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CURRENT STATUS AND FUTURE INNOVATIONS IN TRANSDERMAL DRUG DELIVERY

Shalini Chhabaria*, Ankur Namdeo, Rajat Kheri, Gaurav Saraogi and Akhilesh Singhai

Lakshmi Narain College of Pharmacy, Kalchuri Nagar Raisen Road, Bhopal- 462 021, Madhya Pradesh, India

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Correspondence to Author:

Shalini Chhabaria

Lakshmi Narain College of Pharmacy, Kalchuri Nagar Raisen Road, Bhopal- 462 021, Madhya Pradesh, India

Email: shalini_pharmac_3108@yahoo.com

ABSTRACT

Transdermal drug delivery system (TDDS) in comparison to conventional system offers sustained drug release as well as decrease the intensity of action and decrease in the side effects associated with conventional therapy. Presently only about 40 products of more than 20 drug molecules are available in market. The barrier property of the stratum corneum is the main obstructer in the release of drug from the transdermal patch. Various approaches to overcome this barrier function of skin have been broadly studied. Innovations in technologies continue to occur at a positive rate, making the technology a productive and exciting area of innovation, research and product development. In this review, various new development in the field of TDDS are included which are intended to be a need base system. In this review, we have summarized various physical and chemical approaches for transdermal flux enhancement as well as the application of electricity, ultrasound, microneedle and chemical enhancers.

INTRODUCTION: Transdermal Drug Delivery System (TDDS) is the advancing area of novel drug delivery, which is designed to transport a therapeutically effective amount of drug across a patient's skin [1]. The first commercially available TDDS patch of scopolamine was accepted by the U.S Food and Drug Administration in December 1979 for treatment of motion sickness. Although transdermal drug delivery system (TDDS) is not a mean to attain rapid bolus-type or chronopharmacological drug input, it has been proved useful in reducing the frequency of dose, achieving target delivery and avoiding hepatic first pass metabolism [2].

The administration is easier and there is possibility of instant withdrawal of the treatment if necessary. Furthermore, steady absorption of drug over hours or days is frequently preferable to the blood level spikes and troughs produced by oral dosage forms.

Using the skin as a means to mediate and facilitate systemic drug delivery has been a subject of intense interest since the 1960s. The main challenges to obtaining clinically relevant transdermal therapies are in understanding the physiological nature of the skin, mostly the stratum corneum, and in rising formulation strategies to overcome this barrier. As well as a broad range of formulation strategies many methods of enhancement have been employed to overcome this barrier [3].

The first transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness. In past 22 years, approx 35 transdermal patch products, spanning 13 molecules [4]. Transdermal drug delivery system was first introduced more than 20 years ago; the technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980s and 90s.

Innovations in transdermal drug delivery technologies continue to occur at a positive rate, making the technology abundant and vibrant area of innovation, research and product development.

Transdermal Permeation Enhancement Techniques: There are various techniques which are reported in literature are available for TDDS. These techniques can be classified into two class i.e. physical and chemical techniques.

Physical techniques:

Iontophoresis: Iontophoresis involves the application of a small electrical potential across the skin to transport hydrophilic and charged molecules through skin [5]. Products have already reached the US market using iontophoresis technique e.g., recently, FDA approved a pre-filled, pre-programmed iontophoric device for sale in the United States, under the tradename Lidosite™ , which delivers lidocaine and epinephrine to intact skin to supply local anesthesia for superficial dermatological procedures. Improved drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-pertubation (for both charged and uncharged). Various iontophoretic devices are currently under commercial development including the Phoresor device developed by Iomed Inc. and the Vyteris and E-TRANS devices developed by Alza Corp [6, 7].

The limitations of ionotophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA cm^{-2}) and the irreversible damage such current could do to the barrier properties of the skin. In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules of >7000 Da.

Electroporation: In electroporation, short electric pulse (milliseconds or microseconds) is applied to the skin for the transitory structural perturbation of the lipid bilayer membranes. It is usually known that 0.5 to 1.0 volt of transmembrane potential difference should be applied for the electroporation to occur for a single lipid bilayer. It has been shown that electroporation can also induce the alteration of stratum corneum lipid domain[8]. It will enhance the permeation of small compounds like fentanyl to moderately sized molecules like calcein and macromolecules like calcitonin [9]. Enhanced transport has also been reported with lipophilic (e.g. timolol), hydrophilic (e.g. metoprolol), charged (e.g. heparin) and neutral molecules (e.g. mannitol) [10-12].

Genetronics, Inc. has developed a prototype electroporation transdermal system, which has been tested with various compounds with a view to achieving gene delivery, improving drug delivery and aiding the application of cosmetics.

Sonophoresis: Ultrasound, especially in the frequencies between 20 to 100 KHz, has shown to significantly increase the permeability of skin for facilitating transdermal drug delivery[13]. Ultrasound induced cavitation leads to the formation of localized regions of high permeability [14]. Skin could either be permeabilized with short application of ultrasound before the application of drug or drug and ultrasound could be applied simultaneously to the skin [15]. Some parameters including frequency, intensity, function cycle and application time, can be adjusted to achieve a safe reversible breach in the skin [16].

The SonoPrep R device uses low frequency ultrasound (55 kHz) for an average duration of 15 s to enhance skin permeability. This battery operated hand held device consists of a control unit, ultrasonic horn with control panel a disposable coupling medium cartridge, and a return electrode. The ability of the SonoPrep device to reduce the time of onset of action associated with the dermal delivery of local anaesthetic. The use of other small, lightweight novel ultrasound transducers to enhance the in vitro skin transport of insulin has also been reported by a range of workers.

Microneedles: Microneedles painlessly disrupt the barrier of the skin and create pores resulting in an enhanced penetration. First reported application of microneedles demonstrated enhanced permeation of calcein [17]. In the recent years, microneedles have been broadly investigated for the delivery of compounds like diclofenac, desmopressin and even vectors for gene therapy [18]. First, microneedle systems were described in 1976 consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the

stratum corneum and epidermis to deliver the drug [19]. Recently, as a result of the rapid advancement in microfabrication technology in the last 10 years, several cost-effective methods of producing microneedle devices have been developed [20-22].

Recently, The ALZA Corp. has commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir [23] or by dry coating the drug on the microprojection array [24]; the latter being better for intracutaneous immunization.

Skin Abrasion: Skin abrasion involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. These devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

Microscissuining is a method in which microchannels are created in the skin by eroding the impermeable outer layers with sharp microscopic metal granules. Currently, Carlisle Scientific is in the process of developing a pen-like handheld device called the microscissioner. In addition, MedPharm Ltd. has recently invented a novel dermal abrasion device (D3S) for the transport of difficult to formulate therapeutics ranging from hydrophilic low molecular weight compounds to biopharmaceuticals. By *in vitro* data, it has proved that the application of the device can increase the penetration of angiotensin into the skin 100-fold compared to untreated human skin. This device is non-invasive and histological studies on human skin show that the effects on the stratum corneum are reversible and non-irritating.

Needle-less Injection: In this technique drugs are painlessly administered to the skin. This method therefore avoids the issues of safety, pain and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. Over the years, there have been several examples of both liquid (Ped-O-Jet, Iject, Biojector 2000, Medi-jector and Intraject) and powder (PMED device formerly known as Powderject injector) systems. The latter device has been reported to successfully deliver testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin [25-27].

Laser Radiation: This technique involves direct and controlled exposure of a laser to the skin which leads to the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to increase the delivery of lipophilic and hydrophilic drugs [28-30]. Norwood Abbey Ltd. (Victoria, Australia) has been developed a handheld portable laser device, which, in a study involving human volunteers, was found to reduce the onset of action of lidocaine to 3-5 minutes, while 60 minutes was required to achieve a similar effect in the control group.

The Norwood Abbey system has been approved by the U.S. and Australian regulatory bodies for the administration of a topically-applied anaesthetic. Laser systems are also being developed to ablate the stratum corneum from the epidermal layer [31]. As with microneedles, the ablated regions offer lower resistance to drug diffusion than non-ablated skin. One company has recently received FDA approval to market this device with a lidocaine cream.

Magnetophoresis: This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability [32]. Murthy *et al*., investigated the mechanistic aspects of magnetophoretic transdermal drug delivery and also assessed the feasibility of designing a magnetophoretic transdermal patch system for the delivery of lidocaine. The magnetophoretic drug permeation "flux enhancement factor" was found to increase with the applied magnetic field strength. The dermal bioavailability [AUC (0-6h)] from the magnetophoretic patch system in vivo, in rats was significantly higher than the similarly designed non-magnetic control patch. The research data on animal models suggests that skin penetration can be enhanced by applying a magnetic field to therapeutic molecules that are diamagnetic or paramagnetic in nature [33].

Temperature (Thermophoresis): This method involves the heat treatment of the skin which enhances the drug release. The increased permeation following heat treatment has been attributed to an increase in drug diffusivity in the vehicle and an increase in drug diffusivity in the skin due to increased lipid fluidity. Vasodilation of the subcutaneous blood vessels as a homeostatic response to a increase in skin temperature also plays an important role in enhancing the transdermal delivery of topically applied compounds. The *in vivo* delivery of nitroglycerin, testosterone, lidocaine, tetracaine and fentanyl from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery. The controlled heat-aided drug delivery patch (CHADD) consists of a patch containing a series of holes at the top surface which regulate the flow of oxygen in to the patch. The patch generates heat chemically in a powder filled pouch by an oxidative process regulated by the rate of flow of oxygen through the holes in to the patch. The CHADD technology was used in the delivery of a local anaesthetic system (lidocaine and tetracaine) from a patch and found to enhance the depth and duration of the anaesthetic action in human [34].

TABLE 1: MARKETED PRODUCTS OF MODIFIED TRANSDERMAL DRUG DELIVERY TECHNOLOGIES

Brand Name	Company Name	Enhancement Technique	Drug product available
Macroflux	Alza Corporation	Microprojection	Vaccines and Therapeutic proteins
E-Trans	Alza Corporation	Iontophoresis	Fentanyl
SonoPrep	Sontra Medical Corporation	Ultrasound	Peptides and Other large molecules
SonoDerm	Imarx	Ultrasound	Large molecules (Insulin)
Intraject	Weston Medical	Needleless injectors	Vaccines
Powderject	Powderject Pharmaceutical	Needleless injectors	Insulin
Med-Tat	Lipper-Man Ltd.	Medicated Tattoos	Acetaminophen, Vitamin C
CHADD	Zars, Inc	Heat	S-Caine (Lidocaine and Tetracaine)

Chemical Techniques: As not all the molecules for transdermal administration possess ideal physicochemical properties, manipulation of the drugs or addition of vehicles may become necessary to get therapeutic benefits. Various approaches are given below.

Prodrug: Prodrug could improve transdermal delivery of drugs which have unfavorable partition coefficient or solubility. A promoiety is added to increase the transport of drug across the Stratum corneum. Then parent drug is released by hydrolysis in the viable epidermis. Permeation across the skin is optimized by a balance between lipid and aqueous solubility since drug has to go through a multistep process before it reaches systemic circulation.

So, prodrugs to increase transdermal permeation incorporate functional groups in the promoiety that will increase not only lipid but also aqueous solubility. The permeability of 5-fluorouracil significantly increased by forming a prodrug [35].

Salt Formation: Molecule could be changed to suitable salt form(s) for the optimization of physicochemical properties. Monoethanolamine, diethanolamine and triethanolamine salts of piroxicam were prepared and their permeability across hairless mouse skin was compared with the parent compound. Mono and di-ethanolamine salts had higher solubility in various vehicles tested and also confirmed improved permeation across the hairless mouse skin [36]. Salt formation decreased the melting point and crystalline lattice energy. Although salt formation increased aqueous solubility, it did not bring significant change in octanol/water partition coefficient. When acrylic adhesive based matrix system was used, highest flux was obtained with piroxicam-monoethanolamine salt than di-ethanolamine and triethanolamine salts [37].

Chemical Enhancers: Molecules which decrease the barrier function of stratum corneum are known as chemical enhancers. The enhancer can either disrupt lipid organization and enhance drug diffusion coefficient or interact with keratin in corneocytes, opening up the dense protein structure.

Variation of the chemical environment can also favor the partitioning of drug in the stratum corneum [38]. Chemical enhancers are divided into different chemical classes such as hydrocarbons (n-alkanes having chain lengths between 9 and 18 carbon atoms), alkanols and alkenols (alcohols, polyethylene glycol, propylene glycol), acids (lauric acid, myristic acid, stearic acid, oleic acid), esters (isopropyl myristate, glyceryl monolaurate, glyceryl mono oleate, glyceryl monocaprylate, ethyloleate, ethyldecanoate), alkyl amino esters (N,N-dimethylamino acetate, 1-(N,N-dimethylamino)-2-propanol decanoate), amides (Azone®, dimethyl formamide, dimethylacetamide), amines (polyethyleneglycol oleamine, phenethylamine, stearylamine, triethylamine, dodecylamine), aromatic compounds (carvacrol, thymol, anethole), sulfoxides (dimethyl sulfoxide, N-decylmethyl sulfoxide), cyclic carbohydrates (β-cyclodextrin, hydroxypropyl β-cyclodextrin), terpenes (p-menthane, d-limonene, dipentene, menthol) and pyrrolidones (N-methylpyrrolidone, 1-ethylpyrrolidone, 1-butyl pyrrolidone).

Apart from the formulation type, enhancer should first be released from the transdermal delivery system before it can act on the skin. Hydrating vehicles decrease the lipid phase transition temperature of stratum corneum.

Better understanding of the mechanism for permeation enhancement is valuable in achieving safe and effective reduction of skin barrier. A great deal of research continues to identify generally regarded as safe (GRAS) substances with permeation-enhancing effect [39-41].

Other Innovations:

Dispenser for Transdermal Patches: Recently, 3M core pop-up dispensing technology is being used to develop compact transdermal patch dispensers. The patented dispenser is designed to dispense patches in a manner that makes the patches convenient to apply. The dispenser appearance, size, shape and quantity of patches stored can be customized to meet patients needs.

TABLE 2: COMPARATIVE EFFICACY OF DIFFERENT APPROACHES TO DRUG DELIVERY ACROSS THE SKIN [42]

DELIVERY SYSTEM	INCREASED TRANSPORT	SUSTAINED DELIVERY	NO PAIN / IRRITATION	LOW CAPACITY / COMPLEXITY
Hypodermic needle	High	Moderate	Low	High
Chemical enhancer	Low	High	Moderate	High
Iontophoresis	Moderate	High	High	Low
Electroporation	Moderate	High	Moderate	Low
Sonophoresis	Moderate	High	High	Low
Microneedles	Moderate	High	High	Low
Jet injector	High	Low	Low	Low

Magnetophoresis combined with Chemical enhancers

Currently, magnetophoresis is combined with chemical enhancers which enhanced the permeation of drug across the skin. Sammeta *et al*., investigated the effect of combination of a novel physical permeation enhancement technique, magnetophoresis with chemical permeation enhancers on the transdermal delivery of lidocaine hydrochloride and found that the flux of lidocaine from magnetophoretic patch was ~3-fold higher than that of the control (non-magnetophoretic patch). Incorporation of chemical permeation enhancers in the gel enhanced the magnetophoretic delivery flux by ~4 to 7-fold and concluded that the enhancement factor due to combination of chemical permeation enhancer was additive [43].

CONCLUSION: Various methods including chemicals, electric fields and ultrasound have been used to increase transdermal drug transport. These techniques have rendered transdermal delivery a feasible way of systemically administering drugs. The scientific interest in this area has increased significantly in the last two decades.

Various investigations have been performed to safely break the barrier function of skin enabling administration of therapeutic amount of drug. However, studies performed with solution or suspension formulations have limited application potential.

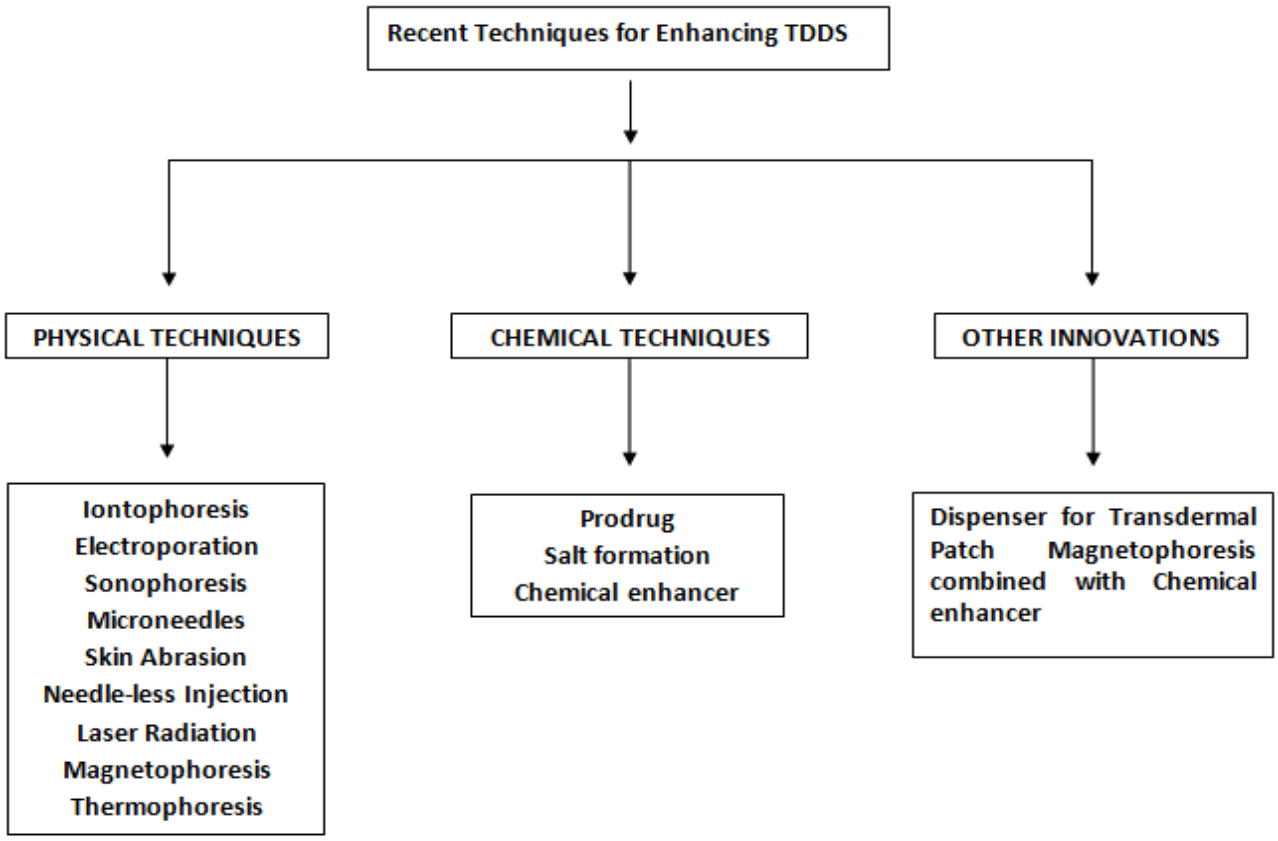

FIGURE 1: RECENT TECHNIQUES FOR ENHANCING TDDS

TABLE 3: LIST OF MARKETED TRANSDERMAL PRODUCTS OF VARIOUS DRUGS[44,45]

TRADE NAME	DRUG	INDICATION	MANUFACTURER
Transderm- Scop[R]	**Scopolamine**	**Motion sickness**	**Alza/Norvatis**
1.Nitrodisc			1.Roberts Pharmaceuticals
2. Deponit			2. Schwarz-Pharma
3. Nitro-dur	**Nitroglycerine**	**Angina pectoris**	3. Key Pharmaceuticals
4. Minitran			4.3M Pharmaceuticals
5.Transderm-Nitro[R]			5. Alza/Norvatis
Catapres TTS[R]	**Clonidine**	**Hypertension**	**Alza/Boehinger Ingelheim**
1.FemPatch			1. Parke-Davis
2.Climaderm			2.Ethical.Holdings/Wyeth- Ayerest
3.Alora	**Estradiol**	**Postmenstrual syndrome**	3.TheraTech/Proctol and Gamble
4. Estraderm			4. Alza/Norvatis
5. Climara			5.3M Pharmaceuticals /Berlex Labs
1.Nuvelle TS	**Estrogen/Progesterone**	**Hormone replacement therapy**	1.Ethical Holdings/Schering
2.Fematrix		**Postmenstrual syndrome**	2.Ethical Holdings/Solvay Healthcare Ltd
Duragesic[R]	**Fentanyl**	**Chronic pain**	**Alza/Janssen Pharmaceutical**
1.Prostep			1.Elan Corp./Lederle Labs
2.Nicotinell[R]	**Nicotine**	**Smoking cessation**	2. Novartis
3.Nicoderm[R]			3. Alza/GlaxoSmithKline
1.Testoderm TTS[R]	**Testosterone**	**Testosterone deficiency**	1. Alza
2.Androderm			2.TheraTech/GlaxoSmithKline
Ionsys	**Fentanyl HCl (Iontophoresis)**	**Acute post operative pain**	**Alza, Mountain View, CA**
NuPatch 100	**Diclofenac diethylamine**	**Anti Inflammatory**	**Zydus Cadila**
Oxytrol	**Oxybutynin**	**Overactive bladder**	**Watson Pharma (Corona, CA)**
Neupro	**Rotigotine**	**Parkinson's disease**	**Schwarz Pharma (Mequon, WI)**
Exelon	**Rivastigmine**	**Dementia**	**Novartis (EastHannover, NJ)**
Emsam	**Selegiline**	**Major depressive disorder**	**Bristol-Myers Squibb (Princeton, NJ)**
SonoPrep	**Lidocaine (Ultrasound)**	**Local dermal anesthesia**	**Echo Therapeutics (Franklin, MA)**

Transdermal devices should be developed considering functional and applicable attributes of the system. However, combining electrical or mechanical device-induced skin penetration methods with improved formulations (comprised of chemical penetration enhancers or nano-drug delivery systems) is likely to produce the ideal transdermal drug delivery devices. The market value for transdermal delivery was $12.7 billion in 2005, and it has grown to $21.5 billion in 2010 and it is expected to increase to the $31.5 billion in the year 2015 – suggesting a significant growth potential over the next 10 years. Future research should be able to ensure improved delivery through better understanding of physicochemical properties of drug, physiology of skin, mechanism of action of enhancers, and the interaction between formulation components. In addition, through improvised design of devices, a greater range of molecules could be covered in transdermal delivery system.

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