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Approaches and Advancement in Transdermal Drug Delivery: A Comprehensive Review

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Abstract

Transdermal therapeutics systems are defined as self contained discrete dosage forms when applied to the intact skin, deliver the drugs through the skin, at controlled rate to the systemic circulation. The advantages of delivering drugs across the skin for systemic therapy are well documented. Some of the main advantages of a transdermal drug delivery system are: The simplified medication regimen leads to improved patient compliance and reduced inter and intra patient variability. In the present paper approaches for Transdermal drug delivery system was highlighted in detail.

Keywords: Transdermal, Approaches, Advantages

Introduction

At present, the most common form of delivery of drugs are the oral route because it has advantage of easy administration. But it also has significant drawbacks namely poor bioavailability due to first pass metabolism and the tendency to produce fluctuation in plasma dug concentration due to the frequency in dosing which can be both cost prohibitive and inconvenient. The continuous intravenous (I.V.) infusion has been recognized as a suitable mode of systemic drug delivery that can maintain a constant and sustained drug levels within therapeutic window for a long period of time throughout the treatment period. But this mode of drug administration have certain health hazards like accidental needle sticks and needle pain especially for patients requiring multiple administrations on a daily basis. Therefore necessitates of continuous hospitalization during treatment and under medical supervision. It has been realized later that the benefits of I.V. infusion could be closely duplicated without its hassles by using skin as the port of entry of drug. This is known as transdermal administration and the drug therapy systems are known as the transdermal therapeutic systems or transdermal drug delivery systems or popularly known as transdermal patches. [1, 3]

Transdermal drug delivery systems that can deliver medicines via the skin portal to the systemic circulation at a predetermined rate and maintain clinically effective concentrations for prolonged period of time. This route of drug administration represents an attractive alternative to oral delivery of drugs and avoids the hazards and discomfort associated with parenteral therapy. The treatment can also be terminated rapidly by simply removing the patch when need arises. Transdermal delivery may also eliminate side effects of that drugs cause when presented in conventional forms.

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The first three day transdermal patch of scopolamine to treat motion sickness was approved in the United States in 1979. [4, 5] A decade later, nicotine patches became the first transdermal blockbuster, raising the profile of transdermal delivery in medicine and for the public in general. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, nitroglycerin and clonidine for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, testosterone for hypogonadism and oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement. Nowadays, the transdermal route has become one of the most successful and innovative focus for research in drug delivery with around 40% of the drug candidates being under clinical evaluation related to transdermal or dermal systems. Transdermal products for depression, Alzheimer's disease, Parkinson's disease, anxiety, attention deficit hyperactivity disorder, cardiovascular disease, skin cancer, postmenopausal bone loss, female sexual dysfunction and urinary incontinence are at various stages of formulation and clinical development. [6,7] Despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues for transdermal products are US$3B, shared between the USA at 56%, Europe at 32% and Japan at 7%. In a recent market report it was suggested that the growth rate for transdermal delivery systems will increase 12% annually and it is estimated that more than one billion transdermal patches are currently manufactured each year. [8, 9]

Approaches for developing transdermal drug delivery systems

Several approaches have been utilized to provide rate control release and permeation of drugs across skin.

Membrane-Moderated system

This system consists of a drug reservoir is sandwiched between a drug impermeable metallic plastic laminate and a rate-controlling polymeric membrane e.g., ethylene-vinyl acetate copolymer which may be micro porous or non-porous controlled permeation of drug molecules. In the drug reservoir compartment, the drug solids are homogeneously dispersed in a solid polymer matrix or form a paste like suspension by viscous liquid medium e.g. silicone fluid. A thin layer of drug compatible, hypoallergenic pressure sensitive adhesive polymer, e.g., silicone adhesive may be applied to provide intimate contact of the system with the skin surface on the external surface of the polymeric membrane. The drug release rate from this type of transdermal drug delivery system depends upon the polymer composition, permeability coefficient and thickness of polymeric rate limiting membrane and adhesive. [10, 11]]

Adhesive diffusion-controlled system

Adhesive diffusion controlled system is the simplified approach of membrane permeation controlled system. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melt onto a flat sheet of drug-impermeable metallic plastic backing to form a thin drug reservoir layer. The thin layers of non-medicated rate-controlling adhesive polymer of a specific permeability and constant thickness are applied on the top of the drug reservoir layer to produce an adhesive diffusion controlled delivery system. [12, 13] The rate of drug release in this system is defined by the following equation:

Matrix dispersion type system

The drug reservoir in matrix dispersion type system is prepared by homogeneously dispersion of drug particles in a hydrophilic or lipophilic polymer matrix and the medicated polymer is then formulated into a medicated disc with a defined surface area and required thickness. This drug reservoir containing polymer disc is then fixed onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc. [12, 13]

Microreservior system

This type can be considered as a combination of the both drug reservoir and matrix dispersion-type drug delivery systems. The drug reservoir is prepared by first suspending the solid drug in an aqueous solution of a water soluble polymers and then homogeneously dispersing the drug suspension in a lipophilic polymer by using high shear mechanical technique to form thousands of unleachable microscopic spheres of drug

reservoirs. The resultant thermodynamically unstable dispersion is stabilized quickly by immediately polymer cross linking chains in situ which produces medicated polymer disk with a constant surface area and a desirable thickness. [12, 13]

Transdermal patches

Transdermal patches are dosage forms that are placed on the skin to deliver a therapeutically effective amount of medication through the skin and into the systemic circulation. [11-13] Several system designs have been used in development and formulation of transdermal patches:

Matrix patch

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophilic polymer. The required quantity of plasticizers like dibutylpthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is mixed properly. The medicated polymer formed is then molded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film. The commonly used polymers for matrix are cross linked polyethylene glycol, Eudragit, ethyl cellulose, polyvinylpyrrolidone and hydroxypropyl methylcellulose. The dispersion of drug particles in the polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive.

Reservoir patch

The main advantage of reservoir type patches is zero order release pattern to achieve a constant serum drug level. The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unleachable viscous liquid medium to form a paste like suspension or gel or a clear solution of drug in a releasable solvent. The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate. The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material or the material may contain fluid filled microspores in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membrane, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the thickness of membrane. Hence the choice of membrane material is dependent on the type of drug being used. By varying the composition and thickness of the membrane the dosage rate per unit area of the device can be controlled. Mostly ethylene vinyl acetate (EVA), ethyl cellulose, silicon rubber and polyurethanes are used to prepare rate controlling membranes.

EVA is used most frequently to prepare rate controlling membrane in transdermal delivery systems because it allows the membrane permeability to be altered by adjusting vinyl acetate content of polymer. Polyurethane membranes are suitable especially for hydrophobic polar compounds having low permeability through hydrophobic polymers such as silicon rubber or EVA membrane. Rate controlling membrane may be prepared by solvent evaporation method or compress-ion method. In case of solvent evaporation method polymer is dissolved in solvent with or without plasticizer. Then, the solution is poured on the horizontal surface and left for evaporation of solvent in order to obtain a thin film. In case of compression method, the polymer is compressed with required force at high temperature for specific period of time. Drugs that require relatively high doses or greater permeation enhancement such as testosterone use liquid reservoir systems. But the application of enhancers and adhesive technologies has allowed many drugs that were initially administered in liquid reservoirs to be used as matrix type systems e.g. estradiol, nicotine, nitroglycerine.

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Membrane matrix hybrid patch

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate.

Micro reservoir patch

The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in lipophilic polymer forming thousands of unleachable microscopic drug reservoirs. The dispersion is quickly stabilized by immediately cross linking the polymer chains in-situ which produces a medicated polymer disc of a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane.

Drug-in-adhesive patch

This type of system is preferred for hydrophobic drugs as it is to be incorporated into organic solvent based hydrophobic adhesive. The drug and other selected excipients are directly incorporated into the organic solvent based pressure sensitive adhesive solution mix, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug-in-adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. Some examples of suitable pressure sensitive adhesives are polysiloxanes, polyacrylates and polyisobutylene. These pressure sensitive adhesives are hydrophobic in nature and are prepared as solutions of polymer dissolved in organic solvents

Vapour patch

The vapor patches are new to the market commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions. In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapor.

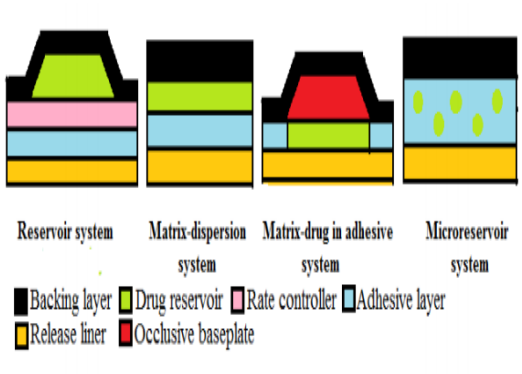

Fig. 1: Types of Trandermal Patches

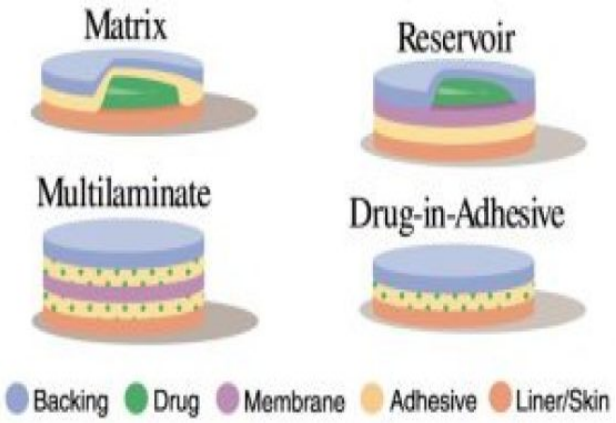

Fig. 2: Components of Trandermal Patches

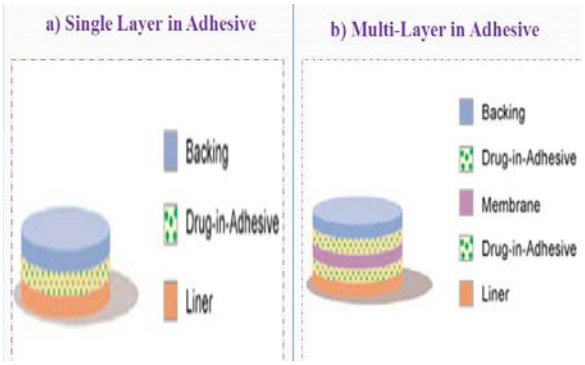

Fig. 3: Single Layer Vs Multi-layer Adhesive

Need of transdermal drug delivery system

The skin is the most readily accessible organ of the body and acts as a barrier against the micro and macromolecules of the environment because of its low permeability to such substances . The skin of an average adult body has approximately 2 m^2 surface area and it receives about one-third of the total blood circulating throughout the body . Percutaneous absorption of drug through skin mainly occurs via stratum corneum. Stratum corneum is made up of dead, keratinized epidermal cells having thickness of 10 µm and acts as a barrier for permeation of drugs. Therefore transport of drug molecules across the skin is difficult. [14]

The goal of drug administration through skin is for topical treatment of skin diseases or for transdermal absorption of drugs in the systemic circulation. The topical route offers a large and varied surface in addition to the ease of application via self-administration and provides an alternative to oral delivery of drugs as well as hypodermic injection. [15] The rate and extent of drug absorption through skin depends on the skin physiology and physicochemical properties of drugs as well as the delivery system. [16-18] The current dosage forms, i.e. patches, ointments, creams, etc., are associated with several limitations. Patches have various disadvantages, most commonly skin irritation , because of their occlusive properties causing obstruction of sweat ducts, which in turn prevents loss of water vapor from skin surface, difficulty in applying on the curved surfaces, pain while peeling off and poor aesthetic appeal. Semisolid preparations like creams and ointments overcome some of these drawbacks but have other limitations. [19-21] These do not ensure persistent contact with the skin surface and can be easily wiped off by patient's clothes. Hence repeated application is required in case of chronic diseases like athlete's foot, ringworm and candidiasis.[17-19] Also these leave a sticky and greasy feel after application leading to poor patient compliance. [22, 23] Therefore there is a need for development of a dosage form which permits less frequent dosing by maintaining a close contact with the skin for prolonged time period thereby improving the patient compliance. [24]

Advantages of Transdermal Drug Delivery

Transdermal drug delivery offers several advantages over conventional dosage forms.

- Reduction of fluctuations in plasma levels of drugs.
- The steady permeation of drug across the skin allows for more consistent serum drug levels. Intravenous infusion also achieves steady plasma levels, but more invasive than transdermal drug delivery.
- The lack of peaks in plasma concentration can reduce the risk of side effects. Thus, drugs that require relatively consistent plasma levels are very good candidates for transdermal drug delivery.
- Easy termination of drug delivery: if toxicity were to develop from a drug administered transdermal, the effects could be limited by removing the patch.
- Dosage can reduced which causes improvement in patient compliance.
- Short biological half life and low therapeutic index drugs are best choice for transdermal drug delivery.
- It is alternative route of administration oral dosage forms. Great advantage in patients who are nauseated or unconscious.
- Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine
- Avoidance of ‘first pass’ metabolism of drugs.
- Drug which is degraded by the enzyme and acid in the G.I. system may also be good targets.
- First pass metabolism, for oral drug delivery can be avoided with transdermal administration. [25-38]

Disadvantages of Transdermal Drug Delivery

1. Local irritation will occur at the site of application. Erythema, edema and itching can be caused by the drug, excipients and adhesive of patch formulation.
2. Drug is not incorporated into a transdermal delivery system, which has following criteria

- Molecular weight of drug is higher than 500 dalton is not penetrate in the stratum corneum.
- Partition coefficient of drug if lower or very higher is not reach into blood circulation. [39]
- Drugs with high melting point are less soluble in aqueous and lipid phase.

Table 1: Trandermal Patches Available in Market

Brand Name	Drug	Manufacturer	Diagnosis
Alora	Estradiol	Proctol and Gamble Thera Tech	Postmenstrual symptoms
Androderm	Testosterone	GSK Thera Tech	Hypogonadism
CatapresTTS	Clonidine	Alza	Hypertension
Clinderm	Estradiol	Wyeth ayerest	Postmenstrual symptoms
Deponit	Nitroglycerin	Schwarz Pharma	Angina pectoris
Duragesic	Fentanyl	Alza	Moderate pain
Habitrol	Nicotine	Novartis	Anti-smoking
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	GSK	Anti-smoking
Transdermscop	Scopolamine	Novartis	Motion sickness

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