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A Review: Different Generation Approaches of Transdermal drug delivery System

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ABSTRACT

Transdermal Delivery of drugs into systemic circulation via skin has generated lot of interest during the last decade. Transdermal drug delivery systems (TDDS) offer many advantages over the conventional dosage forms or controlled release peroral delivery system. First generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs. Second-generation delivery systems using chemical enhancers, non-cavitational ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality. Third generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound. Microneedles and thermal ablation are currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone .

Key words: Non cavitational ultrasound, chemical enhancers, iontophoresis, microneedles, electroporation

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INTRODUCTION

The current systems of medication which require multi dose therapy are not without problems. The newer approach to drug delivery is to deliver drug into systemic circulation at a predetermined rate known as controlled release drug delivery system. The development cost of a new drug may be about $ 250 million (Rs.900crore) and takes about 12 years to reach the market place. Skin is the most extensive and readily accessible organ in the body. Its chief functions are concerned with protection, temperature regulation control of water output and sensation. In an average adult it covers an area of about 1.73 square meter and receives one third of circulating blood through the body at any given time. The first transdermal system for systemic delivery—a three-day patch that delivers scopolamine to treat motion sickness—was approved for use 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. Today, there are 19 transdermal delivery systems[1,2] for such drugs as estradiol, fentanyl, lidocaine and testosterone;

Table1: Characterstic of some commonly used TDDS

Trade name	Active ingredient	Frequency of application	Type of system
Catapress-TTS	Clonidine	Weekly	Reservoir
Esclim	Estradiol	Weekly	Drug in adhesive
Vivelle	Estradiol	Weekly	Drug in adhesive
Vivelle-Dot	Estradiol	Weekly	Drug in adhesive
Climara	Estradiol	Weekly	Drug in adhesive
Ortho-Evra	Ethinyl estradiol	Weekly	Drug in adhesive
Duragesic	Fentanyl	Once in every 3 days	Reservoir
Transdermal system	Fentanyl	Once in every 3 days	Reservoir
Lidoderm	Lidocain	Daily	Drug in adhesive
Nicoderm-CQ	Nicotine	daily	Drug in adhesive
Nicotrol	Nicotine	Daily	Drug in adhesive
Transderm-scop	Scopolamine	Once every 3 days	Reservoir
Nitro-Dur	Nitroglycerine	Daily	Drug in adhesive
Nitrodisc	Nitroglycerine	daily	Reservoir
Androderm	Testosterone	Daily	Reservoir

combination patches containing more than one drug for contraception and hormone replacement; and iontophoretic and ultrasonic delivery systems for analgesia . The greatest challenge for transdermal delivery is that only a limited number of drugs[3] are able to administration by this route. With current delivery methods, successful transdermal drugs have molecular masses up to a few hundred Daltons, exhibit octanol-water partition coefficients that heavily favor lipids and require doses of milligrams per day or less. It has been difficult to use the transdermal route to deliver hydrophilic drugs; the transdermal deliver of peptides and macromolecules, including new genetic treatment employing DNA or small-interfering RNA (siRNA), has posed particular challenges. Another area of great interest is the delivery of vaccines. Indeed, an analgesic patch was recently approved in the United States that uses patient-regulated delivery of fentanyl modulated by electricity to control pain (iontophoresis), which has also been launched in world. Finally, there is the possibility of not only delivering drugs, but also extracting molecules (analytes) through the skin. This has already been achieved for glucose monitoring by extracting interstitial fluid using electrical means and is in clinical trials using other approaches, such as ultrasound[13]. The major barrier within the skin is the stratum corneum[34], the top layer of the epidermis. The stratum corneum consists of keratinized, flattened remnants of once actively dividing epidermal cells . The intercellular space is rich in lipids. The stratum corneum is about ten microns thick, but on the palms and soles it ranges up to 600 microns in thickness . Although the stratum corneum is an efficient barrier, some chemical substances are able to penetrate it and to reach the underlying tissues and blood vessels. These "successful" substances are characterized by low molecular weight (=500 Dalton), lipophilicity, and effectiveness at low dosage. Now let us take a transdermal patch, proceeding from the visible surface inward to the surface apposed to the skin(fig:1), are:

a. An impermeable backing
b. A reservoir holding the active ingredient, together with release-controlling materials
c. An adhesive to hold the patch in place on the skin
d. A protective cover that is peeled away before applying the patch

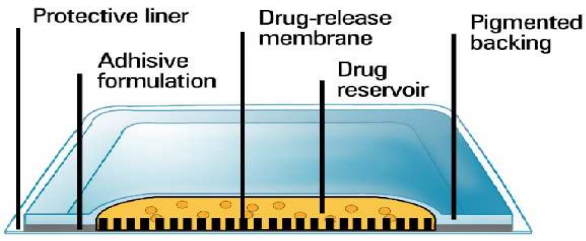

Fig 1: Schematic of a multilayer transdermal system.

Most patches belong to one of two general types – the reservoir system, and the matrix (or drug-in-adhesive) system. Transdermal absorption occurs through a slow process of diffusion driven by the gradient[33] between the high concentration in the delivery system and the zero concentration prevailing in the skin. Thus, the delivery system must be kept in continuous contact with the skin for a considerable time (hours to days).

2. Percutaneous Absorption

It is defined as penetration of the drug into different layers of skin and across the skin into the systemic circulation. Percutaneous Absorption[4] can be divided into three parts as

1.penetration is the entry of a substance into a particular layer.

2.Permeation is the penetration from one layer into another layer.

3.Absorption is the uptake of the drug into systemic circulation.

Stratum corneum is composed of protein bricks and lipid mortar. The lipid part of the stratum corneum plays a major role in determining the permeability of drug through the skin.

2.1 Routes of skin permeation:

There are two major routes of the skin permeation namely transappendageal route and trans epidermal route(fig 3.). Transappendageal route , transports drug via the sweat glands and the hair follicles. Trans epidermal route comprises the continous stratum corneum transport the drug via intracellular and intercellular

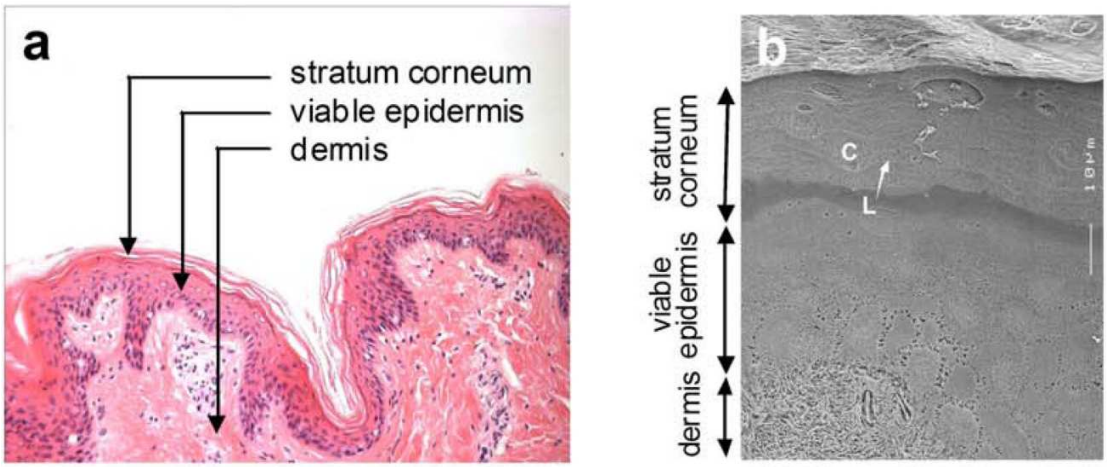

Fig 2: Histological structure of mammalian skin.

a. Skin structure.

b. Stratum corneum structure.

c. Cryo-scanning electron micrograph.

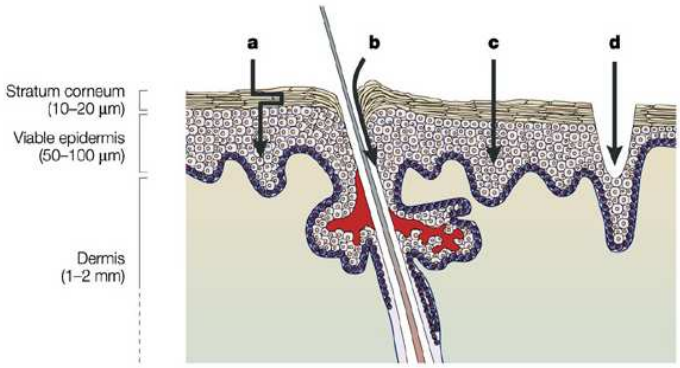

Fig 3: Transverse section of skin.

spaces of the cells. Both polar and non polar molecules diffuse through intracellular and intercellular spaces . transappendageal route is considered to be of minor importance because of their relatively small area(less than 0.1% of the total surface). However this route may be of some importance for larger polar compounds. Several mathematical models to describe the permeability across the stratum corneum have been reported.

3. Factors affecting penetration and permeation:

There are several factors which influence the transdermal absorption namely physicochemical factors and biological factors. The clinical response produced by a TDDS formulation is a three step process as:

1. Release of the drug from formulation.
2. Penetration into and permeation across the skin.
3. Activation of pharmacological response.

3.1 Physicochemical factors:

The Physicochemical properties of both the drug and vehicle plays an important role in determining the percutaneous absorption. These factors are molecular weight, size, structure, partition coefficient, pH, of the drug in the solution inside the formulation.

3.2 Biological factors:

The important biological factors include thickness of the skin(fig 2.), age, blood flow rate, skin conditioning etc. Ultraviolet, infrared, ionizing radiations ,solvents, detergent, acids, alkali and the pathological conditions , such as mechanical damage and skin diseases are the different factors can alter the skin permeability. However in recent formulation skin metabolism is taken into account of activation of pro drugs and design.

From a worldwide perspective, the advancement in the TDDS[3] can be divided into three generation approaches. The Ist generation approach includes the today′s patches. The drug inside these patches can cross the skin at therapeutic rates. The IInd generation approach used the patches that delivers small molecule by increasing the skin permeability. The IIIrd generation approach could deliver transversally small molecular drug, macromolecules (including DNA and proteins) and vaccines via targeted permeabilization of the skin′s stratum corneum. In this review we discuss the different generation approaches and then comment on their potential utilization in the medical field.

4. Ist generation approaches of TDDS:

Most of the transdermal patches present in the market for clinical use are of the Ist generation approaches. The drug in these patches must be of low molecular weight, lipophilic and effective at low dose. The Ist generation approaches to the transdermal delivery is limited due to the barrier presented by the skins outermost layer called stratum corneum which is about 10 to 20μm thick. Under this layer is the viable epidermis which is about 50 to 100 μm and is vascular. Below the epidermis 1 to 2 nm thick dermis contains a capillary bed for systemic drug absorption. The drug transport across the stratum corneum typically involves diffusion through the intercellular lipids. The advancement of the Ist generation approach involves gel or other topical formulation to the skin, a metered liquid spray. The lipophilic drug from these

formulation absorbed into the stratum corneum and slowly released to living epidermis over several hrs. eg Testosterone gel.

5. IInd generation approaches of TDDS:

The second generation approaches of TDDS delivery systems has advanced permeation of small molecules for localized, dermatological, cosmetic and some systemic applications, but has made little impact on delivery of macromolecules also. This approach extensively used chemical enhancer in TDDS. An ideal enhancer should have (i) increase skin permeability by reversibly disrupting stratum corneum structure,
(ii) provide an added driving force for transport into the skin and
(iii) avoid injury to deeper, living tissues.
In this approach chemical enhancers, iontophoresis and non-cavitational ultrasound methods find extensive use.

5.1 Conventional chemical enhancers:

The chemical enhancer[6,7] disrupt the ordered bilayer structures of the intracellular lipids of stratum corneum by inserting amphiphilic molecules into these bilayers to disorganize molecular packing. These chemical extract lipids from the lipid mortar producing nanopores in them. The commonly used chemical enhancers are Azone (1-dodecylazacycloheptan-2-one) and SEPA (2-n-nonyl-1,3dioxolane) . Now a days Liposomes, dendrimers and microemulsions are also used as chemical enhancers. Mitragotri suggested the use of Fourier transform infrared(FTIR) as a chemical enhancer. The infrared rays causes distortion of lipid molecules by CH2 stretching producing nanopores in them. Irritation and toxicity to the living cells is the main disadvantage of chemical enhancer.

5.2 Iontophoresis

In iontophoresis a continous low voltage current (5.5mA/cm2) is applied over the skin through a drug containing electrode in contact with the skin. Oppositely charged electrode is placed elsewhere on the body complete the electrical circuit[5,9]. Transport of the charged molecules is driven primarily by electrical repulsion from the driving electrode. However , Polar neutral molecules can also be delivered by a current induced convective flow of water[10]. Therapeutic peptides and proteins can be delivered by this technique. Iontophoresis find use in rapidly deliver lidocaine for local anesthesia[11], pilocarpine to induce sweating as part of a cystic fibrosis diagnostic test and tap water to treat hyperhydrosis (i.e., excessive sweating), as well as extract glucose from the skin for glucose monitoring.

5.3 Sonophoresis:

It is also known as phonophoresis. The application of ultrasound to enhance the percutaneous drug delivery has been used for over 30 yrs, especially the combination of ultrasound plus steroids or analgesic in order to treat a variety of muscular or arthritic conditions. Recently sonophoresis[12,21,22] has attracted lot of interest in transdermal delivery of peptide/proteins. Especially reports from Langers group from MIT are very encouraging in the area of ultrasound mediated transdermal protein delivery of insulin(MW-6000), interferon(-17000), and erythropoietin(-48000) as model drugs.

6. Third generation TDDS approaches:

The Third generation approaches are more effective than Ist and IInd approaches. These approaches causes stronger disruption of the stratum corneum barriers. Therefore more effective transdermal permeation. In this approach we use novel chemical enhancers, electro oration, cavitational ultrasound, recent micro needles, thermal ablation, and micro abrasion . Microabrasion have been shown to deliver macromolecules including therapeutic proteins, vaccines across the skin in human clinical trials.

6.1 Combination of chemical enhancers:

In this approach we use combinations of chemical enhancers[15,32] rather than a single chemical. Studies shows that certain combinations increased the skin permeability and lowers the irritability as compared to single chemical enhancers. eg. Sodium laureth sulphate and phenylpiperazine at conc of 0.35 and 0.15 wt% in 1:1 mixture of ethanol and phosphate buffered saline for in vitro delivery of a peptide (leuprolide acetate).

6.2 Biochemical Enhancer:

In this approach we use proteins/ peptide instead of chemical as a chemical enhancers. eg magainin[16,17], a natural pore forming peptide. Magainin disrupts the bilayer stratum corneum lipids and increase the skin permeability. The magainin was effective as enhancer when used in combination with a surfactant chemical enhancer.

6.3 Electroporation:

Electroporation is the creation of aqueous pores in the lipid bilayers by the application of short (micro to millisecond) electrical pulses of approximately 100- 1000 V/cm . Flux increases of up to 10000-fold have been obtained for charged molecules[19]. However there is the problem of instrumentation for home use for this potent technique. Electroporation is used for gene transfection peptide such as vasopressin, LHRH (Leuteinizing hormone releasing hormone), neurotensin , calcitonin. Now a days electroporation was shown to deliver a model peptide vaccine into the skin of mice to generate a strong cytotoxic T lymphocyte response[20].

6.4 Microdermabrasion:

Abrasion by microparticulate sandpiper on the skin remove the stratum corneum barrier. Microdermabrasion is a widely used method to alter and remove skin tissue for cosmetic purposes. This technique has been shown to increase skin permeability to many drugs including lidocaine and 5-fluorouracil. However microdermabrasion in animals generated strong immune responses to several vaccines when administered topically in combination with a potent adjuvant (eg enterotoxin of E. coli.).

6.5 Thermal Ablation:

Now a days thermal ablation delivers a number of drug such as human growth hormone[29] and interferone α-2β [31]and insulin[23].

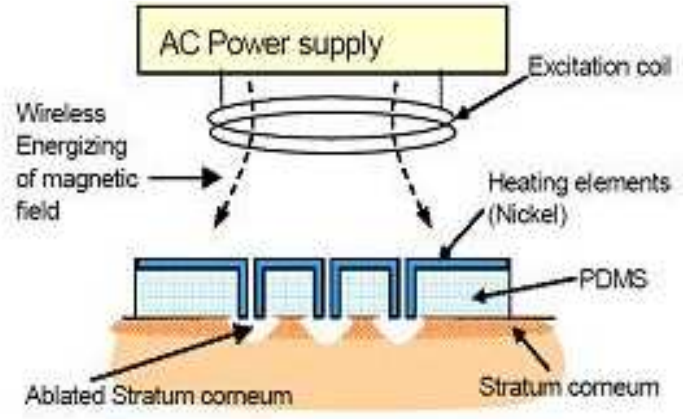

Fig 4: Schematic diagram of wireless inductive heating system for microablation of stratum corneum.

In Thermal Ablation skins surface is heated by hundreds of degrees for microseconds to milliseconds. By applying heat for milliseconds, heat vaporises water in the stratum corneum (fig 4.) and causes microscale pores[30] in the stratum. In thermal Ablation heat does not propagate to the viable tissues below.

6.7 Microneedles:

In general, microneedles

(i) increase skin permeability by creating micron-scale pathways into the skin,

(ii) can actively drive drugs into the skin either as coated or encapsulated cargo introduced during microneedle insertion or via convective flow through hollow microneedles and

(iii) target their effects to the stratum corneum, although microneedles typically pierce across the epidermis and into the superficial dermis too [25].

Microneedles have been dip coated with a variety of compounds, including small molecules, proteins, DNA, and virus particles [26]. Microneedles have also been made of water-soluble polymers that encapsulate various compounds within the needle matrix [27]. These microneedles dissolve in the skin over a timescale of minutes. Administration of influenza vaccine using these microneedles[28] has recently progressed through completion of clinical trials and filing for registration in Europe. Microneedles transdermally deliver Naltrexone, live attenuated virus, inactivated virus, protein subunit and DNA, vaccines against influenza, hepatits B, japanese encephalitis, and anthtrax.

CONCLUSIONS

The first-generation approaches (patch technology) will continue to be used for delivery of small molecule drugs with the right set of properties, especially those drugs that are currently administered orally and by injection that are coming off patent. Second-generation chemical enhancers should find continued use as formulation excipients in topical dermatological creams and ointments and some systemic patches for small molecule drugs.

They will probably have little impact on delivery of hydrophilic drugs and macromolecules, because the most effective chemical enhancers generally diffuse out of the stratum corneum and irritate deeper tissue. Targeted, third-generation combinations of chemical enhancers and biochemical approaches offer strategies for more targeted enhancement, but are still in early stages of development.

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REFERENCES

[1] Gaur PK, Mishra S, Purohit S, Dave K. *Asian Journal of Pharmaceutical and Clinical Research.* **2009**;vol-2,Issue-1,14-20.
[2] Williams, A. London: Pharmaceutical Press; **2003**. Transdermal and Topical Drug Delivery
[3] Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery.
[4] Bronaugh, RL.; Maibach, HI., editors. Vol. Edn. 4th.. New York: Marcel Dekker; **2005**. Percutaneous Absorption.
[5] Mayes S, Ferrone M. *Ann Pharmacother* **2006**;40:2178–2186.
[6] Williams AC, Barry BW. *Adv Drug Deliv Rev* **2004**;56:603–618. Prausnitz and Langer Page 11
[7] Karande P, Jain A, Ergun K, Kispersky V, Mitragotri S. Design principles of chemical penetration enhancers for transdermal drug delivery. Proc Natl Acad Sci U S A 2005;102:4688–4693.
[8] Kiptoo PK, Hamad MO, Crooks PA, Stinchcomb AL. *J Control Release* **2006**;113:137–145.
[9] Kalia YN, Naik A, Garrison J, Guy RH. *Adv Drug Deliv Rev* **2004**;56:619–658.
[10] Subramony JA, Sharma A, Phipps JB. *Int J Pharm* **2006**;317:1–6.
[11] Zempsky WT, Sullivan J, Paulson DM, Hoath SB. *Clin Ther* **2004**;26:1110–1119.
[12] Machet L, Boucaud A. *Int J Pharm* **2002**;243:1–15.
[13] Wu, J.; Nyborg, W., editors. London: Imperial College Press; **2006**. Emerging Therapeutic Ultrasound.
[14] Arora A, Prausnitz MR, Mitragotri S. *Int J Pharm*. **2008**
[15] Karande P, Jain A, Mitragotri S. *Nat Biotechnol* **2004**;22:192–197.
[16] Chen Y, et al. *Nat Biotechnol* **2006**;24:455–460.
[17] Kim YC, Ludovice PJ, Prausnitz MR. *J Control Release* **2007**;122:375–383.
[18] Rothbard JB, et al. *Nat Med* **2000**;6:1253–1257.
[19] Denet AR, Vanbever R, Preat V. *Adv Drug Deliv Rev* **2004**;56:659–674
[20] Zhao YL, et al. *Vaccine* 2006;24:1282–1290.
[21] Ogura M, Paliwal S, Mitragotri S. *Adv Drug Deliv Rev*. **2008**
[22] Paliwal S, Menon GK, Mitragotri S. *J Invest Dermatol* **2006**;126:1095–1101.
[23] Park EJ, Werner J, Smith NB. *Pharm Res* **2007**;24:1396–1401.
[24] Doukas AG, Kollias N. *Adv Drug Deliv Rev* **2004**;56:559–579.
[25] Sivamani RK, Liepmann D, Maibach HI. *Expert Opin Drug Deliv* **2007**;4:19–25.
[26] Gill HS, Prausnitz MR. *J Control Release* **2007**;117:227–237.

[27] Lee JW, Park JH, Prausnitz MR. *Biomaterials* **2008**;29:2113–2124.
[28] Bramson J, et al. *Gene Ther* **2003**;10:251–260.
[29] Levin G, et al. *Pharm Res* **2005**;22:550–555.
[30] Park JH, Lee JW, Kim YC, Prausnitz MR. *Int J Pharm* **2008**;359:94–103.
[31] Badkar AV, Smith AM, Eppstein JA, Banga AK. *Pharm Res* **2007**;24:1389–1395.
[32] Mitragotri S. *Pharm Res* **2000**;17:1354– 1359.
[33] Gennaro, AR, Ed., *Remington's Practice of Pharmacy, 20th ed.*
[34] Baltimore, MD: Lippincott Williams & Wilkins, **2000** p. 836.
[35] Potts RO, Francoeur ML. *J Invest Dermatol* **1991**; 96:495–499.