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Review Article

Transdermal Drug Delivery Systems: A Systematic Review

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ABSTRACT:

Transdermal drug delivery systems (TDDS) have emerged as an effective and patient-friendly alternative to conventional oral and parenteral drug administration routes. By delivering drugs across the skin into systemic circulation, TDDS offer several advantages, including avoidance of first-pass hepatic metabolism, sustained and controlled drug release, improved bioavailability, and enhanced patient compliance. The stratum corneum, however, acts as a major barrier to drug permeation, limiting the transdermal delivery of many therapeutic agents. To overcome this challenge, various strategies such as chemical penetration enhancers, vesicular carriers (ethosomes, transfersomes, invasomes), microneedles, iontophoresis, sonophoresis, and advanced patch designs have been developed. Recent advances in materials science and nanotechnology have further expanded the scope of TDDS, enabling the delivery of macromolecules, peptides, and vaccines. This review provides a comprehensive overview of the principles of transdermal drug delivery, skin anatomy and permeation pathways, formulation components, and different generations of transdermal systems. Current commercial products, regulatory considerations, and recent innovations in TDDS are also discussed. Despite existing challenges related to skin irritation, dose limitations, and inter-individual variability, ongoing research continues to improve the efficacy and applicability of transdermal systems. Overall, TDDS represent a promising platform for controlled and targeted drug delivery in modern therapeutics.

KEY WORDS: TDDS, chemical penetration enhancers, release kinetics.

INTRODUCTION

Transdermal drug delivery system (TDDS) ages from old to modern days where a continuous advancement throughout the centuries made it a modern and very sophisticated drug delivery system. In the earlier a powdered mustard seed layer was spread on a woolen fabric and applied on the chest wrapped with cotton lining which is used to treat severe chest congestion. The mustard seed contain an enzyme myrosin which activates sinigrin which is a glycoside and converts it in to allyl iso thiocynate Later belladonna (0.2-0.3%) an alkaloid used as an analgesic and was sold as plaster in the retail pharmacist. Chinese medicated plasters traced several years back in ancient china. They contain multiple herbal ingredients used for localized action in case of inflammation, pain, bruises, sprains, rheumatic arthritis and the medical effect lasts for 24h. In Japan medicated plaster named cataplasms is available as over the counter product (OTC). In western countries like Germany medicated plaster named ABC plaster (arnica/ belladonna / capsicum) and in USA belladonna plaster, mustard plaster, salicylic acid plasters are available as OTC products. [1,2]

The first and foremost commercially available transdermal patch approved by US FDA in 1979 was scopolamine a three day patch used for motion sickness. Later nicotine patch got nod from FDA in 1991 which is used for treatment smoking cessation. This had revolutionized the usage of transdermal systems in public. In between nitroglycerine, clonidine, fentanyl and estradiol transdermal patches were developed. [3,4]

Transdermal systems are defined as self-contained discrete dosage forms which when applied to skin; deliver the drug through skin at controlled rate to the systemic circulation

US FDA has approved a total 21 drugs or drug combination till 2008 and the transdermal market was growing at a speed of approval of a new molecule for every 7.5 months. The development in transdermal technology was classified in to three generations based on their permeation techniques.

The first generation transdermal systems mainly contain a low molecular weight drug molecule which are lipophilic in nature and are of low dose. The transdermal systems were developed without using any penetration

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enhancer. The drug transport mechanism involves passing of drug through corneocytes and lipid layers which are arranged in brick and mortar fashion. The transport mainly depends on the structure and solubility of the drug molecule in the lipid bilayers of stratum corneum.[5,6]

In the second generation transdermal systems lot of advancement was carried out to enhance the transdermal permeation by using conventional enhancers, Iontophoresis and non-cavitation ultrasound technologies.7 These developments are mainly concerned about increasing the transdermal permeability without damaging the deeper layers of skin. Liposomes, niosomes, solid lipid nanoparticles, dendrimers and micro emulsions are also used as penetration enhancers by modifying the partition coefficient and solubility of drug. Pro-drug approach was also tried in this generation to increase the drug lipophilicity i.e., by adding esters and carbomates as alkyl chain linkage to the drug molecule and the pro drug approach is also used for drugs which are sensitive to skin.8

Third generation transdermal systems involves usage of novel chemical penetration enhancers, cavitational ultrasound, micro needles, electroporation, thermal ablation and dermal abrasion. Chemical penetration enhancers in combinations were tried to enhance the permeation. Biochemical enhancers like peptides eg., maganin peptide was tried for enhancing the penetration of drug molecule. And the results show that the maganin peptide was active only in the presence of surfactant chemical enhancers. In the electroporation technology electric impulses were applied for milli seconds and this will cause the disruption of the lipid bilayer there by promoting the drug delivery. Recent studies show the transdermal delivery of vaccines for cytotoxic studies through the mice skin by electroporation. Micro needle delivery involves formation of micro porous channels in to the skin where the active drug moiety can directly passed through the skin. Silicon based micro needle structures were developed which are of low cost.9,10 Various ranges of molecules, DNA, vaccines, protein and virus particles can pass through skin and this technology is proved to be worthy. The micro needle delivery can be self-administered by the patients and is proved to be painless. Thermal ablation involves heating the skin to hundreds of degrees for fraction of seconds to generate micron scale perforations. Animal studies illustrated the permeation of human growth hormone and interferon α-2b. Micro dermal abrasion involves rubbing the skin with sand paper and the research shows the successful delivery of vaccines.

Transdermal patch has a very distinct advantage over oral dosage forms. They can be particularly used when the drug is having a serious disadvantage of first-pass metabolism, drugs with low oral bioavailability and requires frequent dosing. They can be used as an alternative to hypodermic needle injections, they are non-invasive, self-administered and a patient can terminate the treatment at any time. But there are many limitations for formulating a drug molecule in to transdermal system.[11]

Drug candidates suitable for TDDS [12]

- Molecular weight of a drug must be less than 500 Daltons.
- Drugs with log octanol-water partition coefficient 1 to 4 are suitable.
- Low dosage of less than 10 mg/day.

Advantages of transdermal systems

- A non-invasive and easy to terminate device.
- Avoids hepatic metabolism and improves the bioavailability
- It reduces the dosing to once a day or to once in a week
- Avoids gastrointestinal disorders or side effects
- It provides a constant drug level in plasma and is suitable for drugs with
- narrow therapeutic index and reduces the unwanted side effects
- It is suitable for unconscious patients and age old patients where there is a chance of missing the dose
- Low dose dumping potential
- Reduces the systemic toxicity and
- Patient friendly drug delivery system which improves the patient compliance and quality of life.

Disadvantages of transdermal systems [13]

- The lag time associated with the delivery of the drug across the skin resulting in delay of onset of action
- Not suitable for drugs that produce irritation and contact dermatitis
- Not suitable for drugs that require high plasma levels
- The barrier function of skin changes from one site to another on the same person, from person to person and with age.

Mechanism of transdermal permeation [14]

Transdermal permeation mainly depends on the concentration present in the donor phase and the receptor phase and is represented by the equation

Where Q is represented as the concentration, t is the time, dQ/dt is the rate of change of the concentration, Cd is the concentration in receptor phase and Cr is the concentration in reservoir phase and Ps is the permeability coefficient through the skin. To achieve a constant release concentration gradient has to be maintained between the donor and receptor phase and for this sink conditions has to be achieved.

Types of penetration enhancers [15,16]

• Physical penetration enhancers

a) Iontophoresis

Iontophoresis involves application of low intensity current directly to the skin which penetrates the molecule in to the skin . High molecular weight substances like proteins and peptides eg., insulin can be given through iontophoresis. The possible mechanism includes electro-osmosis, electro-perturbation and electro-repulsion. The limitations in iontophoresis include application of 0.5 mA/cm2 current to human skin, this may cause irreversible damage to the skin and the drugs with molecular weight more than 7000 Da cannot be given.

b) Electroporation

In electroporation electric impulses are applied to the skin. High voltage up to ≥ 100 V was applied for short duration. During this process transient pores are formed which helps the drug molecule to penetrate. High molecular weight drug molecules, proteins and peptides can pass through skin with this process. The disadvantage of this process is that the high electric current applied can cause nerves irritation.

c) Phonophoresis

In this method ultrasounds were applied to skin which helps in penetration of molecule in two ways. First one is by formation of cavitation. This cavitation causes formation of air bubbles in the corneocytes, this increases the intercellular space and enlarges the stratum corneum layers. In the second one by heating of the skin which is caused by ultrasounds will increases the fluidity in the layers of the skin and promotes the passage of drug molecule through the skin. Ultrasounds in the range of 20kHz to 10kHz promote the drug passage.

d) Skin abrasion

In this mechanism the upper layer of the skin was removed by abrasion to enhance the permeation of drug molecules and this was done by using microabraders of length 50 to 200 mm. Molecules of various physico-chemical properties and hydrophilicity can be given like vitamin C vaccine and various biological products.

e) Micro needles

The device consists of a drug reservoir and a plurality of projections extending from the reservoir. These microneedles of length 50 to 110 mm will penetrate the stratum corneum and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel, or solid particulates. In the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir. As a result of the current advancement in microfabrication technology in the past 10 years, cost-effective means of developing devices in this area are now becoming increasingly common.

f) Vesicular carriers

Various vesicular carriers like niosomes, solid lipid nanoparticles, liposomes, transferosomes, ethosomes, aquasomes, multiple emulsions and nano-emulsions can be used as penetration enhancers. The various lipids and non-ionic surfactants used in these formulations will act as carriers to pass through the skin as they can disrupt the lipid layers of skin. They can encapsulate both hydrophilic and hydrophobic drug molecules.

• Chemical penetration enhancers [17]

Mechanism of penetration in chemical enhancers:

a) Pyrrolidines

Pyrrolidines are also used as penetration enhancers they can penetrate both lipophilic and hydrophilic drugs. N-methyl pyrrolidine was successfully used in the matrix transdermal delivery of captopril. Pyrrolidines penetrate in to the skin structure and modifies the fluidity of stratum corneum and forms a reservoir there by promotes the controlled delivery.

b) Sulphoxides and similar compounds

Dimethyl Sulphoxide was one of the early used penetration enhancers and is aprotic solvent. It forms hydrogen bond with the water molecule and is also used as a universal solvent. It penetrates in to the skin by altering the lipid layers, by structural modification of the stratum corneum and by denaturing the proteins in stratum corneum keratin. Concentration up to 60% is used to show the penetration property. Dimethylformamide is another aprotic penetration enhancer which has improved the penetration of caffeine in to skin and enhanced the bioavailability of betamethasone 7-benzoate.

c) Azone

Laurocarpyl was the first specifically designed penetration enhancer which is compatible with many other solvents as it is having octanol water partition coefficient up to 6.2. Azones can show the penetration property at low concentrations at 1-3%. They can be used for various drug molecules like steroids, antivirals and antibiotics.

d) Fatty acids

Oleic acid is the most widely used penetration enhancer is a monounsaturated fatty acid and is used in the combination of co-solvent like propylene glycol for synergistic effect. The penetration property depends up on several factors like concentration of fatty acid used, type of fatty acid, alkyl chain length and the co-solvent used. It was found that for saturated fatty acids alkyl chain length of C10 to C12 has greater penetration property where as for unsaturated fatty acids alkyl chain length of C18 was found to be better.

e) Terpenes, essential oils and terpenoids

Terpenes are the naturally occurring compounds originated from the essential oils in plants. They contain many isoprene units C5H8 usually arranged in a linear form. They are categorized based on oxygenated derivatives like phenols, esters, alcohols and ketones which are branches to linear isoprene units and are again sub divided basing on the number of cyclic rings present in their structure like monocyclic, dicyclic etc.,. Terpenes are having high penetration capacity at a very low concentration of 1-5%. The penetration property of terpenes was found to depend up on the solvent and on the hydrophilicity and lipophilicity of terpenes. Carvacrol and menthol were found to be more potent for hydrophilic drugs whereas for lipophilic drugs monoterpenes were found to be better like limonene and p-mentenene.

f) Surfactants

Among all surfactants non-ionic surfactant was proved to be safe penetration enhancer and non-irritant to skin. Non-ionic surfactants mainly act by increasing the fluidity in the stratum corneum by solubilizing the lipids and by disrupting the corneocytes by binding with the keratin in the intercellular matrix. Polysorbates and sorbiton esters are most widely used non-ionic surfactants. Their activity mainly depends up on the concentration and concentration up to 10%w/w will show better penetration property.

• Bio chemical based penetration enhancers

a) Application of pro-drugs

Application of pro-drug involves modification of an inactive drug in to an active form by reaction with several metabolic enzymes present in the layers of skin in case where in-active drug is having good penetration property compared to active form. This technique is mainly used in hormones like estrogen where they can easily penetrate through skin in esterifide form (estradiol acetate, estradiol diacetate, estradiol valarate) which is in-active and converts in to an active form like estrogen by metabolizing through esterase enzymes.

b) Application of penetration enhancers

Application of enhancers involves modification of skin lipid organization using different penetration enhancers. Each enhancer acts by its own mechanism and the modifications involves changes in sub lattice and lamellar region, formation of separate cells for passage through lamellar region, forming of pathways in intercellular region by making them enhancer rich.

In case of hydrophilic rich enhancers' hydration of skin involves by evaporation of water from skin layers as enhancers are rich in water content when compared to skin and this will increase trans-appendageal transportation.

Lipophilic enhancers form a layer on skin by decreasing the evaporation of endogenous water from skin. The surfactant solubilizes the fatty layer and fastens the transportation through lipid layer.

In vitro drug release kinetics of transdermal drug delivery systems

Therapeutic action of any dosage form depends on the rate at which the drug is released in to the systemic circulation and this depends on the diffusion process i.e., the diffusion of drug through layers of skin in transdermal system. For any diffusion process the layer with high resistance is the rate limiting step.

The percutaneous absorption generally occurs in three steps

Step1: Penetration of molecule in to the stratum corneum

Step2: Permeation of molecule from stratum corneum in to different layers

Step3: Absorption of molecule in to the blood or lymph vessels.

In case of transdermal release stratum corneum is the rate limiting step. Mathematically the diffusion process through these rate limiting barriers was explained by Fick's laws.

• Fick's first law

Fick's first law explains that the rate of diffusion is directly proportional to the concentration gradient and indirectly proportional to the thickness of the layer and is defined as flux.

$$J = -D\frac{\delta C}{\delta x}$$

Where J is the rate of transfer of flux (g/cm2/h), D is the diffusion coefficient (cm2/h), δC is the concentration gradient (g/cm3) and δx is the thickness of the layer (cm). The negative sign indicates the transfer of molecules from high concentration gradient to low concentration gradient as the flux is always positive. Fick's first law in mainly used in infinite dose condition. [17,18]

• Fick's second law

Fick's second law is mainly used in the condition of fixed dose and the simplified equation is.

Jss = Kp. Co

Jss is the steady state flux in the unit area and Kp is the permeability coefficient for a given solute in a vehicle (cm/h) and Co is the concentration of solute in the donor compartment. Kp is mainly used to find-out the permeability rate of a concentration in the given vehicle. Kp is site specific and it generally represents first order rate constant. [19]

K_p is represented by the equation

$$D = \frac{KpX}{Km}$$

Where K_m is the permeability coefficient of drug through the membrane it may be subcutaneous layer of skin. Fick's laws indicate that the steady flux will be achieved when the permeability coefficient was constant. The time to reach the constant release rate or a linear release or a steady state release at infinite dose conditions is called lag time and the preceding period is called lag phase. Lag time is calculated from by extrapolating the drug release curve on to the X-axis.

Mathematically lag time is calculated by the following equation [20]

$$\tau = \frac{x^2}{6D}$$

However these mathematical models will fit to the *in vitro* models without considering the residuals present in the skin and are used for quantification tools for skin permeation data .

References:

1. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: current and future prospects. Drug Deliv. 2006;13(3):175–187.
2. Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015;7(4):438–470.
3. Jeong WY, Kwon M, Choi HE, Kim KS, Kim YB, Kim HJ, et al. Recent advances in transdermal drug delivery systems: a review. Biomater Res. 2021;25:24.
4. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261–1268.
5. Ita K. Transdermal drug delivery: progress and challenges. J Drug Deliv Sci Technol.2014;24(3):245–250
6. Bos JD, Meinardi MMHM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol. 2000;9(3):165–169.
7. Hadgraft J. Skin, the final frontier. Int J Pharm. 1999;184(1):1–6.
8. Mitragotri S. Modeling skin permeability to hydrophilic solutes. J Pharm Sci. 2003;92(4):841–848.
9. Marwah H, Garg T, Goyal AK, Rath G. Permeation enhancer strategies in transdermal drug delivery. Drug Deliv. 2016;23(2):564–578.
10. Kathe K, Kathpalia H. Film-forming systems for topical and transdermal drug delivery. Asian J Pharm Sci. 2017;12(6):487–497.
11. Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug delivery system. J Pharm Pharmacol. 2012;64(1):11–29.
12. Prausnitz MR. Microneedles for transdermal drug delivery. Adv Drug Deliv Rev. 2004;56(5):581–587.
13. Tekko IA, Donnelly RF. Advances in transdermal drug delivery systems and clinical applications in inflammatory skin diseases. Pharmaceutics. 2025;17(1):Article number pending.
14. Nguyen HX, Banga AK. Delivery of drugs across the skin using hydrogel microneedles. J Pharm Pharmacol. 2018;70(4):1–15.
15. Larrañeta E, Courtenay AJ, Donnelly RF. Microneedles: a new frontier in nanomedicine delivery. Pharm Res. 2016;33(6):1263–1280.
16. Honeywell-Nguyen PL, Bouwstra JA. Invasomes as vesicular carriers for enhanced skin permeation. Nanomaterials. 2020;10(5):Article number.
17. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release. 2000;65(3):403–418.
18. Araújo F, Shrestha N, Shahbazi MA, Fonte P, Mäkilä E, Salonen J, et al. Ultrafine nanoemulsions for transdermal drug delivery. ACS Appl Mater Interfaces. 2015;7(30):17012–17025.
19. Qvist MH, Hoeck U, Kreilgaard B, Madson F, Frokjaer S. Release of chemical penetration enhancers from drug-in-adhesive transdermal patches. Int J Pharm. 2002;231(2):253–263.
20. Guy RH, Hadgraft J. Transdermal drug delivery. In: Drug Delivery and Targeting. London: Taylor & Francis; 2001. p. 139–176.