects, and to enjoythe higher profits on products developed and manufactured in house. Another reason is that only a limited numberof drugs fit the molecular weight, lipophilicity, andpotency requirements for transdermal absorption.

PRINCIPLES OF TRANSDERMAL PERMEATION:

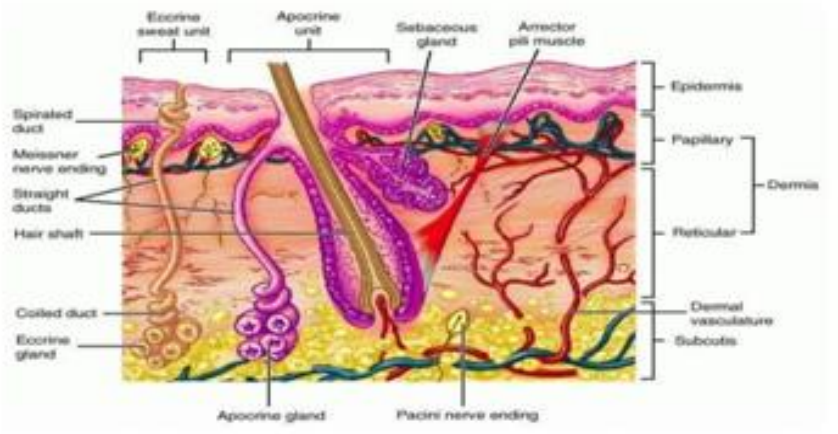


Figure 1: Anatomy of Skin

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimetre of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows.

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ.

MECHANISM OF TRANSDERMAL PERMEATION:

Transdermal permeation of a drug delivery system based onthe

1. Permeation of drug by feasible epidermis
2. Sorption through stratum corneum
3. Take up of the drug moiety through the capillarysystem in the dermal papillary layer The rate of transdermal drug permeation, dQ/dt, through several layers of skin tissues which can be expressed as

$$dQ/dt = Ps(Cd - Cr) \quad \ldots\ldots (1)$$

Where,

The vapours patches release essential oils anddQ/dt = Rate of skin permeation

Cd and Cr = the concentrations of skin penetrate inthe donor phase (stratum corneum) and the receptor phase (systemic circulation)

Ps = overall permeability coefficient of the skin

Ps is defined as by L john

$$PS = KSDSS/HS \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where,

Ks = Partition coefficient of the penetrant

Dss = Apparent diffusivity of penetrant

Hs = Thickness of skin

At constant rate of drug permeation is achieved when Cd>Cr Then equation (1) becomes

$$dQ/dt = PS.CD \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

(dQ/dt) becomes as constant when Cd value remains genuinely constant done the span of skin permeation. To retain the Cd at a constant value, it is simple to e the drug to be released at a rate (Rr)h is regularly more prominent than the rate of skin take-up (Ra) therefore Rr>>Ra.

Thusly, the drug concentration on the skin surface (Cd) is kept up at a level which is constantly more prominent than the equilibrium (or saturation) solubility of the drug in the stratum corneum (CeS), i.e., Cd>>Ce S; and a most extreme rate of skin permeation (dQ/dt)m, as written by equation.(dQ/dt)m = PSCe S

Where,
(dQ/dt)m=Magnitude of Rate of skin permeation
PS = the skin permeability coefficient of drug
CeS- equilibrium solubility in the stratum corneum

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

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

patches.

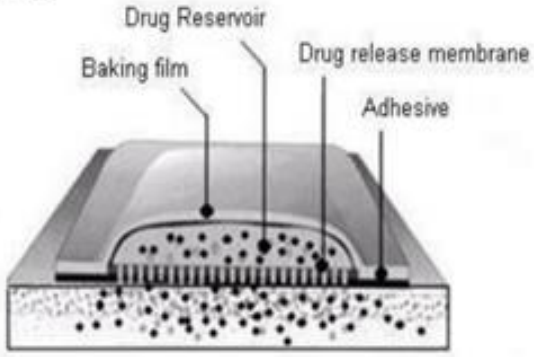
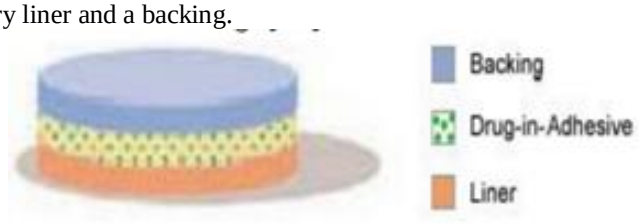


Fig. 2: Different parts of transdermal patch

TYPES OF TRANSDERMAL PATCHES:

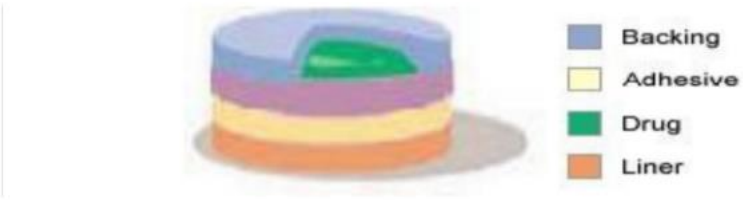
Single-layer Drug-in-Adhesive:
The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere thebvarious layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.



Multi-layer Drug-in-Adhesive:
The multi-layer drugin adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-inadhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

Reservoir:
Unlike the Single-layer and Multi-layer Drug-inadhesive systems the reservoir transdermalsystem has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system, the rate of release is zero order.

Matrix:
The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. [33]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 on the market.



CONCLUSION:
This article providesa valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. 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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