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Review Article

Transdermal drug delivery system: An overview

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ABSTRACT

Transdermal drug delivery systems (TDDS) are the topically applied "patches" designed to deliver a therapeutically effective amount of a drug across a patient's skin at a controlled rate for the systemic action. TDDS has emerged as a potential novel drug delivery system in the last 30 years. It is intended to improve the therapeutic efficacy and safety, maintain the steady state plasma level of drugs and overcome the significant drawbacks of the conventional oral dosage forms and parenteral preparations. It is ideally suited for the diseases that demand chronic treatment with frequent dosing. This review deals with a brief insight on the introduction, the formulation aspects, the physical and chemical enhancers explored or being explored to enhance the transdermal delivery of drugs across the stratum corneum, the evaluation parameters (physicochemical, *in vitro*, *in vivo* studies) and therapeutic applications of TDDS.

Keywords: First pass metabolism; Permeation enhancers; Stratum corneum; TDDS

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

1. Unlike the limited controlled release from oral and intravenous routes, TDDS provides steady infusion of drug over an extended period of time, suitable for the drugs with short biological half life requiring frequent dosing, leading to increased patient compliance and decreased inter and intra patient variability.
2. Therapeutic failure or adverse effects frequently associated with intermittent dosing for the chronic diseases can be avoided.
3. Self administration and removal when required.
4. Poor and variable absorption, low bioavailability and formation of fatal metabolites from the first pass metabolism, and gastric irritation associated with the oral dosing are avoided.
5. Pain, inconvenience of injections can be overcomed by this non- invasive and safe parenteral route of drug delivery (Mishra, 1997; Patel et al., 2011; Magnusson et al., 1997; Gondaliya et al., 2003; Koteshwar et al., 1992).

Composition of TDDS

1. Polymer matrix.
2. Drug.
3. Permeation enhancers.
4. Pressure sensitive adhesives (PSAs).
5. Backing membrane.
6. Release liner.
7. Other excipients.

1. Polymer matrix / Drug reservoir

Polymer matrix, prepared by the dispersion of a drug in a suitable polymer, controls the release of the drug from the device. Polymers used in TDDS should be stable, compatible and non-reactive with the drug and other components of the system, should provide effec-

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tive release of the drug throughout the device. They should be easily fabricated to the desired product. Polymers and their degradation products must be non-toxic and non- antigenic to the host (Mishra, 1997).

The polymers used for TDDS can be classified as:

Natural polymers: Hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (sodium CMC), cellulose acetate, methyl cellulose, ethyl cellulose, gelatin, chitosan, sodium carboxymethylguar, sodium alginate, polymerized rosin etc (Hassan et al., 1993; Rana et al., 1999; Pandey et al., 2000; Murthy et al., 2001; Bagyalakshmi et al., 2007; Paranjothy et al., 1997; Bhaskaran et al., 2000; Koteshwar et al., 1992; Murthy et al., 1995; Rao et al., 1998; Kulkarni et al., 2004; Satturwar et al., 2005).

Synthetic polymers: Polyvinyl alcohol, polyethylene, polyethylene glycol, polyvinylpyrrolidone, eudragits, ethylene vinyl acetate copolymer, ethyl vinyl acetate, silicon rubber etc (Paranjothy et al., 1997; Suwanpidokkul et al., 2004; Hassan et al., 1993; Satturwar et al., 2005; Gondaliya et al., 2003; Rana et al., 1999; Chakkapan et al., 1994; Panigrahi et al., 2005; Aqil et al., 2006; Rajendran et al., 1997; Schroeder et al., 2007).

2. Drug

Drugs, having the following properties, are selected for TDDS (Mishra, 1997; Patel et al., 2011):

a. Physicochemical properties

- Low molecular weight (less than 500 Daltons).
- Affinity for both hydrophilic and lipophilic phases.
- Low melting point (less than 200°C).

b. Biological properties

- Extensive first pass metabolism.
- Narrow therapeutic window.
- Short biological half-life, requiring frequent dosing.
- Potent requiring few mg daily doses.
- Should not induce cutaneous irritation and allergic response.

3. Permeation enhancers

a. Chemical permeation enhancers

They disrupt the highly ordered intercellular lipid bilayers of the stratum corneum by inserting amphiphilic molecules or by extracting lipids, reversibly decreasing the barrier resistance and allowing better permeation of the co-administered drugs (Prausnitzet al., 2008; Phillips et al., 1995; Williams et al., 2004). An ideal enhancer should be inert, non-toxic, non-allergenic, non-irritating, work unidirectionally and compatible with the excipients and drugs. Their potency appears to be drug, skin and concentration dependent (Williams et al., 2004).

Some examples of permeants are ethanol (the most common permeation enhancer), essential oils or terpenes (cineole, carveol, menthone, citral, menthol, d-limonene), dimethyl sulfoxide, propylene glycol, N-methyl-2-pyrrolidine, ethyl pyrrolidine, polyethylene glycol 400, isopropyl myristate, myristic acid, succinic acid, laurocapram (azone), methyl laureate, lauric acid, sodium lauryl sulfate, non-ionic surfactant (spans, tweens), pluronic, oleic acid, diethylene glycol monoethyl ether, urea etc (Dubey et al., 2010; Magnusson et al., 1997; Schroeder et al., 2007; Kulkarni et al., 2007; Yener et al., 2003; Calpena et al., 1994; Ohara et al., 1994; Bhaskaran et al., 2000; Aqil et al., 2006; Gondaliya et al., 2003; Suwanpidokkul et al., 2004; Rana et al., 1999; Murthy et al., 2001; Panigrahi et al., 2005; Phillips et al., 1995; Ruland et al., 1994; Ogiso et al., 1994; Rajendran et al., 1997; Chakkapan et al., 1994; Williams et al., 2004).

b. Physical permeation enhancers

Iontophoresis enhance and control drug penetration through the skin by applying low density electric current. Electroporation applies high voltage pulses across the skin for a fraction of second, creating new aqueous pathways in the stratum corneum for drug diffusion (Jadoul et al., 1997). Erbium: yttrium-aluminium-garnet (Er:YAG) laser applies single pulse of low energy to ablate the stratum corneum layers (Lee et al., 2008). Ultrasound or micro needle application breach the stratum corneum and create micro channels for the drug permeation (Lanke et al., 2009).

c. Other permeation enhancers

Ethanolic liposomes, niosomes, protransferosome gel and prodrug approach are reported to increase permeability by increasing the drug solubilization and partitioning into the skin (Dubey et al., 2010; El-Laithy et al., 2011; Jain et al., 2005; Puglia et al., 2006).

4. Pressure sensitive adhesives (PSAs)

PSAs affix TDDS firmly to the skin on applying light pressure. They should be skin-compatible, non- irritant, easily removable without leaving a residue or inflicting pain. They ensure intimate contact between the drug releasing area of TDDS and the skin surface which is critical for the controlled release of drug. Commercially available PSAs include polyacrylate, polyisobutylene and silicones (Murthy et al., 2001; Dimas et al., 2000; Ho et al., 2007).

5. Backing membrane

Backing membrane is flexible with good tensile strength, having low water vapour transmission rates to promote increased skin hydration and thus greater skin permeability. Aluminized plastic laminate (Alupoly foil) and polyvinyl alcohol are commonly used backing

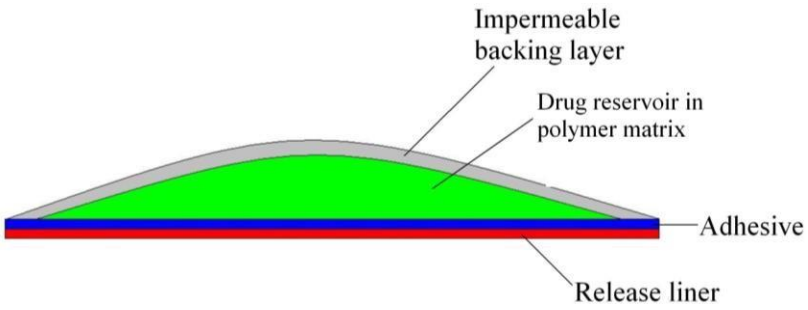

Figure 1: Matrix diffusion controlled film

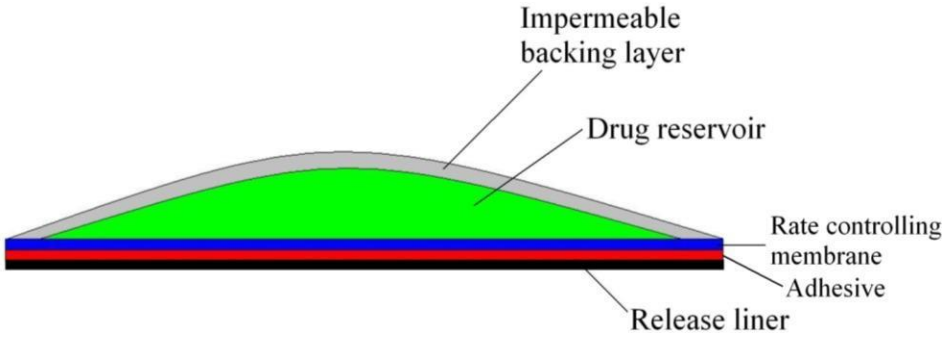

Figure 2: Membrane permeation controlled film

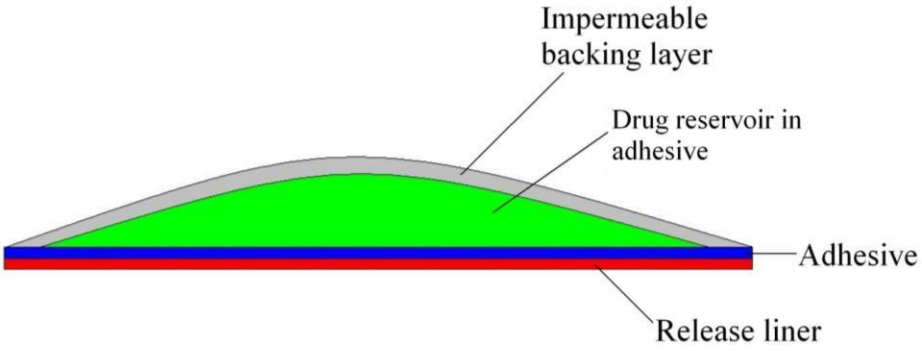

Figure 3: Adhesive diffusion controlled film

membranes (Paranjothy et al., 1997; Bhaskaran et al., 2000; Aqil et al., 2006; Dey et al., 2007; Satturwar et al., 2005).

6. Release Liner

Release liner is a protective liner for the TDDS patch that is removed prior to the application on the skin. Typically, it consists of a base layer which may be non-occlusive (*e.g*. paper fabric) or occlusive (*e.g*. polyethylene, polyvinylchloride) and a release coating layer of silicon (Aqil et al., 2006; Dimas et al., 2000).

7. Other excipients

Various solvents such as water, ethanol, isopropylmyristate, isopropyl alcohol, and dichloromethane are used alone or in combination to prepare the drug reservoir (Suwanpidokkul et al., 2004; Bagyalakshmi et al., 2007; Aqil et al., 2006). Propylene glycol, ethanol are used as co solvents along with the permeation enhancer (Magnusson et al., 1997; Ruland et al., 1994). Plasticizers like diethyl phthalate, dibutylpthalate, glycerol, triethyl citrate, polyethylene glycol 400, eudraflex and propylene glycol provide plasticity to the transdermal patch (Rajendran et al., 1997; Dey et al., 2007; Hassan et al., 1993; Gondaliya et al., 2003; Aqil et al., 2006; Panigrahi et al., 2005; Bhaskaran et al., 2000).

FABRICATION OF TDDS

TDDS is mainly fabricated in the form of a matrix diffusion controlled film (Figure 1) containing a specific amount of drug per unit area (sq. cm) by the glass substrate casting-solvent evaporation technique. Here, the drug and permeation enhancer solution is dispersed in the polymer and plasticizer or adhesive solution. Then, the mixture is casted or poured into a glass ring on mercury substrate or backing membrane foil cup and allowed to dry at room temperature for 24 hours or hot air oven at 40^{o}C for 6 hours. The evaporation rate can be controlled by inverting a funnel over the substrate. Adhesive solution is poured onto the dried film and solvent is evaporated to form a thin uniform layer of adhesive on the film (Hassan et al., 1993; Murthy et al., 2001; Paranjothy et al., 1997; Dey et al., 2007). Membrane permeation controlled film can be obtained

by casting the rate controlling polymers onto the matrix film (Figure 2) (Hassan et al., 1993). Adhesive diffusion controlled film can be obtained by directly incorporating the drug into the adhesive (Figure 3) (Chakkapan et al., 1994).

CHARACTERIZATION OF TDDS

TDDS can be characterized in terms of the following parameters:

a. Evaluation of adhesion

Adhesion of transdermal patch is evaluated for peel adhesion, tack properties (thumb tack test, rolling ball tack test, quick stick or peel tack test, probe tack test) and shear strength properties (Mishra, 1997).

b. Patch thickness

Thickness of patches is measured by using a micrometer screw gauge and average thickness and standard deviation are calculated (Satturwar et al., 2005).

c. Weight variation

Each patch is weighed individually and average weight and standard deviation are calculated (Koteshwar et al., 1992).

d. Folding endurance

The number of times a patch can be folded manually at the same place till it breaks gives the folding endurance (Dey et al., 2007).

e. Mechanical properties

The mechanical property is determined using plastic tensile test with Instron Instrument (Satturwar et al., 2005).

f. Moisture content

Accurately weighed patches of specific area are kept in a dessicator using activated silica and reweighed individually until a constant weight is obtained. Percentage of moisture content is calculated based on the change in the weight with respect to the initial weight (Satturwar et al., 2005; Dey et al., 2007).

g. Moisture uptake

Dry patches are exposed to higher relative humidity conditions and weight is taken periodically until a constant weight is obtained. The moisture uptake is calculated in terms of the percentage increase in weight of patch over its initial weight (Satturwar et al., 2005; Dey et al., 2007).

h. Interaction study

Any interaction among drug, polymer, excipients and stratum corneum is analyzed by Fourier Transform Infrared Spectroscopy (FTIR) or Differential Scanning Colorimetry (DSC) (Bagyalakshmi et al., 2007; Lanke et al., 2009; El-Laithy et al., 2011).

i. Stability test

TDDS is analyzed for drug content, specific decomposition rate, color, consistency etc (Pandey et al., 2000; Murthy et al., 1995).

j. Drug content and uniformity

Patches of specific area are cut and weighed accurately. Drug is extracted in a suitable solvent and analyzed by ultraviolet- visible spectroscopy (uv-vis spectroscopy) or High Performance Liquid Chromatography (HPLC) (Hassan et al., 1993; Satturwar et al., 2005; Prabhakar et al., 1999).

k. *In vitro* drug release studies

The paddle over disc method (USP apparatus V) is used to assess the release of the drug from the prepared patches. Dry films of definite shape is weighed, and fixed over a glass plate with an adhesive. The glass plate is then placed in a 500 mL of phosphate buffer pH 7.4 as the dissolution medium and the apparatus is equilibrated to 37±2°C. The paddle is operated at a speed of 50 rpm. Samples (5ml aliquots) are withdrawn at appropriate time intervals and analyzed by spectrophotometry or spectrofluorimetry (Bagyalakshmi et al., 2007; Satturwar et al., 2005; Yener et al., 2003).

l. *In vitro* skin permeation studies

Various diffusion cells such as Kehsary chain diffusion cell, Franz diffusion cell, modified Franz diffusion cell (vertical type), cylindrical diffusion cell etc. are used for the *in vitro* skin permeation studies (Hassan et al., 1993; Barichelloet al., 2008; Satturwar et al., 2005; Koteshwar et al., 1992). Skin of human cadaver, rat, mouse, guinea pig or pig can be excised from the abdominal or dorsal region and the whole, delipidised or stripped form of definite area and thickness is mounted between the compartments of the diffusion cell with the stratum corneum facing into the donor compartment (Gondaliya et al., 2003; Rana et al., 1999; Phillips et al., 1995; Paranjothy et al., 1997; Suwanpidokkul et al., 2004). The receptor compartment is filled with definite volume of phosphate buffer pH 7.4 and stirred by magnetic stirrer at a constant speed. Samples of definite volume are withdrawn from the receptor compartment at regular intervals and an equal volume of fresh medium is replaced. Samples are filtered and analyzed by radioimmunoassay, spectrophotometry or HPLC (Magnusson et al., 1997; Rana et al., 1999; Barichelloet al., 2008).

m. *In vivo* evaluation

The *in vivo* studies explore the pharmacokinetic and pharmacodynamic parameters which cannot be taken into account during the *in vitro* studies. *In vivo* evaluation of TDDS can be carried out using the animal models or healthy human volunteers. The most common animal species used are mouse, rat, dog and guinea pig (Lee et al., 2008; Jain et al., 2005; Koteshwar et al., 1992; Murthy et al., 2001). However, animal models

are not very good predictive models for human because the penetration in the animals is higher than that in the human. Rhesus monkey is one of the most reliable models for *in vivo* evaluation but the ethical consideration limits its use (Mishra, 1997). Healthy human volunteers can be used for reliable results (Murthy et al., 2001; Bagyalakshmi et al., 2007; El-Laithy et al., 2011). The parameters studied are plasma concentration by Gas Liquid Chromatography (GLC), i*n vivo* absorption study, *in vivo* delivery and deposition by confocal laser scanning microscopy, *in vivo* permeation by Gas Chromatography- Mass Spectrometry (GC-MS), ultra structure of skin by Transmission Electron Microscopy (TEM) and various pharmacodynamic studies (Ogiso et al., 1994; Ohara et al., 1994; Lee et al., 2008; Schroeder et al., 2007; Murthy et al., 2001; Aqil et al., 2006; Jain et al., 2005).

n. Skin Irritation study

Skin irritation or sensitization testing is performed on the hairless dorsal skin of healthy rats or rabbits. The patch is applied over the skin for 24 hours and removed and the skin is observed and classified into 4 grades (none, mild, moderate and severe) on the basis of the severity of erythema/edema and compared with that of the standard irritant, 0.8% formalin (Paranjothy et al., 1997; Murthy et al., 1995; Chakkapan et al., 1994; Panigrahi et al., 2005).

o. Histological examination

It is carried out to access the anatomical changes caused by the enhancers (El-Laithy et al., 2011; Prasad et al., 2007).

p. Localized superficial infection

Bacteria, fungi may proliferate under the occlusive dressing due to favorable conditions like increased temperature, hydration etc. It can be tested by the quantitative bacteriological cultures of the skin site before and after application of the transdermal patches (Mishra, 1997).

THERAPEUTIC APPLICATIONS

Hisetal, used in the treatment of multiple sclerosis may be formulated in TDDS using oleic acid as permeation enhancer to achieve sufficient drug delivery (Ruland et al., 1994).

Diclofenac sodium, celecoxib used as Non- Steroidal Anti Inflammatory Drugs (NSAIDs), formulated in TDDS may overcome the gastric lesions associated with oral dosing (Rana et al., 1999; Yener et al., 2003).

Drugs used for long term dosing in the chronic diseases like captopril, verapamil, terbutaline sulphate, pinacidil, propranolol which have a short biological half life, considerable first pass metabolism may be formulated as TDDS to achieve prolonged steady state plasma concentration (Koteshwar et al., 1992; Paranjothy et al., 1997; Kulkarni et al., 2004; Aqilet al., 2006; Dey et al., 2007).

Hydrophilic polymers like polyvinylpyrrolidone may provide faster drug release whereas hydrophobic polymers like ethyl cellulose can provide prolonged drug delivery (Dey et al., 2007).

Gel formulation with lipid disperse system of betahistine has potential for the development of an efficient controlled release transdermal system (Ogiso et al., 1994).

Enhancer and co-solvent may synergistically enhance the delivery of peptides like thyrotropin releasing hormone across the human skin (Magnusson et al., 1997).

Prazosin Hydrochloride in membrane controlled TDDS may deliver the drug enough to maintain the minimum effective concentration and can avoid hypotension associated with high initial oral dosing (Rajendran et al., 1997).

TDDS of indomethacin in polyvinylpyrrolidone polymer (acting as antinucleating agent) may provide better anti-inflammatory activity and lower ulcer indices compared to oral administration (Rao et al., 1998).

Diclofenac sodium, existing in anionic form at skin pH may be formulated as ion-pairs with oppositely charged enhancers to enhance the transdermal delivery compared to non-ion paired forms (Rana et al., 1999).

Iontophoresis may increase the permeation rate of hydrophilic atenolol to a greater extent than permeation enhancer and overcome incomplete absorption in the gastrointestinal (GI) tract (Bhaskaran et al., 2000).

Nimesulide in sodium alginate transdermal gel may provide better analgesic and anti-inflammatory activity and avoid the adverse effects associated with long term treatment with high oral dosing (Pandey et al., 2000).

Terbutaline sulphate, being diamagnetic, may be incorporated in the magnetic TDDS to experience driving force to escape from the applied magnetic field and enhance diffusion across the skin (Murthy et al., 2001).

Bupropion Hydrochloride, an antidepressant drug may be converted to free base to increase the lipophilicity and transdermal delivery and avoid the release of fatal metabolites associated with oral dosing (Gondaliya et al., 2003).

Zidovudine, an anti-Human Immuno Deficiency Virus (anti-HIV) drug, formulated in TDDS may overcome toxic effects associated with frequent higher oral dose (Suwanpidokkul et al., 2004).

Levonorgestrel, a potent contraceptive agent, formulated as transdermal protransferosome gel may provide enhanced, prolonged and controlled delivery and overcome the GI disturbances, weight gain, irregular

bleeding, headache etc. associated with oral dosing (Jain et al., 2005).

Polymerized rosin may be used to design the matrix type TDDS of Diltiazem Hydrochloride to prolong the drug release and avoid the variable and extensive first pass metabolism on oral dose (Satturwar et al., 2005).

Ester prodrug of ketorolac may provide enhanced permeation whereas nanostructured lipid carrier can act as controlled release system and avoid the gastric ulceration and renal failure associated with frequent long term oral dosing (Puglia et al., 2006).

CONCLUSION

TDDS has gained realistic potential as the next generation drug delivery system for the prolonged, controlled release of both hydrophobic and hydrophilic drugs, efficiently addressing the low oral bioavailability and inconvenience of injections. Future research will be aimed at better transdermal device design with greater understanding of the different mechanisms of biological interactions with permeation enhancers and improving the flux for a wide variety of molecules especially macromolecules and vaccines using cost effective, novel physical enhancement techniques along with the existing chemical enhancers.

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