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AN OVERVIEW ON TRANSDERMAL PATCHES

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ABSTRACT

Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The administration of drugs by transdermal route offers the advantage of being relatively painless. The appeal of using the skin as a portal of drug entry lies in case of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. The main objective of transdermal patches system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation.

Key words: Transdermal drug delivery, Transdermal patches, Controlled release.

INTRODUCTION

Oral route is the popular route of drug delivery. Although it has some disadvantages including first pass metabolism, drug degradation in gastrointestinal tract due to enzymes, PH etc. To cross these problems, a novel drug delivery system was developed. In this transdermal delivery system medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin when it placed on skin. Medicated adhesive patches or transdermal patches are of different sizes, having more than one ingredient. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers. A patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process. Drug can penetrate through skin via three pathways-through hair follicals, through sebaceous glands, through sweat duct. Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation& neurological disorders such as Parkinson's disease.[1,2] The transdermal route has become one of\the most successful and innovative drug delivery system for research in pharmaceutical sciences. Transdermal drug delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal drug delivery is not only provides controlled, constant administration of the drug ,but also allows continuous input of drugs with short biological half lives and eliminates pulsed entry into systemic circulation. The success of dermatological drug to be used for systemic drug delivery depends on ability of the drug to penetrate through skin insufficient quantities to achieve the desired therapeutic effect .The first transdermal patch was approved in 1981 for the relief of motion sickness, nausea and vomiting. The transdermal drug delivery market was until recently, solely based on passive patch technology that relied on sample diffusion across the skin. Active patches in which the agent in some way driven through barrier offer a wide array of capabilities allowing delivery compounds over 500Da and those with challenging physical properties. This has permitted the development of active patches to deliver pain management drugs, proteins and vaccines. Passive patch technology is creating smaller patches with better adhesion. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Hence transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. [3,4,5] It can include Transdermal drug delivery system in which rate of drug Absorption is increases, the rate of drug absorption is increases ultimately Bioavailability of drug is increases. In Transdermal drug delivery system in which the drug

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Preparation or medicament is applied on the external surface of skin and Mucus membrane. It is Novel drug delivery system or Targeted drug delivery system having important application to prevent the problem related Presystemic metabolism or systemic circulation. In this type of drug delivery system can produces both type of effect local as well as systemic effect. It is important to prevent the GI toxicity, Gastric irritation and GI Mucosal damages. Transdermal drug delivery system is important to maintain the health of skin and prevent the infection of skin or mucus membrane, It can includes in Transdermal Medicament such as Ointment, creams, gels, Micro emulsions, Transdermal patches is important to prevent the infection of skin and maintain the appropriate health of skin.[6-11] Transdermal patches were introduced in the late 1970's, starting with a 3 day patch to treat motion sickness. Since then, the market for drug administration through patches has been steadily increasing. However transdermal delivery is severely limited by the inability of the majority of drugs to cross skin at therapeutic rates due to the barrier imposed by the skin's outer stratum corneum layer.[12,13]

Advantage

- Transdermal medication delivers a steady infusion of a drug over an extended period of time.
- An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, e.g. the drug is given orally.
- Self administration is possible with these systems.
- They are easily and rapidly identified in emergencies (e.g. unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.
- They can be used for drugs with narrow therapeutic window.
- Longer duration of action resulting in a reduction in dosing frequency.
- Increased convenience to administer drugs which would otherwise require frequent dosing.
- Improved bioavailability.
- More uniform plasma levels and maintain plasma concentration of potent drugs.
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- Flexibility of terminating the drug administration by simply removing patch from the skin.
- Improved patient compliance and\comfort via non-invasive, painless and simple application.
- Avoid inter and intra patient variation and enhance therapeutic efficacy.[14-17]
- Reduce dosing frequency.
- Avoid hepatic first pass metabolism.
- Increase patient compliance mainly in pediatric and geriatric patients.
- Maintains stable or constant and controlled blood levels for longer period of time.
- They provide extended therapy with a single application.[18,19]

Disadvantages

- Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
- Not suitable for high drug doses.
- Adhesion may vary with patch type and environmental conditions.
- Skin irritation and hypersensitivity reactions may occur.
- Drugs that require high blood levels cannot be administered.

Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product [14,20,21].

METHOD OF PREPARATION OF TRANSDERMAL PATCHES

a. Asymmetric TPX membrane method

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. [(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a Gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.

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 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.

b. Mercury substrate method

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

c. By using "IPM membranes" method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers 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.

d. 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.

e. 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

f. Preparation of TDDS by using Proliposomes

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

g. 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 Petridish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petridish. 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 [24-32].

EVALUATION PARAMETERS

Thickness of the patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by travelling microscope dial gauge, screw gauge or micrometer at different points of the film.

Weight uniformity

The prepared patches are 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.

Folding endurance

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

Percentage Moisture content

The prepared films are to be weighed individually and to be kept in a desiccators 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 2, 13.

% Moisture content = Initial weight – Final weight /Final weight. X 100

Content uniformity test

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content 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.

Moisture Uptake

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

% moisture uptake = Final weight – Initial weight/Initial weight. X 100

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 analyze the drug

contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

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 cross linking 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.

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.

Water vapour transmission studies (WVT)

For the determination of WVT, weigh one gram of calcium chloride and place it in previously dried empty vials having equal diameter. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials are again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated.

WVT = W/ ST W is the increase in weight in 24 h; S is area of film exposed (cm2); T is exposure time.

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.

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.

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.

***In vitro* drug release studies**

The paddle over disc method (USP apparatus V) is employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness are to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate is then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus is equilibrated to 32± 0.5°C. The paddle is 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.

***In vitro* skin permeation studies**

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats is 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 is 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 is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is 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 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).

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.

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 are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content [33-40,22].

Table 1. Ideal properties of transdermal drug delivery system [22]

S.No.	Properties	Range
1.	Shelf life	Should be up to 2.5 years
2.	Patch size	Should be less than 40 cm^2
3.	Dose frequency	Once a daily - once a week
4.	Appearance	Should be clear or white color
5.	Packaging properties	Should be easily removable of release liner
6.	Skin reaction	Should be non-irritating
7.	Release Properties	Should have consistent pharmacokinetic and pharmacodynamic profiles over time
8.	Packaging properties	Should be easily removable of release liner

Table 2. Ideal properties of drug for TDDS [22, 23]

S. No.	Parameter	Properties
1.	Dose	Should be low
2.	Half life in hr	Should be 10 or less
3.	Molecular weight	Should be less than 500
4.	Partition coefficient	Log P (octanol-water) between –1 and 3
5.	Skin permeability coefficient	Should be less than 0.5 x10-3cm/hr
6.	Skin reaction	Should be non-irritating
7.	Oral bioavailability	Should be low
8.	Therapeutic index	Should be low
9.	Concentration	Minute
10.	pH of saturated aqueous solubility	5-9
11.	Dose deliverable	<10mg/day

CONCLUSION

Their prospective role in controlled release is being worldwide exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. Transdermal patches can be divided into various types like matrix, reservoir, Membrane matrix hybrid, micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS. After preparation of transdermal patches, they are evaluated for physicochemical studies, *in vitro* permeation studies, skin irritation studies, animal studies, human studies and stability studies. Future developments of TDDSs will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use.

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