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TRANSDERMAL DRUG DELIVERY SYSTEM-A NOVEL DRUG DELIVERY SYSTEM AND ITS MARKET SCOPE AND OPPORTUNITIES

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ABSTRACT

As a substitute for the oral route Transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pit falls of enzymatic and pH associated deactivation. Transdermal delivery has many advantages over conventional modes of drug administrations, it thus avoids hepatic first pass metabolism and improves patient compliance. This approach of drug delivery is more permanent in case chronic disorders like hypertension which requires long term dosing to maintain therapeutic drug concentration. These systems are easy to apply and remove as when desired. In Intensive research has shown that Transdermal route is a potential mode of delivery of lipophilic drugs in systemic circulation. The market for Transdermal devices is currently estimated at US$ 1.2 billion, approximately 10% of the entire US $ 28 billion drug delivery market. In addition, Transdermal drug delivery market is currently based on only 10 drugs. Hence, Pharmaceutical scientists are striving to add new deliverables to the short list of approved Transdermal products. This proposed method also allows for reduce therapeutic dosaging due to the shortened metabolization pathway of the Transdermal route versus the gastrointestinal pathway. The main aim and objective of Transdermal drug delivery system are topical administered medicaments in the form of patches that deliver drugs for systemic effect at a predetermined and controlled rate. Transdermal systems deliver drugs direct through the skin. Worldwide market revenues for transdermal drug delivery systems are at US$3 billion with the growth rate expected to increase 12% annually through 2007. The market value for transdermal delivery was $12.7 billion in 2005 and it is expected to increase to $21.5 billion in the year 2010 and $31.5 billion in the year 2015.

INTRODUCTION

This report deals with transdermal drug delivery - an approach used to deliver drugs through the skin for therapeutic use as an alternative to oral, intravascular, subcutaneous and transmucosal routes. Various transdermal drug delivery technologies are described including the use of suitable formulations, carriers and penetration enhancers. The most commonly used transdermal system is the skin patch using various types of technologies. Nanoparticles as well as the use of physicalagents to facilitate transcutaneous drug delivery are described. Micro needle and needleless technologies are also described. Transdermal technologies may be applied for several categories of pharmaceuticals used for the treatment of disorders of the skin or for systemic effect to treat diseases of other organs. Several transdermal products and applications include hormonereplacement therapy, management of pain, angina pectoris, smoking cessation and

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neurological disorders such as Parkinson's disease. The market for transdermal drug delivery is analyzed according to technologies and therapeutic areas from 2008 to 2018.Transdermal delivery has many advantages over conventional modes of drug administration; it thus avoids hepatic first pass metabolism and improves patient compliance. Intensive research has shown that transdermal route is a potential mode of delivery of lipophilic drugs in systemic circulation. Matrix-based transdermal formulations have been developed for a number of drugs such as nitroglycerin , ephedrine, ketoprofen , propranolol and estradiolThe past few years have witnessed great development in the novel or new drug delivery systems (NDDS). The introduction of (NDDS) technologies in Pharmaceutical industry has markedly enhanced the treatment regimens and improved the therapeutic systems, in general. However, such technologies presented new challenges to academics, researchers in Pharmaceutical industry and the regulatory authorities. Drug are active substances which bind with the receptors usually located deep within the body – (to particular cells or tissues) to alter the unwanted physiological Process that create disease. Sometimes the scientists come across the right chemical or natural Product that can bind to the receptor and control an unwanted physiological process in insolated tissue or cells but fail to reach the target tissue in adequate quantity when administered in a functioning living systems. Novel drug delivery is a vital research area which strive to solve this problem and aim to achieve a programmed delivery of the therapeutic substances for the optimal beneficial effects while avoiding the side effect of drugs. Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth. Patients often forget to take their medicine, and eventhe most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate theGI irritation that frequently occurs and avoid partial first-pass inactivation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood levelspikes and troughs produced by oral dosage forms. These advantages are offered by the currently marketedtransdermal products. One of the most successful, the nicotine patch, releases nicotine over sixteen hours, continuously suppressing the smoker's craving for a cigarette. The scopolamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically. The fentanyl patch acts for seventy-two hours, providing long-lasting pain relief. And an

Estrogen–progestin contraceptive patch needs to be applied only once a week, a boon for women who find it onerous totake one pill every day. The transdermal route is indeed desirable, but there is one small obstacle: whereas the function of the GI tract is to render ingested material suitable for absorption, the skin's function is to keep things out of the body. The major barrier within the skin is the stratum corneum, the top layer of the epidermis. The stratum corneum consists of keratinized, flattened remnants of once actively dividing epidermal cells). Hygroscopic, but impermeable to water, it behaves as a tough, flexible membrane. 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 Da), lipophilicity, and effectiveness at low dosage. The largest daily dose of drug in patch form is that of nicotine: twenty-one

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milligrams .Transdermal absorption occurs through a slow process of diffusion driven by the gradient 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).Transdermal delivery is an attractive method to deliver drugs or biological compounds into human body, for its distinct advantage of eliminating pain and inconvenient intravenous injections. However, the efficiency of transdermal delivery is greatly limited by the poor permeability of the hard layer of skin at the stratumcorneum which is the outmost layer of skin that forms theprimary transport barrier. The rate of diffusion also depends in part on the size and hydrophilicity of the drug molecules. So far, a number of chemical enhancers, electroporation, physical enhancers have been proposed to promote the transdermal drug delivery . As one of the enhancers, the micro needle array devices have been well developed for controlled transdermal drug delivery in a minimum invasion and convenient manner. Themicroneedles are used to penetrate the stratum corneum and generate pathways or micro channels, so to delivery drugs into the epidermis layer. No pain is induced as the needles do not reach the nerves in deep dermis. The systemic treatment of disease via transdermal route is not a recent innovation. But, in the last two decades, transdermal drug delivery has gained increasing interest. So, transdermal controlled drug delivery systems have been investigated or developed in order either to avoid hepatic first-pass effect improving drugs bioavailability or to decrease the dosing frequency required for oral treatment. However, at present, marketed transdermal drug delivery patches are available only for a few drugs. Most investigated drugs don't cross the skin in adequate amount to produce the therapeutic effect. Formulation of transdermal therapeutic system(TTS) involves optimization of several factors such as release rate, stability, safety, convenience of use,etc. The key component in a TTS, which monitors therelease of an active ingredient, is the rate controlling polymeric membrane. The polymer should possess good film forming properties, should be non-irritating, inert, and stable. Hence, selection of polymer is a challenging task because of the inherent diversity of structures and requires a thorough understanding ofthe surface and bulk properties of the polymer that cangive the desired chemical, interfacial, mechanical and biological functions. Though several polymers are alreadyin use, a constant research is on, to explore newpolymers for the TTS utility. Such an approach towardsestablishing new polymers is necessary, as notall the existing polymers possess all the ideal qualities. One of the major disadvantages of transdermaldrug-delivery system as compared to other controlledrelease formulations is its high cost. A major percentage of formulation cost is due to the utility of expensive synthetic polymers. Hence, several less expensive natural and semi synthetic polymers have been evaluated for their suitability for TTS.Transdermal patches are innovative drug delivery systems intended for skin application in view of achieving asystemic effect. Among the different types of systems, the drug-in-adhesive products, in which the drug is included in the adhesive layer contacting the skin, are very commonly used, being thin, conformable and comfortable. More and more efficient systems are introduced into the market, with the advantage of reducing the size ofthe patch to the size of a stamp. The development of transdermal drug delivery systems isa multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of a drug molecule to the demonstration of sufficient drug flux in an ex vivo and/or in vivo model the fabrication of a drug delivery system that meets all the stringent needs that are

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specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale-up and manufacturability),and most important, the economy.

APPROACHES OF TRANSDERMAL DRUG DELIVERY SYSTEM

Drug delivery technologies are now receiving considerable attention from pharmaceutical companies. The main purpose of developing alternative drug delivery technologies is to increase efficiency and safety of drug delivery and provide more convenience for the patient. Substantial research conducted during the past several years has lead to the development of technologies that meet the requisite criteria for delivering the drug through a non-invasive route. One of such technologies is transdermal drug delivery.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. Medication delivery is carried out by a patch that is attached to the body surface. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It is also called skin patch. 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. The first transdermal patch was approved by the FDA in 1979. It was a patch for the treatment of motion sickness. 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), aroma patches, and patches that measure sunlight exposure.

Role of adhesion in drug delivery

Transdermal drug delivery systems (TDDS), also known as ‘‘patches,’’ are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin.

Several TDDS containing drugs such as clonidine, estradiol, fentanyl, nicotine, nitroglycerin, oxybutynin and scopoloamine are available in the United States. In the Drug Quality Reporting System (DQRS), the United States Food and Drug Administration (FDA) has received numerous reports of ‘‘adhesion lacking’’ for transdermaldrug delivery systems The adhesive of the TDDS is critical to the safety, efficacy and quality of the product. To begin with, the therapeutic effect of the drug is linked to the adhesive performance of the TDDS. Reduction in the surface area of contact as a result of patch lift, or even the patch falling off, diminishes the delivery of drug from the patch. In other words, poor adhesion results in improper dosing of patients. Secondly, patches that fail to adhere for their prescribed time period must be replaced more often, thereby increasing the patient’s cost. Thirdly, lack of adhesion is a safety issue. There is potential accidental dosing of children who may pick up fallen patches. Death and other serious medical problems have occurred when accidentally exposed to certain patches

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(e.g. transfer of a patch from an adult to a child while hugging, accidentally sitting or lying on a patch) . Many prescribing information sheets forTDDS state that adhesion has not been studied. This article provides an overview of the significance of the adhesive in a transdermal drug delivery system and the necessity for adhesion testing. Adhesion or the lack of adhesion of transdermal systems to the skin is a critical factor directly related to drug delivery and therapeutic effect. Since the drug absorption processes related to the drug partition between the TDDSand the skin and the drug permeation process, completes kin contact over the entire delivery surface for the entire label application period is essential. If the TDDS lifts or partially detaches, the effective area of TDDS/skin contact, and thus the drug absorption, changes in an unpredictable manner. Therapeutic failure can then occur. Only a constantTDDS/skin contact over the whole application period allows a consistent delivery and absorption of the drug. In other words, the quality of contact between patch and skin is directly reflected in the consistency of drugdelivery.Absorption of drug through the skin is affected by a number of factors such as skin sites, skin thickness, skin temperature, body temperature, blood flow, lipid concentration, number of hair follicles, skin cleansing, hydration status, sweat gland function, ethnic group, pH of skin surface and the state and integrity of the stratum corneum. Occlusion can change the hydration and temperature of the skin . Average skin thickness varies as a function of age, gender and race. For thinner skin, serum drug concentrations may increase. Also, if a TDDSis applied to compromised skin, serum drug concentrations may increase. Aged skin has lower moisture content and is less elastic, while younger skin is more hydrated and consequently more elastic .For an adhesive to adhere to a substrate, a fundamental thermodynamic requirement has to be satisfied: the measured surface energy of the adhesive must be equal to or less than that of the adherend (e.g. human skin). Ginnet al. reported that the surface energy of clean, dryhuman skin is about 27 dyn/cm and that this value increased when the surface energy was measured on dirty or unwashed skin. Wet or unclean skin may be thought of as being more hydrophilic (having higher surface energy)and clean and dry skin as mostly lipophilic (lower surface energy). Kenney et al. showed that the surface energy of in vivo human skin increases with humidity and temperature.Therefore, the surface energy of the TDDS should be less than the lowest critical surface energy value reported for the skin (27 dyn/cm). This is a necessary but not sufficient condition for adhesion. The other requirements for combination of adhesive and cohesive failure. Failures other than Case I may be considered as a sign of a flawedtransdermal drug delivery system. Based on the type of failure mode, it may be possible to identify potential causes ofthe failure.

Advantages and disadvantages of transdermal drug delivery

Transdermal drug delivery systems offer several important advantages over more traditional approaches, including:

- longer duration of action resulting in a reduction in dosing frequency
- Increased convenience to administer drugs which would otherwise require frequent dosing
- improved bioavailability
- more uniform plasma levels
- reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval
- flexibility of terminating the drug administration by simply removing the patch from the skin

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- Improved patient compliance and comfort via non-invasive, painless and simple application

Some of the greatest disadvantages to transdermal drug delivery are:

- possibility that a local irritation at the site of application
- Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation

The main components of a transdermal patch are:

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
- Backing - Protects the patch from the outer environment .

Types of transdermal patches

There are four main types of transdermal patches:

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. The adhesive layer is surrounded by a temporary liner and a backing.

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.

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.

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.

THE FUTURE OF TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery is theoretically ideal for many injected and orally delivered drugs, but many drugs cannot pass through the skin because of skin's low permeability. Pharmaceutical companies develop new adhesives, molecular absorption enhancers, and penetration enhancers that will enhance skin permeability and thus greatly expand the range of drugs that can be delivered transdermally.Two of the better-known technologies that can help achieve significant skin permeation enhancement are iontophoresis and phonophoresis (sonophoresis). Iontophoresis involves passing a direct electrical current between two electrodes on the skin surface. Phonophoresis uses ultrasonic frequencies to help transfer high molecular weight drugs through the skin.A newer and potentially

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more promising technology is micro needle-enhanced delivery. These systems use an array of tiny needle-like structures to open pores in the stratum corneum and facilitate drug transport. The structures are small enough that they do not reach the nerve endings, so there is no sensation of pain. These systems have been reported to greatly enhance (up to 100,000 fold) the permeation of macromolecules through skin.The primary function of human skin is to act as a protective barrier and as such, it does impose physicochemical limitations to the type of permeate that can transverse it's highly stratified structure. It is generally accepted that for a drug to be delivered passively via the skin it needs to have adequate lipophilicity and also a molecular weight < 500 Da. The US Food and Drug Administration (FDA) approved the first transdermal 'patch' products in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of motion sickness (Transderm-Scop®, ALZA Corp.) and nitroglycerine for the prevention of angina pectoris associated with coronary artery disease (Transderm-Nitro®). Until the commercial success of these products, it was still perceived too difficult for an active molecule to overcome the barrier properties of human skin and penetrate into the blood system at adequate quantities to elicit a therapeutic effect. However, the obvious benefits of transdermal drug delivery compared to more conventional, oral or parenteral drug delivery soon became apparent. The avoidance of hepatic first-pass metabolism, improved patient compliance and ease of access to the absorbing membrane, i.e. the skin.. all helped to open the way for a wide range of effective transdermal products As such, over the last two decades more than 35 transdermal products have been approved generating a multibillion dollar market. This rapid increase in market value has lead to transdermal drug delivery becoming one of the fastest growing sectors within the pharmaceutical industry.

There are three traditional designs for transdermal patches as described below::

• **Adhesive systems**

– simplest, consist of a drug containing adhesive with a backing layer

– degree of control often small

– no rate controlling membrane,

– adhesive controls drug release

• **Matrix or layered systems**

– more complex, different polymer compositions to provide drug containing matrix and adhesive

– often no rate controlling membrane

– Matrix may control drug release

• **Reservoir system**

– comprises

(i) an enclosed reservoir of drug (solution or suspension),

(ii) a polymeric rate controlling membrane

All present common surfaces and hold an excessive payload of drug within a patch to ensure that the drug is absorbed systemically at a rate sufficient for a sustained pharmacological effect. This often means that over 95% of the drug payload is still remaining when the patch is removed.

Basic Components of Transdermal Drug Delivery Systems

The components of transdermal devices include:

1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Other excipients

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1.Polymer Matrix

The Polymer controls the release of the drug from the device.
Possible useful polymers for transdermal devices are:

a) Natural Polymers:
e.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers:
e.g. Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c) Synthetic Polymers:
e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

2.Drug

For successfully developing a transdermal drug delivery system,the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 daltons.

2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.

3. The drug should have low melting point.

Along with these propertiesthe drug should be potent, having short half life and be non irritating.

3.Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant.

These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide ; pyrrolidones – 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

b) Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs.The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.

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Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
Bile Salts: e.g. Sodium ms taurocholate, Sodium deoxycholate,
Sodium tauroglycocholate.
Biary system: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways.e.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

c) Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents.

Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.

4.Other Excipients

a) Adhesives:
The fastening of all transdermal devices to the skin has so far been done byusing a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesivesystems should fulfill the following criteria

(i)Should adhere to the skin aggressively, should be easily removed.
(ii)Should not leave an unwashable residue on the skin.
(iii) Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria.

(i)Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
(ii) Permeation of drug should not be affected.
(iii) The delivery of simple or blended permeation enhancers should not be affected.

b) Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

RECENT TRENDS OF SCOPE AND OPPORTUNITIES MARKETED TRANSDERMAL DRUGS

These developments have led to a vastly increased market potential. The U.S. market for transdermal products was $5.7 billion in 2006, and is forecast to grow to almost $8 billion by 2010. Some market analysts predict that the global market could reach as high as $32 billion by 2015.In addition to new technology, another factor driving the upward market trend is the fact that the development time and cost for transdermal products is significantly less than that of conventional drugs. Average R&D for a typical drug is $500 million over 15 years, while for a transdermal drug development time is roughly 4-8 years and costs $10 million to $15 million. This has attracted a large

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number of specialty pharmaceutical companies to the field, which have chosen to create niches in transdermal delivery rather than pure. generics. Transdermal delivery offers compelling opportunities to improve vaccine administration. Although vaccines are typically macromolecules, viral particles, or other large supramolecular constructs, their small (microgram) doses facilitate the possibility of transdermal delivery. Vaccine delivery via the skin is even more attractive because it targets the potent epidermal Langerhans and dermal dendritic cells that may generate a strong immune response at much lower doses than deeper injection[7]. The most successful vaccine of all time—the smallpox vaccine, which eradicated the disease worldwide—was administered via the skin with the aid of a small needle device to breach the stratum corneum barrier. Although effective, this approach does not provide good control over delivery, which has motivated development of new delivery methods. Elimination of the need for hypodermic needles further motivates transdermal vaccine development. In a world where needle reuse kills at least 1.3 million people per year from hepatitis B and AIDS[5], needle-free, patch-based vaccination could have large impact. In addition, the possibility of administering vaccine patches by minimally trained personnel or patients themselves could not only facilitate compliance with routine, seasonal and pandemic vaccination needs, but could also expedite vaccination campaigns in developing countries where medical personnel are in short supply. Effective vaccination via the skin may be achieved by increasing skin permeability to the vaccine using the methods discussed in this review. Some of the physical enhancement methods have been shown to have additional adjuvant effects that increase immune response further The immune response can also be heightened by adding chemical adjuvants.

Table-1

Transdermal drugs approved by the US FDA.

Approval year	Drug	Indication	Product Name	Marketing company
1979	Scopolamine	Motion sickness	Transderm-Scop	Novartis Consumer Health (Parsippany, NJ)
1981	Nitroglycerin	Angina pectoris	Transderm-Nitro	Novartis (East Hannover, NJ)
1984	Clonidine	Hypertension	Catapres-TTS	Boehringer Ingelheim (Ridgefield, CT)
1986	Estradiol	Menopausal symptoms	Estraderm	Novartis (East Hannover, NJ)
1990	Fentanyl	Chronic pain	Duragesic	Janssen Pharmaceutica (Titusville,

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Approval year	Drug	Indication	Product Name	Marketing company
				NJ)
1991	nicotine	Smoking cessation	Nicoderm, Habitrol, ProStep	GlaxoSmithKline (Philadelphia, PA), Novartis Consumer Health (Parsippany, NJ) Elan (Gainesville, GA)
1993	Testosterone	Testosterone deficiency	Testoderm	Alza, Mountain View, CA
1995	Lidocaine/epinephrine (iontophoresis)	Local dermal analgesia	Iontocaine	Iomed (Salt Lake City, UT)
1998	Estradiol/norethidrone	Menopausal symptoms	Combipatch	Novartis (East Hannover, NJ)
1999	Lidocaine	Post-herpetic neuralgia pain	Lidoderm	Endo Pharmaceuticals (Chadds Ford, PA)
2001	Ethinyl estradiol/norelgestromin	Contraception	Ortho Evra	Ortho-McNeil Pharmaceutical (Raritan, NJ)
2003	Estradiol/levonorgestrel	Menopausal symptoms	Climara Pro	Bayer Healthcare Pharmaceuticals (Wayne, NJ)
2003	Oxybutynin	Overactive bladder	Oxytrol	Watson Pharma (Corona, CA)
2004	Lidocaine (ultrasound)	Local dermal anesthesia	SonoPrep	Echo Therapeutics (Franklin, MA)
2005	Lidocaine/tetracaine	Local dermal analgesia	Synera	Endo Pharmaceuticals (Chadds Ford, PA)
2006	Fentanyl HCl (iontophoresis)	Acute postoperative pain	Ionsys	Alza, Mountain View, CA
2006	Methylphenidate	Attention deficit hyperactivity disorder	Daytrana	Shire (Wayne, PA)
2006	Selegiline	Major depressive	Emsam	Bristol-Myers Squibb (Princeton,

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Approval year	Drug	Indication	Product Name	Marketing company
		disorder		NJ)
2007	Rotigotine	Parkinson's disease	Neupro	Schwarz Pharma (Mequon, WI)
2007	Rivastigmine	Dementia	Exelon	Novartis (East Hannover, NJ)

Table-2
Representative transdermal drugs in clinical development

Drug	Company	Indication	Clinical phase	Delivery technology
AB-1001	Abeille	Nausea and vomiting	Phase 3	Passive
acyclovir	Transport	Herpes labialis	Phase 2	Iontophoresis
buprenorphine	Purdue Pharma	Pain	Phase 3*	Passive
fertility hormone	Vyteris / Ferring	Female infertility	Phase 1	Iontophoresis
granisetron	Prostrakan	Nausea and vomiting	Pre-registration	Passive
heat-labile enterotoxin of *E. coli*.	Iomai	Travelers' diarrhea	Phase 2	Skin abrasion
human growth hormone	TransPharma / Teva	Growth hormone deficiency	Phase 1	Thermal ablation
influenza vaccine	Becton Dickinson / Sanofi-Pasteur	Influenza prophylaxis	Pre-registration	Microneedles
insulin	Altea	Diabetes mellitus	Phase 1	Thermal ablation
insulin	Phosphagenics	Diabetes mellitus	Phase 2	Vesicular carrier
ketoprofen	ZARS	Osteoarthritis	Phase 3	Heat enhancement
parathyroid hormone (1–34)	Zosano	Osteoporosis	Phase 2	Microneedles

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Drug	Company	Indication	Clinical phase	Delivery technology
sufentanil	Durect / Endo	Chronic pain	Phase 2	Passive
testosterone	Acrux / VIVUS	Female sexual dysfunction	Phase 2	Metered dose transdermal spray
testosterone	MacroChem	Male hypogonadism	Phase 2	Chemical enhancer (SEPA)
testosterone	Procter & Gamble / Watson	Hypoactive sexual desire disorder	Pre-registration*	Passive
triamcinolone acetonide	Echo Therapeutics	Dermatoses	Pre-registration	Chemical enhancer (AzoneTS)

RECENT ASPECT OF TRANDERMAL DRUG DELIVERY SYSTEM

Transdermal delivery of therapeutic agents has been used successfully for several decades. Transdermal systems for hormone replacement therapy, smoking cessation, and pain management are well accepted; however, there have been challenges in expanding use of the technology to the delivery of peptides, proteins, and other macromolecules. Throughout the past 2 decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Because transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. In addition, because transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing, it is generally accepted that they offer improved patient compliance .Transdermal delivery of medications to veterinary patients is becoming increasingly popular. An effective, non-invasive method of medicating animals is welcomed by veterinarians and owners alike. Advances in molecular biology have given us a wide range of protein and peptide-based drugs that are unsuitable for oral delivery because of their high degree of first-pass metabolism. Though parenteral delivery is the obvious answer, for the successful development of commercial chronic and self-administration usage formulations it is not the ideal choice. Transdermal delivery is emerging as the biggest application target for these agents, however, the skin is extremely efficient at keeping out such large molecular weight compounds and therapeutic levels are never going to be realistically achieved by passive absorption. The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. While it is true that product approvals for new Transdermal drug delivery products have not exploded as some predicted following the rapid success of Transdermal drug delivery nicotine products in the early and mid 90s, an increasing number of Transdermal drug delivery products continue to deliver real therapeutic benefit to patients around the world. The outlook for continued growth of the Transdermal drug delivery market is very optimistic.

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Market analysts forecast a low double-digit compound annual growth rate for the US Transdermal drug delivery market throughout the next decade. Given the recent trend and product pipeline, this may actually under predict the potential of the Transdermal drug delivery market throughout this time period .

Clinical Issues of Transdermal Delivery

Transdermal preparations for nicotine replacement therapy, treatment of incontinence, hormone replacement therapy, and oral contraceptives are commonly prescribed by the obstetrician-gynecologist. Following a brief review of issues relating to the use of the nicotine patch and oxybutynin, we will focus on the hormone replacement therapy and oral contraceptives to illustrate key concepts about the strengths and disadvantages of transdermal delivery. One key focus will be direct head-to-head comparisons of the pharmacodynamic effects of oral and transdermal preparations in hormone replacement therapy. Oral and transdermal preparations can have different metabolic effects that have relevance to some patients with certain risk factors. Surprisingly, no head-to-head studies of oral and transdermal contraceptives that report on pharmacodynamic endpoints (such as lipid profile, insulin sensitivity, and procoagulation factors) were identified. Head-to-head data on oral versus transdermal contraceptives are limited to efficacy and compliance rates. For a review of hormone replacement therapy and oral contraceptives in general, the reader is referred to a recent review by Godsland.

Nicotine Replacement Therapy

Absorption of nicotine is poor via the gastrointestinal tract but good via the respiratory tract, buccal membranes, and skin. Consequently, several delivery methods exploiting these routes (inhalers, nasal sprays, gums, and patches) have been developed for the delivery of nicotine for replacement therapy. The rapid uptake of nicotine and its immediate effect on mood and cognition are primary factors in the development of a nicotine addiction. Smoking delivers a rapid bolus dose of nicotine, reaching the brain within 10-20 seconds. The half-life of nicotine is 2 hours. In general, mean peak plasma concentrations with nicotine replacement therapies are about 50% lower than those achieved with smoking, perhaps explaining their limited efficacy. The primary benefit of nicotine patches is enhanced compliance relative to other routes of delivery. Other methods, such as inhalers, may provide a psychological benefit by mimicking the behavioral/psychological aspects of smoking (eg, puffing) but at the cost of local adverse effects (eg, throat irritation, coughing). Regardless of method used, long-term success rates are modest. For example, a randomized, controlled trial of gum, patch, spray, and inhaler therapies demonstrated comparable 12-week abstinence rates of 20-24% for all 4 approaches. Success can be enhanced, however, by combining pharmacologic and/or behavioral approaches.

Treatment of Incontinence

Overactive bladder affects approximately 17% of the U.S. population, but women tend to have a disproportionately higher prevalence of urge incontinence. Oxybutynin is an oral daily medication commonly used to treat overactive bladder. First-pass metabolism of oxybutynin results in desethyloxybutynin, which is thought to be the primary mediator of the anticholinergic adverse effects (such as dry mouth) associated with oxybutynin. Transdermal oxybutynin is dosed twice weekly and results in much lower concentrations of this metabolite. Clinical studies suggest that the incidence of dry mouth is lower with transdermal oxybutynin (38%) than with immediate-release oxybutynin (94%, $P < .001$).Thus, transdermal

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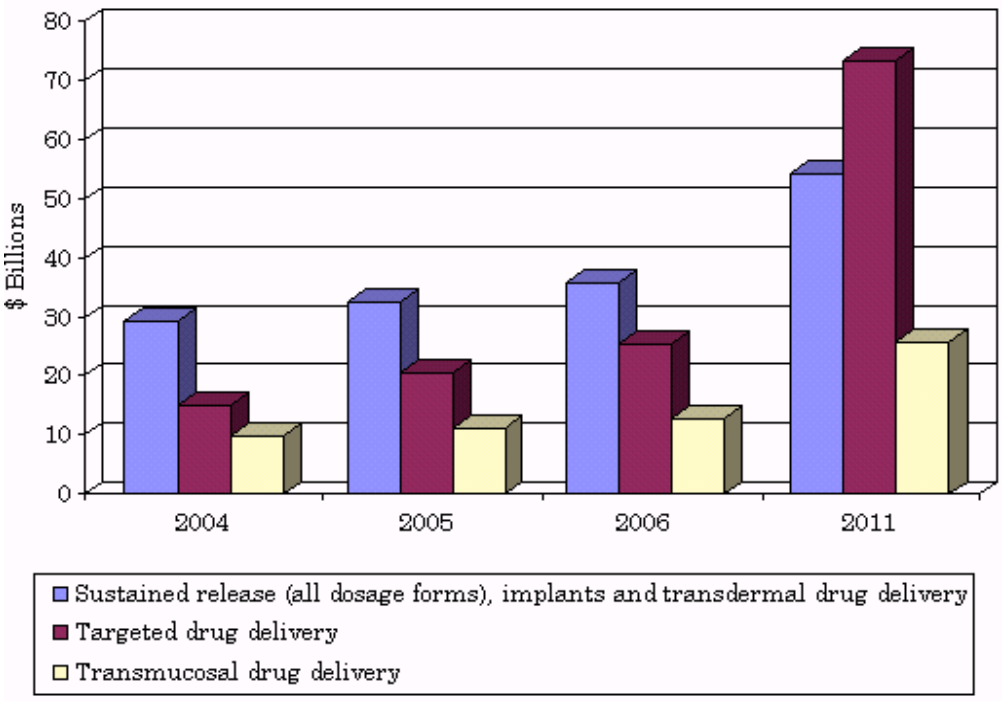
delivery leads to lower concentration of metabolites and fewer adverse effects than oral delivery.

Hormone Replacement Therapy

Transdermal hormone replacement therapy enhances compliance. Cano studied 331 postmenopausal women treated in an academic center with oral or transdermal hormone replacement therapy. Good compliance was obtained in 58% of women taking an oral estrogen and 53% of patients taking an oral estrogen plus a progestin. In contrast, in women taking transdermal estrogen or transdermal estrogen plus an oral progestin, good compliance was obtained in 88% and 75% of patients, respectively. Two factors associated with lack of compliance were oral route of administration ($P < .01$) and the inclusion of progestins in the regimen ($P < .02$).

MARKETED TRANSDERMAL DRUGS

The U.S. sales of advanced drug delivery systems were over $54.2 billion in 2004. In 2005 they reached $64.1 billion and will eventually grow to $74.4 billion by the end of 2006. Over 5 years, this market will continue to grow at an average annual growth rate (AAGR) of 15.6% to reach $153.5 billion by 2011.The largest sector of the market consists of sustained release/implants/transdermal drug delivery systems, with more than 50% of the total U.S. market in 2005. Through the forecast period this sector will gradually give way to targeted drug delivery systems, which should control almost 48% of the market in 2011.



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The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally. The FDA approved a total of 35 transdermal products over the past 20 years, the majority of which use passive transport that allows the drug to be continually absorbed into the skin via natural processes. Delivery of scopolamine, nicotine, estrogen, and fentanyl made up the bulk of sales, and the industry steered clear of what they considered to be extremely limited market potential with other drugs. In recent years, however, great strides have been made in the application of "active transport" to assist and regulate the movement of drug molecules across the skin membrane. This opened up the field to a much wider range of drugs, such as those with high molecular weights or those requiring blood levels to be controlled. Penetration enhancers, microporation, electroporation, iontophoresis, and ultrasound are some of the methods currently being employed. New materials and advances in polymer technology have also paved the way for innovative new products. Improvements in solubility and diffusion, better adhesive polymers, the integration of hydrogels, enzyme films and biosensors have led to smaller patches, improved wear, and even products with diagnostic and monitoring capabilities. In spite of intensive research on transdermal drug delivery systems (TDDSs), only four--nitroglycerin, clonidine, estradiol, and scopolamine--have reached the market, and the clinical effectiveness of these systems has yet to be clearly demonstrated. Ideally, a candidate for transdermal drug delivery should demonstrate clinical significance within a wide therapeutic range for a well-documented indication for use. Continuous administration of a drug should result in better control of the disease with fewer side effects and a marked increase in patient compliance than when traditional dosage forms are used. It appears that nitroglycerin is a poor candidate for transdermal drug delivery by virtue of the ambiguity associated with its clinical pharmacology, substantial interpatient variation in dose-response relationship, and development of tolerance with potential toxicity risks in chronic administration. Clonidine's well-defined indication for use coupled with its high potency and low molecular weight with high lipid solubility is well suited to transdermal therapy. Because estradiol is unsuitable for use in people who smoke and has dermatologic potential, it is a marginal candidate for use in TDDSs. Transdermal scopolamine was not reviewed because it is a unique entity (no conventional dosage forms of this product are available) intended for short-term use. Its use is dictated more by the patient's unique circumstances, such as travel requirements, than by physiological condition. Although TDDSs provide a convenient and effective means of administering medications, the aforementioned clinical constraints need to be evaluated in depth before more widespread application of TDDSs can be recommended.

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Table-3

Different drugs which are administered by this route and the common names by which they are marketed

Product name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/Norethindrone	Noven , Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome

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Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Transderm Scop	Scopolamine	Alza/Norvatis	Motion sickness
Transderm Nitro	Nitroglycerin	Alza/Norvatis	Angina pectoris
Vivelle	Estradiol	Noven Pharmaceuticals/Norvatis	Postmenstrual syndrome

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CONCLUSION

Transdermal delivery of a drug product which is currently approved as oral dosage form, allows for the avoidance of first pass metabolism by the liver and the delivery of a more even level of the therapeutic agent over the course of 24 hours. Dermal patches are the most common form of transdermal delivery of drugs.Transdermal drug delivery provides excellent control of the rate of delivery directly into the bloodstream. It also offers a predictable pharmacokinetic profile and constant drug levels over extended periods of time without the extreme peak/trough fluctuations inherent in oral administration. And discontinuation of therapy can be achieved immediately by simply removing the patch. In conclusion, a number of drugs prescribed by the clinician benefit from transdermal delivery. These drugs are generally small and relatively lipophilic compounds with high potency. For these drugs there are several potential advantages of transdermal relative to oral delivery. The major advantages of transdermal delivery include increased compliance and lowered systemic levels of harmful metabolites (because of decreased first-pass metabolism), yet equivalent efficacy. For localized therapy, such as treatment of localized breast conditions, transdermal delivery can result in substantially lower systemic exposure to toxic chemotherapeutic agents, yet achieve therapeutic levels in the affected tissue. Thus, with drugs for hormone replacement therapy, contraception, treatment of incontinence, and localized treatment of breast cancer, transdermal drug delivery may be the preferred route of administration. Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. 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 and influenza vaccine. Using these novel second- and third-generation enhancement strategies, transdermal delivery is poised to significantly increase impact on medicine.

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