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Review article

Transdermal drug delivery system: Innovations in skin permeation

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Abstract

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 systems. TDDS provides; constant blood levels (l-7 days), avoids first-pass metabolism, increased patient compliance, and dose dumping never occurs. The choice of drugs delivered transdermally, clinical needs, and drug pharmacokinetics are some of the important considerations in the development of TDDS. In addition to methods to enhance transdermal absorption of drugs such as sorption promoters and prodrugs, the physicochemical and biological factors affecting transdermal permeation of drugs are discussed. Although, novel approaches like iontophoresis and ultrasound are gaining importance as a means to increase drug permeation into systemic circulation, clinical products based on these approaches are still far away. The cost per milligram of drug delivered transdermally is more expensive than peroral route. The added cost could be justified, if TDDS improve patient compliance and reduces toxic/side effects.

Keywords: Transdermal delivery, controlled release, penetration and permeation.

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1. Introduction

Transdermal therapeutic systems consitute a major advance in controlled drug release; they have been designed for constant transdermal drug delivery with the intention of maintaining a constant plasma level [1]. Transdermal drug delivery system (TDDS) also known as “patches”, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin [2]. Transdermal drug delivery has considered a niche technology, effective only for a limited number of drugs with unique characteristics [3]. The journey of transdermal research had commenced with a lot of enthusiasm, as it heralded the promise of Non-invasive cutaneous application [4]. Transdermal drug delivery is the non-invasive delivery of medications from the surface of the skin - the largest and most accessible organ of the human body - through its layers, to the circulatory system. A skin patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into the bloodstream.

In the past 24 years, transdermal drug delivery has moved from a clinical reality beginning with the first scopolamine patches approved in 1979, to the point where transdermal delivery represents a viable way of delivering a number of drugs with the potential, as research is pursued along many lines, to deliver many more[5]. Some of the earliest contributions related to transdermal delivery involved understanding the principal permeation barrier in the skin. In the mid-1980s, the pharmaceutical companies started the development of a nicotine patch to help smokers quit smoking, and within a few months at the end of 1991 and beginning of 1992 the FDA approved four nicotine patches. Today drugs administered through skin patches include scopolamine (for motion sickness), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), lidocaine to relieve the pain of shingles (herpes zoster). Non-medicated patches include thermal and cold patches, weight loss patches, nutrient patches, skin care patches (therapeutic and cosmetic), and aroma patches, and patches that measure sunlight exposure. The current U.S. market for such patches is over $3 billion annually. Depending on the drug, the time of duration of delivery is generally from 1 to 7 days. Patches have been useful in enabling new therapies and in reducing first pass effects. For example, transdermal estradiol patches are used by over a million patients per year and, in contrast to oral

formulations, are not associated with liver damage. Transdermal clonidine, nitroglycerin, and fentanyl patches exhibit fewer adverse effects than conventional oral dosage forms [6]. Nicotine patches have been used in preventing smoking and prolonging life. For example, 2 years after being on transdermal nicotine patches for 12 weeks, four times as many patch wearers did not smoke compared to patients who received placebos [7].

Despite early successes patches collectively comprise a relatively small portion of available dosage forms, in part due to hurdles that must be overcome for the development of a successful transdermal delivery system. Challenges for patch development include

- Achieving sufficient skin permeability to match dose requirements.
- Achieving optimal adhesive performance.
- Avoiding application site skin irritation.

These factors, along with patient compliance and preference, contributed to a perception that patch technology was tapped out and that the inherent problems could not overcome.
Now, after more than 24 years in marketplace, patches account for approximately three dozen prescription medication products, containing about 16 active drugs.
Improvement in physical and chemical permeation-enhancement technologies has led to renewed interest in transdermal drug delivery. Efforts from research work to increase skin permeation initiated in the late 90s are beginning to emerge. Various academic and industrial laboratories have explored iontophoresis, electroporation, ultrasound, and microporation using electrical current/voltage, radio frequency, and microneedles to open up the skin [8]. Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

Advantages of Transdermal Drug Delivery Systems

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivery drugs across the skin to achieve systemic effects are [8-12]:

- Avoidance of first pass metabolism.
- Avoidance of gastro-intestinal incompatibility.
- Predictable and extended duration of activity.
- Minimizing undesirable side effects.
- Provides utilization of drugs with short biological half lives, narrow therapeutic window.
- Improving physiological and pharmacological response.
- Avoiding the fluctuation in drug levels.
- Inter and intra-patient variations.
- Maintain plasma concentration of potent drugs.
- Termination of therapy is easy at any point of time.
- Greater patient compliance due to elimination of multiple dosing profiles.
- Ability to deliver drug more selectively to a specific site.
- Provide suitability for self-administration.
- Enhance therapeutic efficacy.

Limitations of Transdermal Drug Delivery Systems [2, 13-14]

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin.
- Cannot administer drugs that require high blood levels.
- Drug or drug formulation may cause irritation or sensitization.
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favourable, o/w partition coefficient.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

Anatomy of the Human Skin [15-16]

The skin of an average adult body covers a surface area of approximately 2 sq.m. And receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and biological agent. It is one of the most readily available organs of the body with a thickness of only a few millimeters **(**2.97 ± 0.28 mm**)**.
The skin,

- Separates the underlying blood circulation network from the outside environment.
- Serves as a barrier against physical, chemical & microbiological attacks
- Acts as a thermostat in maintaining body temperature.
- Plays role in the regulation of blood pressure.
- Protects against the penetration of UV rays.

As skin is major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis .The diffusional resistance of the skin is greatly dependent on its anatomy and ultrastructure[17-18]. The skin is capable of metabolizing many substances and through its microvasculature, limits the transport of most substances into regions below the dermis. Although the flux of solutes through the skin should be identical for different vehicles when the solute exists as a saturated solution, the fluxes vary in accordance with the skin penetration enhancement properties of the vehicle. It is therefore desirable that the regulatory standards required for the bio-equivalence of topical products include skin studies. Deep tissue penetration can be related to solute protein binding, solute molecular size and dermal blood flow.

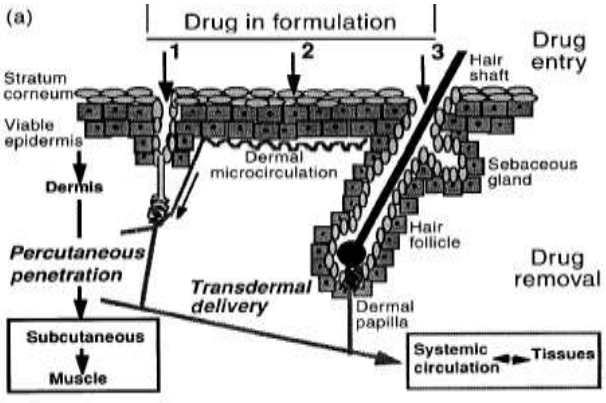


Figure 1.1Stratified Organization of the Skin

Principles of Transdermal Permeation [16, 19]

Before a topically applied drug can act either locally or systemically, it must penetrate the *stratum corneum* – the skin permeation barrier. Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands **(**transfollicular or shunt pathway**)**. In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact *Stratum corneum* becomes the primary pathway for transdermal permeation.

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves

- Dissolution within and release from the formulation
- Partitioning into the skin's outermost layer, the stratum corneum **(**SC**)**
- Diffusion through the SC, principally via a lipidic intercellular pathway, **(**i.e., the rate-limiting step for most compounds**)**
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake **into** the papillary dermis and into the microcirculation.

Kinetics of Transdermal Permeation

Knowledge of skin permeation kinetics is vital to the successful development of transdermal systems. Transdermal permeation of a drug involves the following steps [19].

(a) Sorption by *stratum corneum*,

(b) Penetration of drug through viable epidermis,

(c) Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible if the drug possesses certain physico-chemical properties. The rate of permeation across the skin **(**dQ/ dt**)** is given by:

$$\frac{dQ}{dt} = P_s (C_d - C_r) \qquad \text{Eq. 1}$$

Where,

C_d = concentration of skin penetrant in the donar compartment **(**e.g., on the surface of *stratum corneum***)**

C_r = concentration in the receptor compartment **(**e.g., body**)** respectively

P_s = the overall permeability constant of the skin tissue to the penetrant

$$P_s = \frac{K_s D_{ss}}{h_s} \qquad \text{Eq. 2}$$

Where,

K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system onto the stratum corneum,

D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and h_s is the overall thickness of skin tissues.

As K_s, D_{ss} and h_s are constant under given conditions, the permeability coefficient **(**P_s**)** for a skin penetrant can be considered to be constant.

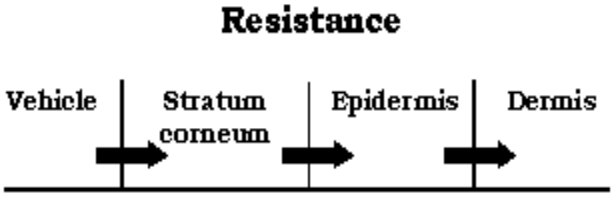
From Eq.1 it is clear that a constant rate of drug permeation can be obtained only when $C_d >> C_r$ i.e., the drug concentration at the surface of the stratum corneum **(**C_d**)** is constistently and substantially greater than the drug concentration in the body **(**C_r**)**, then Eq. 1 becomes:

$$\frac{dQ}{dt} = P_s C_s \qquad \text{Eq. 3}$$

Permeability coffiecient = $K_s D_{ss} / h_s = 1/$ resistance

Resistance has many components[20]

- Vehicle
- Stratum corneum (usually most significant)
- Epidermis
- Dermis



The resistance occurs one after another 'in series'

$R_{total} = R_{vehicle} + R_{stratum\ corneum} + R_{epidermis} + R_{dermis}$

$$\text{Total Permeability} = \frac{1}{R_{\text{vehical}}} + \frac{1}{R_{\text{stratum corneum}}} + \frac{1}{R_{\text{epidermis}}} + \frac{1}{R_{\text{dermis}}}$$

Membrane-limited flux **(J)** under steady state condition is described by equation:

$$J = \frac{DKo/wC}{h} \qquad \text{Eq. 4}$$

Where,
J = Amount of drug passing through membrane system per unit area per unit time.
D = Diffusion coefficient within the membrane
h = Membrane thickness
K = Membrane / vehicle partition coefficient
C = Concentration gradient across the membrane

Basic Components of Transdermal Drug Delivery Systems

Transdermal patch may include the following components:

- Liner - Protects the patch during storage. The liner is removed prior to use.
- Drug - Drug solution in direct contact with release liner
- Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin
- Membrane - Controls the release of the drug from the reservoir and multi-layer patches

Polymer Matrix: [19]

Polymer is an integral and foremost important component of Transdermal Drug Delivery. Different classes of polymeric materials have been used to achieve rate controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer used in the manufacture of the device.
The following criteria should be satisfied for a polymer to be used in a transdermal system.

1. Molecular weight, glass transition temperature, chemical functionality of polymer must allow diffusion and release of the specific drug.
2. The polymer should permit the incorporation of a large amount of drug
3. The polymer should not react, physically or chemically with the drug.
4. The polymer should be easily manufactured and fabricated into the desired product and inexpensive.
5. The polymer must be stable and must not decompose in the presence of drug and other excipients used in the formulation, at high humidity conditions, or at body temperature.
6. Polymers and its degradation products must be non-toxic

No single material may have all these attributes; certain excipients may be incorporated to alter some properties. e.g., Cosolvents such as ethanol, propylene glycol, PEG 400 could be added to increase drug solubility.

Table No 1: Useful Polymers for Transdermal Devices

Natural polymers	Synthetic elastomers	Synthetic polymers
Cellulose derivatives Zein Gelatin Proteins Shellac Arabino Galactan Starch	Polybutadiene Hydrinrubber Polysiloxane Acrylonitrile Neoprene Chloroprene Silicone rubber	Polyvinyl alcohol Polyethylene PVC Polyacrylates Polyamide Acetal copolymer Polystyrene

Various techniques have been employed to modify the polymer properties and thus drug release rates [20].

1) **Cross-linked polymers:** The higher the degree of cross-linking, the more dense the polymer and slower the diffusion of drug molecules through the matrix.
2) **Polymer blends:** Polymers have been blended on varying ratios to combine the advantages of the individual polymers. Advantages of polymer blends include easy fabrication of devices, manipulation of drug loading and other devices properties such as hydration, degradation rate and mechanical strength.
3) **Plasticizers:** Plasticizers have been known to reduce the stiffness of the polymer backbone, thereby increasing the diffusion characteristics of the drug. Common used plasticizers are polyethylene glycol, propylene glycol, glycerol, dibutyl phthalate.

Drug Substance

Judicious choice of the drug plays an important role in the successful development of a transdermal product. Points to be considered for selection of a drug for TDD are as follows [12]:

- Daily systemic dose should be =20 mg
- Drug must have adequate lipophilicity. The log P should be in the range 1-3.
- Molecular Size if drug should be less than 500 Daltons.
- The drug should not be a direct irritant to the skin
- Melting point should be <200 ºC
- A saturated aqueous solution of the drug should have a pH value between 5 and 9.
- Hydrogen bonding groups should be less than 2.
- The drug should have short biological half-life.
- The drug should not stimulate an immune reaction to the skin.

Penetration Enhancers: These are the compounds, which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant and are considered as an integral part of most transdermal formulations [21].

To achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin **(***stratum* corneum**)** to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood [22-24]. They can modify the skin's barrier to penetration either by interacting with the formulation that applied or with the skin itself

Various criteria that ideal penetration enhancers must meet are:

- Ability to act specifically, reversibly and for predictable duration.
- Pharmacological inertness.
- Non-toxic, non-allergenic, non-irritating.
- Controlled and reverse enhancing action.
- Should not cause loss of body fluids, electrolytes or other endogeneous materials.
- Chemical and physical compatibility with drugs and other pharmaceutical excipients with which it is used.
- Following removal of the enhancer, the *stratum corneum* should immediately and fully recover its normal barrier property.
- Odourless, colorless and economical and cosmetically acceptable.

Other Excipients [25, 26]:

Class	Examples	Mechanism	Transport Pathway
Surfactant	Na-laurylsulfate Polyoxyethylene-9-laurylether **Bile salts**: Na-deoxycholate Na-glycocholate Na-taurocholate	Phospholipid acyl chain perturbation Reduction mucus viscosity Peptidase inhibition	Transcellular Paracellular
Fatty acids	Oleic acid	Phospholipid acyl chain perturbation	Transcellular
Cyclodextrins	α-, β- and γ cyclodextrins	Inclusion of membrane compounds	Transcellular Paracellular
Chelators	Methylated β-cyclodextrins EDTA	Complexation of Ca^{2+} Opening of tight junctions	Transcellular Paracellular
Positively charged polymers	Polyacrylates Chitosan salts	Ionic interactions	Paracellular

Patch Design and Technology [27]

There are two major types of transdermal delivery system **(**TDS**)** products:

- Thin flexible colored or nearly invisible matrix patches
- Flexible colored or transparent liquid or semisolid filled reservoir patches

Four Major Transdermal Systems [28]

There are four main types of transdermal patches:

1. **Single-layer Drug-in-Adhesive:** In this system the drug is included directly within the skin-contacting adhesive. In this type of patch the adhesive layer is responsible for the releasing of the drug, and serves to adhere the various layers together, along with the entire system to the skin. A temporary liner and a backing surround the adhesive layer.

2. **Multi-layer Drug-in-Adhesive**: The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. The multi-layer system adds another layer of drug-in-adhesive, usually separated by a membrane. This patch also has a temporary liner-layer and a permanent backing.

3. **Reservoir**: The Reservoir transdermal system design includes a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product can either be as a continuous layer between the membrane and the release liner or as a concentric configuration around the membrane.

4. **Matrix:** The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension, which is in direct contact with the release liner. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

Ideal Product Requirements

The product requirements for transdermal drug delivery are based on the biopharmaceutical product profile, physical attributes of the dosage form, consumer preference, and

compliance as it relates to easy use, medical rational, and minimization of adverse side effects and include the following[29]:

- Shelf life up to 2 years
- Small size patch **(**i.e., less than 40 cm^2**)**
- Convenient dose frequency **(**i.e., once a day to once a week**)**
- Cosmetically acceptable **(**i.e., clear, tan or white color**)**
- Simple packaging **(**i.e., minimum number of pouches and steps required to apply the system**)**
- Easy removal of the release liner **(**e.g., for children and elderly patients**)**
- Adequate skin adhesion **(**i.e., no falloff during the dosing interval and easy removal without skin trauma**)**
- No residue **(**i.e., "cold flow" around the edge of the patch in storage or after application to skin or beneath the patch after removal**)**
- No unacceptable dermal reactions **(**i.e., contact dermatitis, skin sensitization, phototoxicity, photosensitization, erythema, masceration, itching, stinging, burning, etc**)**
- Consistent biopharmaceutical performance **(**i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same individual over time**)**

All of these requirements are rarely ever achieved and acceptable balance must be met to ensure efficacy, safety and patient compliance.

New and Evolving Technologies for Transdermal Drug Delivery

1. **Iontophoresis**: Iontophoresis is an electrically facilitating methodology to deliver a precise dosage of drugs into the body through skin and control its plasma level in the circulation at the specific site to the required therapeutical level [30]. Iontophoresis enhances transdermal drug delivery by three mechanisms:

- The ion electrical field interaction provides the directional force, which drives ions through the skin.
- Flow of electric current increase the permeability of the skin.

Electrophoresis produces bulk motion of the solvent itself that carries ions or neutral species, with the solvent 'stems'.

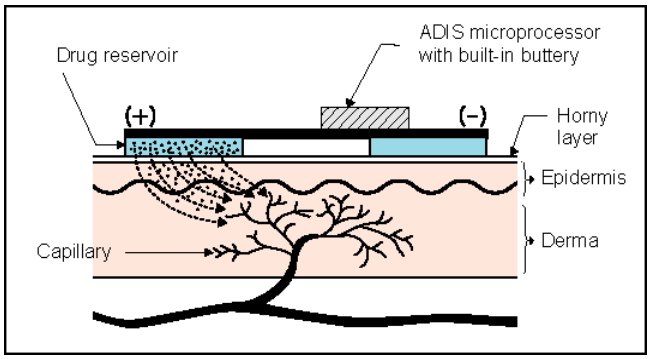


Figure No 1.2: Schematic expression of drug administration facilitated by iontophoresis

A number of factors influence the iontophoretic transport of drug.

(a) **The pH of the medium***:* As the ionization of the drugs is controlled by pH, transport is optimum in the pH range in which the drug is fully ionized although uncharged species can be carried by the electro osmotic solvent flow.

(b) **The nature** of the other ions in the formulation, which compete for transport of the current.

(c) **The current density***:* The drug flux is proportional to the current density, but the allowable density is limited by safety and patient tolerance to about 0.5 mA cm^{-2}.

(d) **Molecular weight:** Larger drug have lower transport number and so are delivered less effectively. As the drug size increases, the importance of ionic transport decreases and the drug becomes predominantly carried by the electro-osmotic solvent flow.

(e) **Concentration of drug in the delivery system***:* As the drug concentration at the donar site is increased, the flux across the skin increases.

(f) **Physiological variations:** A major advantage of iontophoresis is that relatively low level of variation is observed. This is probably due to the fact that the applied voltage is adjusted to achieve a specific current, and this will take amount of much variability between the subjects due to site, age and color of skin.

(g) **Wavelength of applied current:** A number of authors have studied the effect of using AC voltages instead of a steady DC voltage, which can reduce efficiency due to polarization of the skin.

Products have already reached the US market using iontophoresis. One example is Iomed's Iontocaine (Numby Stuff- Lidocaine HCL and epinephrine in the Phoresor iontophoresis system), which is marketed for local dermal analgesia. Similarly, Vyteris is awaiting approval for its iontophoretic system, which also delivers Lidocaine for dermal anesthesia in children. Several other companies have completed various stages of clinical iontophoresis studies, most notable among them being ALZA with its E-TRANS system using fentanyl for the management of post operative pain [8].

2. **Electroporation**: Electroporation is the creation of aqueous pores in the lipid bilayer by the application of short electrical pulses of approximately 100-1000 V/cm. Flux increases of upto 10,000 folds have been obtained for charged molecules. Electroporation may combine with iontophoresis to enhance the permeation of peptides such as vasopressin, LHRH, neurotensin and calcitonin[31].
Although DNA introduction is the most common use for electrophoresis, it has been used on isolated cells for introduction of enzyme, antibodies and viruses and more recently, tissue electroporation has begun to be explored, with potential application including enhanced cancer tumor chemotherapy, gene therapy and transdermal drug delivery.

3. Sonophoresis: Another technique beside electroporation attempting to overcome the challenges of transdermal drug

delivery involves the usage of high frequency waves. Conical microscopy indicates that cavitations occur in the keratinocytes of the stratum corneum upon ultrasound exposure. Recent studies have shown that ultrasound can increase up to 5,000 times the ability of protein the size of insulin to penetrate the skin. Using a transdermal patch design in conjunction with ultrasound may provide an improved method for Insulin delivery [32].

4. Microfabrication technology: The microfabricated microneedles technology employs micron-sized needles made from silicon. These microneedle arrays after insertion into the skin create conduits for transport of drug across the stratum corneum. Removal of the device after ten seconds increases skin permeability by a factor of 10,000 and after one hour, permeability increases 25,000-fold. Current technologies have combined these needles with pressurized reservoirs, creating a transdermal insulin pump. The incorporation of microprobes (biosensors), channels, and further modification of needle dimension will allow for more optimal, self-regulating insulin delivery platforms [33].

5. Heat-enhanced transdermal delivery: Heat is expected to enhance the transdermal delivery of various drugs by increasing skin permeability, body fluid circulation, blood vessel wall permeability, rate-limiting membrane permeability, and drug solubility. According to Kligman, diffusion through the skin, as elsewhere, is a temperature-dependent process, so raising the skin temperature should add thermodynamic drive. Heat is known to increase the kinetic energy of the drug molecules and the proteins, lipids, and carbohydrates in the cell membrane. Heating prior to or during topical application of a drug will dilate penetration pathways in the skin, increase kinetic energy and the movement of particles in the treated area, and facilitate drug absorption. Heating the skin after the topical application of a drug will increase drug absorption into the vascular network, enhancing the systemic delivery but decreasing the local delivery as the drug molecules are carried away from the local delivery site [34].

6. Vesicular approaches: The encapsulation of drug in lipid vesicles prepared from phospholipids and nonionic surfactant is used for transport of drug into and across the skin. The rationale for use of lipid vesicles as a topical drug carrier is as follows

- Vesicles serve as a rate-limiting barrier for absorption of drug.
- Because of the amphiphillic nature of the vesicles, these vesicles may serve as non-toxic penetration enhancers for drugs.
- They may serve as "organic solvent" for the solubilization of poorly soluble drugs.
- Vesicles can incorporate both hydrophilic and lipophilic drugs [34].

7. Transferosomes: Transferosomes are self optimized aggregates, with the ultra flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the stratum corneum. They can deform and pass through narrow constriction without measurable loss. This high deformability gives better penetration of intact vesicles [32].

8. Supersaturation: A thermodynamic option for increasing drug flux across the skin is the use of supersaturated solutions. In this approach saturated solutions of drug in miscible cosolvent mixtures of different compositions are combined to create a resulting formulation in which the drug is present at n-fold its saturation concentration. With such systems it has been shown that drug flux can be increased proportionately over that achievable using a simply saturated solution [28].

9. Dispenser for transdermal patches: 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 patient's needs [35][5].

10. Microstructured Transdermal Systems (MTS*):* Microstructured Transdermal Systems enables the disruption of the outermost layer of the skin, the stratum corneum, without causing pain. MTS expands the range of drugs that can be delivered transdermally and potentially reduces variation in transdermal drug delivery caused by different skin types and application sites. It is suited for vaccines, protein or peptide based drugs [35, 36].

Recent research and development efforts have been channelized into the development of new high technology based analytical probes. Electron microscopy is used for quantitative ultrastructural studies in the skin, and to detect many changes in the various layers and organelles of the skin after treatment with a penetration enhancer.

ATR-FTIR is a powerful in-vivo technique for studying the biophysics of skin functions. Thermal analysis techniques such as DTA and DSC are used to investigate the physical properties of stratum corneum and the measurement of lipid and protein thermodynamic behavior in model and biological membranes.

New market opportunities:

Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive patches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. It promises to eliminate needles for administration of a wide variety of drugs in the future.

Clearly, the opportunities for transdermal drug delivery have been greatly expanded through the application of new

technologies. Now, a much wider set of drug compounds, including macromolecules, may be delivered transdermally at greater therapeutic levels that were possible just a decade ago.

A closer look at transdermal technology seems especially timely today, considering the prospect of impending patent expirations, a drought of new drugs in the pipeline, increasing costs of development of new chemical entities, an increasing aggressive generics industry, and pressures for cost effective therapies that promote a higher level of efficacy and compliance.

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