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A comprehensive review on Transdermal drug delivery

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Abstract

The skin is a very important route for the dermal or transdermal delivery of pharmaceutically active substances. 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. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects. Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drugs. The present review highlights the details about transdermal drug delivery system.

Key-words: Transdermal drug delivery, Topical, 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]

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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. The first three day transdermal patch of scopolamine to treat motion sickness was approved in the United States in 1979. 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. 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.[4-9]

Approaches for developing transdermal drug delivery systems[11-13]

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.

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. 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.

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.

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. 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.

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.

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.[14-16]

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 . 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. 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. 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. 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.[20-24]

Transdermal patches: Antifungal drug

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs. Fluconazole, itraconazole and another triazole derivatives i.e., synthetic antifungal agent It is one of the commonly used antifungal agents for most kinds of fungal infections including superficial and invasive fungal infections. **Boddeda et al 2016** studied design, evaluation and optimization of fluconazole trandermal patch by 22 factorial method. The itrazonazole transdemal patches were formulated and evaluated by **Reddy et al, 2017**. Adhesive transdermal patches containing Miconazole Nitrate were prepared as an antifungal therapy. The patches were assessed for release using a model drug as Miconazole Nitrate by diffusion method. Subsequently, the permeation enhancement effect of DMSO and 2-pyrrolidone was studied. The investigated was performed by **Nazarkar et al 2014**.**Hemanag et al 2012** developed transdermal patches containing sertaconazole as an antifungal drug. **Kumar et al., 2012** developed transdermal patches for terbinafine HCl. Topical therapy is highly desirable in treating nail disorders due to its localized effects which results in minimal adverse systemic effects and possibly improved adherence. Fungal infection of nails is common. The infection causes thickened and unsightly nails which sometime become painful. Nail infections are common in people who live in hot or humid climate. In this regard **Prasanna et al**., **2011** developed transdermal patches for nail infection containg ciclopiroxolamine.[20-25]

Transdermal patches: Antihistaminic drug

Gordon et al., (2012) investigated the effects of dimenhydrinate, cinnarizine and transdermal scopolamine on performance the influence of dimenhydrinate, cinnarizine and transdermal scopolamine on the ability to perform simulated naval crew tasks. **Gil et al., (2012)** studied a comparison of cinnarizine and transdermal scopolamine for the prevention of seasickness in naval crew. **Bektas et al., (2014)** developed matrix-type polysaccharide based transdermal films of nifedipine (NFD). **Idrees et al., (2014)** investigate the effects of penetration enhancers and plasticizers on drug release from matrix type transdermal patches of flurbiprofen. **Nukaraju et al., (2014)** prepared matrix monolithic transdermal system of cetrizine dihydrochloride using hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), ethylcellulose and methylcellulose either individually or in combination with glycerin as a plasticizer. **Wu et al., (2014)** developed arecoline patches using Eudragit RS-100, Eudragit RL-100 and polyvinylpyrrolidone K30 with polyethylene glycol 400 as a plasticizer. **Reddy et al., (2014)** prepared trandolapril patches

containing hydroxypropyl methylcellulose, Eudragit RL-100, gantrez and carbopol. **Ganju and Ganju (2016)** studied formulation & evaluation of transdermal patch of acetohexamide. **Pokala et al., (2016)** studied formulation and evaluation of transdermal patches of salbutamol. **Barish et al., (2016)** formulation and evaluation of transdermal patches of amlodipine besylate.[26-35]

Transdermal patches: Cardiovascular drugs

Thorngkham et al (2015) Formulated and evaluated Indomethacin loaded into polycarbazole (PCz) as a conductive polymer drug host to promote the efficient transportation of the drug. The IN-loaded PCz was blended with DCNR to form a transdermal patch. The diffusion of the drug from the membrane by through the electrorepulsive force and electro-reduced PCz expansion. The PCz/DCNR films are show potential transdermal patch under applied electric field. **Kai et al (2015)** formulated novel time-dependent ATR-FTIR technique and two-dimensional correlation analysis (2Dcos), the migration behavior of drugs with varying water solubilities was investigated with ethyl cellulose (EC) films prepared with different kinds of pore formers and/or plasticizers. These results offer a mechanistic understanding of water and drug migration across EC films not previously studied the new formulation prepared with pharmaceutical coating with desired drug release behavior. **Heim (2015)** formulated and evaluated Fentanyl TDDS for chronic, cancer, and noncancer pain. After 1 and 2 months treatment, there were significant decreases in patients' ratings of pain intensity, and impairment of walking, general activity, sleep quality, and QoL. For each parameter, the patient response rate was good. From this study, population-based data, that the proprietary, transdermal fentanyl matrix patch was effective and safe for chronic pain management. **Gupta et al (2014)** fabricated controlled release contraceptive TDDS of Centchroman using ethyl-cellulose as film-forming polymer, polydimethylsiloxane as pressure sensitive adhesive with propylene glycol and Di-n-butyl-phthalate for their penetration enhancer and plasticizing properties, respectively. In vitro permeation of Centchroman through rats abdominal skin using Franz's diffusion cell were evaluated. All formulation follows zero-order release kinetics with r2 > 0.990. **Yousuf et al (2013)** developed and evaluated TDDS of combined salbutamol sulphate and ketotifen fumarate. Effects of different enhancers were evaluated on release and permeation of drugs. F3 formulations having isopropyl myristate as permeation enhancer, showed maximum amounts of drugs release of salbutamol sulphate and ketotifen fumarate at 24 h. The results suggested controlled release transdermal formulations of combined antiasthmatic drugs can be suitably developed as an alternate to conventional dosage forms. **Zhenwei et al (2013)** prepared a hot-melt pressure-sensitive adhesive (HMPSA) based on styrene–isoprene–styrene and investigated its compatibility with various transdermal penetration enhancers. A drug-inadhesive patch was formulating using α-asarone drug, and penetration enhancers were screened by an in vitro transdermal study across excised pig skin. Penetration enhancers had a plasticizer-like effect that decreased the peel strength and shear strength of HMPSA. The formulated Transdermal drug delivery showed a relative bioavailability of 1.494%. which proves that HMPSA may be a promising material for drug-delivery patches. **Dandigi et al (2013)**, conducted a study to develop and characterize Diclofenac Diethylamine (DDEA) transdermal patch using silicone and acrylic adhesives combination. A 7-day skin irritancy test on albino rabbits and an in vivo antiinflammatory study on wistar rats by carrageenan induced paw edema method were also performed. The results indicated the high percent drug permeation (% CDP-23.582) and low solubility nature (1%) of silicone adhesive and high solubility (20%) and low% CDP (10.72%) of acrylic adhesive.[36-42]

The skin is a very important route for the dermal or transdermal delivery of pharmaceutically active substances. Polymeric film are a novel approach that might present an alternative to the conventional dosage forms used on the skin, such as ointments, creams, gels or patches[43].. Numerous controlled or sustained delivery systems have been described whereby the active ingredient has been dissolved or dispersed within this films[44]. Polymer blending is an effective method for providing new materials for a variety of applications. Plasticizing agents are generally essential to overcome the brittleness of the films. Brittleness is an inherent quality attributed to the complex/branched primary structure and weak intermolecular forces of natural polymers. Plasticizers soften the rigidity of the film structure and increase themobility of the polymerchains by reducing the intermolecular forces, thus improving their mechanical.

Conclusion

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Targeted drug delivery seeks

to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects. Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drugs. Topical drug delivery is the term used for localized treatment of dermatological condition where the medication is not targeted for systemic delivery as in transdermal drug delivery.

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