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Recent Trends in Challenges and Opportunities in Transdermal Drug Delivery System

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Transdermal delivery constitutes one of the most important routes for new drug delivery system. Transdermal delivery of drugs offers several advantages over conventional delivery methods including oral and injection methods. Transdermal delivery that traditionally uses a patch containing drug substance pressed on to the skin, is noninvasive, convenient and painless, and avoid gastrointestinal toxicity (e.g. peptic ulcer disease) and the therapeutic first pass metabolism. Introduction Transdermal drug delivery is hardly an old technology, since 1800's and the technology is no longer just adhesive patches. Due to recent advances in technology and the ability to apply the drug to the site of action without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration. Over the last two decades more than 35 Transdermal patch products have been approved in US. In the 21st century, the pharmaceutical industry is caught between the downward pressure on prices and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (approximately$500 million and 10–12 years) than those required to develop a novel drug delivery system (NDDS) ($20–50 million and3–4 years). Transdermal drug delivery system can deliver the drugs through the skin portal to systemic circulation at a predetermined rate and maintain clinically the effective concentrations over a prolonged period of time. The market value for transdermal delivery was $12.7 billion in 2005, and is expected to increase to $21.5 billion in the year 2010 and $31.5 billion in the year 2015 – suggesting a significant growth potential over the next 10 years.

Keyword: Transdermal drug delivery system, prolonged period of time, painless, avoid gastrointestinal toxicity

INTRODUCTION: For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquid aerosols, injectables and suppositories, as carriers. Recently, several technical advancements have been made. They have resulted in the development of new techniques of drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targetting the delivery of drug to a tissue. In responses to these advances, several transdermal drug delivery systems have recently been developed, aiming to achieve the objective of

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systemic medication through topical application on the intact skin surface. The principal of transdermal drug delivery systems is that they could provide sustained drug delivery (and hence constant drug concentrations in plasma) over a prolonged period of time. For these attributes, it is often extrapolated that sustained therapeutic activity will also be obtained with transdermal drug delivery systems. Thus, it is anticipated that transdermal drug delivery systems can be designed to input drugs at appropriate rates to maintain suitable plasma-drug levels for therapeutic efficacy, with out the periodic sojourns into plasma concentrations that would accompany toxicity or lack of efficacy. Today, four drugs have been successfully incorporated into transdermal drug delivery systems for clinical use (Scopolamine, Nitroglycerine, Clonidine and Estradiol), which establishes the dermal route for systemic drug delivery. Ultimately, the success of all transdermal systems depends on the ability of the drug to permeate skin in sufficient quantities to achieve its desired therapeutic effect. Transdermal drug delivery systems were first introduced more than 20 years ago. The technology generated tremendous excitement and interest amongst the major pharmaceutical companies in the 1980s and 90s. The advantages of avoidance of first-pass liver metabolism, avoidance of exposure to chemical and biological conditions of the gastrointestinal tract, reduction or avoidance of adverse events, improved patient compliance, and the ability to provide a controlled delivery of drugs with short half-lives and/or narrow therapeutic windows were all attractive features that the pharmaceutical industry was looking for. Excitement dwindled to disappointment however, when the limitations of the existing transdermal technology became evident and the numbers of drug candidates were limited to nitroglycerin, scopolamine, clonidine, estrogen, testosterone, nicotine, and fentanyl. Factors limiting the success of transdermal technology included such things as local skin irritation associated with certain drugs and formulations, limitation on the dose of drug that could be delivered transdermally, a lag time associated with the delivery of the drug across the skin (resulting in a delay in onset of action), variation of absorption rate based on site of application, skin type and patient age, and variation in adhesive effectiveness across skin types. These limitations, in addition to the rise in other non-oral drug delivery systems, such as pulmonary delivery systems, caused interest in transdermal technology to decline. Without the interest of big pharma and the funding partnerships that it provided, few transdermal drug delivery companies could sustain themselves without a large pipeline that led products to the marketplace. By the mid to late 1990s, the trend of TDS companies merging into larger organizations (ie, J&J acquiring ALZA and a part of Cygnus, Watson acquiring Theratech, and Elan acquiring Sano) combined with the increasing number of mega-pharmaceutical mergers, left fewer companies that wanted to develop transdermal products. Acceptance of transdermal technology by larger pharmaceutical companies became more conservative, and development efforts remained focused on oral drug delivery. In 2001, only 15% of R&D budgets of major pharmaceutical companies were spent on projects incorporating drug delivery technology, with almost half of the research dollars being dedicated to oral drug delivery.[2] This article will attempt to describe the condition of the transdermal drug delivery platform and its related patch-like market and its future here in the United States. Patch-like products refer to those products that are applied to the skin or mucosa and may consist of a flat film-like structure by itself (similar to TDS) or be integrated as part of the product. In the 21st century, the pharmaceutical industry is caught between the downward pressure on prices and the increasing cost of successful drug discovery and development

TRANSDERMAL DRUG DELIVERY

During the last decade, controlled release concept and technology have received increasing attention in the face of growing awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional methods.

Thus, drugs administered in the form of tablets, capsules, injectables and ointments, etc usually produce wide ranging fluctuations in drug concentration in the blood stream and tissues and consequently undesirable toxicity and poor efficiency.[1] The potential of using the intact skin as the port of drug administration has been recognised for several decades as evidenced by the development of medicated plasters in china and japan. This triggered the research curiosity of several biomedical scientists to evaluate the feasibility of transdermal delivery of systemically-effective drugs. The findings accumulated over the years have practically revolutionized the old concept of impermeable skin barrier and also motivated a number of pharmaceutical scientists to develop patch-type drug delivery systems for transdermal rate controlled administration of drugs for systemic medication[4]. The transdermal drug delivery system (TDDS) is a therapeutic system designed to transfer drugs through intact skin for systemic treatment. It offers controlled drug release pattern by a simple application to the skin surface, eliminating the vagaries influencing the gastrointestinal absorption associated with oral administration and providing for more efficient drug utilization. Continuous percutaneous administration of a drug at a controlled rate permits elimination of pulse entry into the systemic circulation, a phenomenon often associated with side effects. It also allows the option of rapidly terminating absorption of medication, whenever therapy needs to be interrupted.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY

The perceived advantages for transdermal drug delivery include [1,2,3]

1. Avoids vagaries associated with gastrointestinal absorption due to pH, enzymatic activity, drug-food interactions etc.
2. Substitutes oral administration when the route is unsuitable as in case of vomiting, diarrhoea.
3. Avoids hepatic "first pass" effect.
4. Avoids the risks and inconveniences of parenteral therapy.
5. Reduces daily dosing, thus, improving patient compliance.
6. Extends the activity of drugs having short plasma half-life through the reservoir of drug present in the therapeutic delivery system and its controlled release characteristics.
7. Rapid termination of drug effect by removal of drug application from the surface of the skin.
8. Rapid identification of the medication in emergencies. (eg. Non-responsive, unconscious, or comatose patient.) Elimination of the hazards and difficulties of I.V. infusions or I.M. injections.
9. Enhance therapeutic efficacy, reduced side effects due to optimization of the blood concentration-time profile and elimination of pulse entry of drugs into the systemic circulation.
10. Provide predictable activity over extended duration of time and ability to approximate zero-order kinetics
11. Improved control of the concentrations of drug with small therapeutic indices.
12. Minimize inter and intrapatient. variation.
13. Provide suitability for self-administration.

MECHANISMS OF TRANSDERMAL PERMEATION

For a systemically active drug to reach a target tissue, it has to possess some physicochemical properties which facilitate the sorption of the drug through the skin and enter the microcirculation.

The rate of permeation, dq/dt, across various layers of skin tissues can be expressas : [4]

$$dq/dt = P_s (C_d — C_r) \quad \text{..... (1)}$$

where C_d and C_r are respectively, the concentrations of a skin penetrant in the donor phase (stratum corneum) and in the receptor phase (systemic circulation), and P_s is the overall permeability coefficient of the skin and is defined by :[4]

$$P_s = K_s D_{ss} / h_s \quad .....(2)$$

Where ,
K_s = partition coefficient of the penetrant.
D_{ss} = apparent diffusivity of penetrant,
h_s = thickness of skin

Molecular penetration through the various regions of the skin is limited by the diffusional resistances encountered. The total diffusional resistance (R_{skin}) to permeation through the skin has been described by Chien as : [6]

$$R_{skin} = R_{sc} + R_e + R_{pd} \quad .....(4)$$

Where R is the diffusional resistance and subscripts sc , e , pd refer to stratum

corneum, epidermis and papillary layer of the dermis respectively. Of these layers, the greatest resistance is put up by the stratum corneum and tends to be the rate –limiting step in percutaneous absorption. When more than one phase of the membrane is capable of supporting separate diffusional currents through each. In this instance, the pathways are configured in parallel to one another and the total fluxes of matter across the membrane is the sum of the fluxes of each route and is expressed by : [7]

$$J = A (f_1 p_1 + f_2 p_2 + ...+ f_n p_n) \ DC$$

Where J = diffusional flux and the term $f_1p_1 + f_2p_2 + ...f_np_n$, defines the overall permeability coefficient, DC being the concentration drop.

COMPONENTS OF TRANSDERMAL DEVICES [1,2,3]

Transdermal drug delivery devices have come of age. It is 24 years since the first US patents were issued to these systems, today more than 100 patents describing transdermal devices have been issued. Transdermal devices are of 3 types. Adhesive device, Monolithic matrix device and the Reservoir system. These devices basically contain : [8,9,10]

1. Backing layer
2. Drug reservoir
3. Release control layer (polymer matrix)
4. Adhesive and peel strip
5. Enhancers and excipients.

The backing layer/membrane 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. Eg., 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. The drug reservoir is generally made up of adhesives and allow for the transport of drug at a desired rate. The drug should be selected depending upon clinical need and its physicochemical properties. The following are some of the desirable properties of a drug for transdermal drug 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
3. Hydrophilic phases.
4. The drug should have a low melting point.

Biological properties:

1. The drug should be potent with a daily dose of the order of a few mg/day.
2. The half life ($t_{1/2}$) of thedrug should be short.
3. The drug must not induce a cutaneous irritant or allergic response.
4. Drugs which degrade in the GI tract or/are inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.
5. Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
6. Drugs which have to administered for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

Polymer Matrix

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a transdermal system.

1. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
2. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive. The polymer and its degradation products must be non-toxic or non-antagonistic to the host.
3. The mechanical properties of the polymer should not deteriorate excessively when large amounts of active agent are incorporated into it.

Possible useful polymers for Transdermal devices are :

Natural Polymers

Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

Synthetic Elastomers

Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Neoprene etc.

Synthetic Polymers

Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate,

Polyamide, Polyurea, Polyvinylpyrrolidine, Polymethylmethacrylate, Epoxy etc.

ADHESIVES

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfil the following criteria.

1. Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the skin.
2. Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.
3. Should be easily removed.
4. Should not leave an unwashable residue on the skin.
5. Should have excellent (intimate) contact with the skin at macroscopic and microscopic level.

The face adhesive system should also fulfil the following criteria.

1. Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
2. Permeation of drug should not be affected.
3. The delivery of simple or blended permeation enhancers should not be affected.
4. Some widely used pressure sensitive adhesives include polyisobutylenes, acrylics and silicones.

Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Permeation enhancers are hypothesized to affect one or more of these layers to achieve skin penetration enhancement. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability. These may be conveniently be classified under the following main headings:

Solvents

These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Eg.,water alcohols-methanol and ethanol ; alkyl methyl sulfoxides-dimethyl sulfoxide, dimethyl acetamide and dimethyl formamide, miscellaneous solvents-propylene glycol, glycerol, isopropyl palmitate.

Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. Anionic surfactants can penetrate and interact strongly with the skin. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the 3 major classes of surfactants, the nonionics have long been recognised as those with the least potential for irritation and have been widely studied. Egs., of commonly used surfactants are :

Anionic surfactants : Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.

Nonionic surfactants : Pluronic F127, Pluronic F68, etc.

Binary systems

These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways.
Eg. Propylene glycol-oleic acid and 1,4-butane diol-linoleic acid.

Miscellaneous chemicals

Eg. Urea, N,N-dimethyl-m-toluamide, Calcium thioglycolate,

Anticholinergic agents

The enhancers used should be pharmacologically inert, non-toxic, non-allergenic and non-irritating. They should show a quick onset of action, reduction of barrier function of the skin only in one direction. On removal from skin, the tissues should quickly and fully recover normal barrier function. It should be compatible with all the formulation components and should be an excellent solvent for drugs. Finally the permeation enhancers should spread well, be inexpensive, tasteless, odourless and colourless. The permeation enhancers act by the disruption of tightly packed lipid domains in the stratum corneum and facilitate the passage of drug molecules.

TECHNOLOGIES OF TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)[4,6,8]

Several technologies have been successfully developed to provide a rate-control over the release and skin permeation of drugs. These technolgies can be classified into the following approaches.

Membrane permeation controlled TDDS

In this system, the drug reservoir is sandwiched between a backing membrane and a rate-controlling membrane, through which the drug is released. In the drug reservoir, drugs are either dispersed uniformly in the solid adhesive matrix

(polyisobutylene) or suspended in a viscous, leachable liquid (silicone fluid) or dissolved in a releasable solvent (alkyl alcohol).

The rate controlling membrane can be either

- Microporous or
- Non-porous membrane (Ethylene vinyl acetate copolymers)

Adhesive type TDDS

In this system, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer (polyisobutylene or polyacrylate), then spreading the medicated adhesive by solvent casting or hot melt, onto a backing support to form

- a single layer or
- multiple layers of drug reservoir

Matrix type TDDS

The drug reservoir here is formed by homogeneously dispersing the drug in a hydrophilic or lipophilic polymer matrix and the medicated polymer formed is then moulded into medicated discs with a defined surface area and controlled thickness. This is then mounted onto a backing membrane and the adhesive is applied outside the disc along the circumference to form a strip of adhesive rim.

Microreservoir TDDS

This type of drug delivery system is formed by first suspending the drug in the aqueous solution of a water-soluble polymer (eg.PEG) and then dispersing homogeneously, the drug suspension in a lipophilic polymer, by high shear force, to form unleachable microscopic drug reservoirs. These are also known as 'Microsealed Delivery Devices.'

Poroplastic or Moleculon Type Devices

These systems, developed at Moleculon, (Cambridge, Massachusetts) utilise poroplastic films. The film is made utilizing the concept of water coagulation of cellulose triacetate solution in organic acids at low temperature. The coagulation is performed under controlled conditions and the extent of water content may be varied to a great condition and degree.

TRANSDERMALS TODAY & NEW MARKET OPPORTUNITIES

Interest in Transdermals has increased on several fronts over the past several years. Technology companies have generated additional clinical data demonstrating the potential of advanced transdermal technology; pharmaceutical companies have become more aggressive in exploring alternate formulations to extend patent life; and several OTC transdermal products have increased consumer awareness, acceptance, and education on the benefit these systems have to offer.

Improved Transdermal Technology

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 is 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.

MARKET OPPORTUNITIES IN THE FUTURE

The future of transdermal drug delivery and patch-like delivery platforms and systems has had a rich past and are now emerging as a major alternative to other delivery platforms. As this platform has matured and new elements have been incorporated into its system, new products and applications in diagnostic and medical devices have shown new ways the skin and

mucosa can play a larger part in healthcare and quality of life. This paper has attempted to point out the various markets that are possible, expanding to larger molecular weight drugs and further incorporation of 21st century technology into its systems.

DERMAL AND TRANSDERMAL DRUG DELIVERY SYSTEMS: CURRENT AND FUTURE PROSPECTS

The protective function of human skin imposes physicochemical limitations to the type of permeant that can traverse the barrier. For a drug to be delivered passively via the skin it needs to have adequate lipophilicity and also a molecular weight <500 Da. These requirements have limited the number of commercially available products based on transdermal or dermal delivery. Various strategies have emerged over recent years to optimize delivery and these can be categorized into passive and active methods. The passive approach entails the optimization of formulation or drug carrying vehicle to increase skin permeability. Passive methods, however do not greatly improve the permeation of drugs with molecular weights >500 Da. In contrast active methods that normally involve physical or mechanical methods of enhancing delivery have been shown to be generally superior. Improved delivery has been shown for drugs of differing lipophilicity and molecular weight including proteins, peptides, and oligonucletides using electrical methods (iontophoresis, electroporation), mechanical (abrasion, ablation, perforation), and other energy-related techniques such as ultrasound and needless injection. However, for these novel delivery methods to succeed and compete with those already on the market, the prime issues that require consideration include device design and safety, efficacy, ease of handling, and cost-effectiveness.

Electrically Assisted methods :

Electrically Assisted methods 1.Ultrasound (Phonophoresis / Sonophoresis) Used originally in physiotherapy and sports medicine, applies a preparation topically and massages the site with an ultrasound source. The ultrasonic energy (at low frequency) disturbs the lipid packing in stratum corneum by cavitation. Sonicators operating at frequencies in the range of 20kHz to 3MHz are available commercially and can be used for Sonophoresis. Therapeutic ultrasound (1–3MHz) - for massage, Low-frequency ultrasound (23-40kHz) - in dentistry, High-frequency ultrasound (3–10 MHz) - diagnostic purposes.

Enhanced Transdermal Permeation by Cavitation of stratum corneum upon application of Ultrasound:

Enhanced Transdermal Permeation by Cavitation of stratum corneum upon application of Ultrasound.

1. Iontophoresis :

Iontophoresis The electrical driving of charged molecules into tissue, passes a small direct current (approximately 0.5 mA/cm2) through a drug containing electrode in contact with the skin. The most popular electrodes are based on the silver/silver chloride redox couple. Three main mechanisms enhance molecular transport: Charged species are driven primarily by electrical repulsion from the driving electrode. Flow of electric current may increase the permeability of skin and Electroosmosis may affect uncharged molecules and large polar peptides. Limitations: Hair follicle damage is possible.

2. Electroporation :

Electroporation Skin electroporation (electropermeabilization) creates transient aqueous pores in the lipid by application of high voltage of electrical pulses of approximately 100–1000 V/Cm for short time(milliseconds). These pores provide pathways for drug penetration that travel straight through the horny layer. This technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size including

biopharmaceuticals with molecular weights greater that 7kDA.

Basic components of TDDS :

Basic components of TDDS Drug Polymer matrix Penetration enhancers Other Excipients Rate controlling membrane Adhesive Release liner Backing membrane.

Types of Transdermal delivery devices :

Types of Transdermal delivery devices

Transdermal matrix system :

Transdermal matrix system 36 Rate controlling factors Drug concentration in polymer matrix Chemical nature of polymer matrix Geometry of device Polymers: PVC, PVP, Ethylene vinyl acetate, microporous polypropylene. Initially the drug is released rapidly, then rate declines as matrix is depleted. Advantages: Sleeker and thinner, daily or multiple-day Applications. Appropriate for drugs that penetrate readily and/or have low dosage requirements.

Transdermal reservoir system :

Transdermal reservoir system 37 Rate controlling factors Membrane thickness Membrane permeability Polymers: Cellulosic esters, polyamides or PVC. Advantages: Used when matrix systems cannot penetrate skin and drugs require significant penetration enhancement and/or high dosage levels.

CHALLENGES AND OPPORTUNITIES OF TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery is an exciting and challenging area. There are numerous transdermal delivery systems currently available on the market. However, the transdermal market still remains limited to a narrow range of drugs. Further advances in transdermal delivery depend on the ability to overcome the challenges faced regarding the permeation and skin irritation of the drug molecules. Emergence of novel techniques for skin permeation enhancement and development of methods to lessen skin irritation would widen the transdermal market for hydrophilic compounds, macromolecules and conventional drugs for new therapeutic indications. As evident from the ongoing clinical trials of a wide variety of drugs for various clinical conditions, there is a great future for transdermal delivery of drugs. Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Advances in modern technologies are resulting in a larger number of drugs being delivered Transdermally including conventional hydrophobic small molecule drugs, hydrophilic drugs and macromolecules.

Transdermal systems are a desirable form of drug delivery because of the obvious advantages over other routes of delivery. Transdermal delivery provides convenient and pain-free self-administration for patients. It eliminates frequent dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain a constant drug concentration, and a drug with a short half-life can be delivered easily.

All this leads to enhanced patient compliance, especially when long-term treatment is required, as in chronic pain treatment and smoking cessation therapy. Avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs is another advantage of transdermal delivery. Elimination of this first-pass effect allows the amount of drug administered to be lower, and hence safer in hepato-compromised patients, resulting in the reduction of adverse effects. Transdermal systems are generally inexpensive when compared with other therapies on a monthly cost basis, as patches are designed to deliver drugs from 1 to 7 days. The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs, is possible with the latest programmable systems, adding more benefits to the conventional patch dosage forms.

The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products. The transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion in 2015 Transdermal delivery systems (TDS) were introduced onto the US market in the late 1970s but transdermal delivery of drugs had been around for a very long time.

There have been previous reports about the use of mustard plasters to alleviate chest congestion and belladonna plasters used as analgesics. The mustard plasters were homemade as well as available commercially where mustard seeds were ground and mixed with water to form a paste, which was in turn used to form a dispersion type of delivery system. Once applied to the skin, enzymes activated by body heat led to the formation of an active ingredient (allyl isothiocyanate). Transport of the active drug component took place by passive diffusion across the skin – the very basis of transdermal drug delivery Since then a long path has been traversed in the field where we have seen the development of numerous transdermal patches ranging from nicotine to methylphenidate and testosterone to lidocaine . The TDSs that have been developed over the years have been classified into different generations by Prausnitz *et al.* . According to the classification, the first generation dealt mostly with small, lipophilic and uncharged molecules that can be delivered in the therapeutic range by passive diffusion alone.

Most of the TDS that are currently on the market belong to this generation. But with the advancement of science and engineering we have seen the use of chemical enhancers and techniques such as ultrasound and iontophoresis for the delivery of drug molecules that cannot undergo passive diffusion. These belong to the second generation of transdermal products that target reversible disruption of the skin's outer layer, the stratum corneum or use an additional driving force for drug delivery. One of the best examples is the delivery of lidocaine (a charged molecule), for which an iontophoretic delivery system was developed and marketed. A third generation of delivery systems is currently under development employing techniques such as microneedles and electroporation for delivery of macromolecules. This third generation of systems targets its effect towards the stratum corneum, rather than modification of the drug molecule itself.

A number of recently published reviews deal with various aspects of transdermal delivery, for example, classification of transdermals into generations and the transdermal market, and nanotechnology in transdermal delivery . Patent reviews on formulation aspects of transdermal delivery and enhanced transdermal delivery techniques have also been published. The first aim of this article is to provide an updated overview of the transdermal products currently on the US market and in clinical trials. The second aim is to focus on the challenges and solutions for overcoming skin permeation and skin irritation.

TRANSDERMAL MARKET

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 table 1 gives detail information of the different drugs which are administered by this route and the common names by which they are marketed; it also gives the conditions for which the individual system is used. The pie diagram given below shows that Fentanyl and nitroglycerine are the drugs most popularly marketed using transdermal patches.

TABLE – 1 Transdermal Drugs and its indication

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	Esrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
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

ADVANCE DEVELOPMENT IN TDDS

Drug in adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.A rich area of research over the past 10 to 15 years has been focusedon developing transdermal technologies that utilize mechanical energy to increasethe drug flux across the skin by either altering the skin barrier (primarilythe stratum corneum) or increasing the energy of the drug molecules. These so-called"active" transdermal technologies include iontophoresis (which uses low voltageelectrical current to drive charged drugs through the skin), electroporation(which uses short electrical pulses of high voltage to create transient aqueouspores in the skin), sonophoresis (which uses low frequency ultrasonic energyto disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the

energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

TRANSDERMAL SYSTEMS IN USE

Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects.

1. Transdermal Scopolamine:

Transdermal scopolamine was the first TDDS to receive FDA approval.

Doses:

It contains 1.5mg of scopolamine and is designed to deliver approximately 1mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the system.

Layers:

Transderm Scop is four-layer system.

1. Backing layer of aluminized polyester film.
2. Reservoir of scopolamine, mineral oil, polyisobutylene.
3. Microporous polypropylene membrane.
4. Adhesive of polyisobutylene, mineral oil, scopolamine.

Application Technique of Scopolamine Patch:

The patch is worn in a hairless area behind the ear. Because of the small size of the patch, the system is convenient and well accepted by the patient. The TDDS is applied at least 4 hours before the antinausea effect is required.

USES:

It is a belladonna alkaloid, used to prevent:

- Motion sickness,
- Nausea and vomiting.

Side effects:

- Dryness of mouth.
- Drowsiness.
- Interfere with memory.

Precautions:

Only one disk should be worn at a time and may be kept in place for up to 3 days.
If continued treatment is required, a fresh disk is placed behind the other ear.
The TDDS is not intended for use in children.

2. Transdermal Nitroglycerin:

Mechanism of action:

When a TDDS is applied to skin, nitroglycerin is absorbed continuously, resulting in active drug reaching the target organs before inactivation by the liver. Only a portion of the total nitroglycerin in the system is delivered over the usual 24 hour use period. The remainder serves as the thermodynamic energy source to release the drug and remains in the system.

Layers:

Deponit is a three layer system:

1. Covering foil.
2. Nitroglycerin matrix with polyisobutylene adhesive, plasticizer.
3. Protective foil, removed before use.

Application Technique of Transdermal Nitroglycerin Patch:

These are placed on the chest, back, upper arms or shoulders. The site should be free of hair, clean and dry so the patch adheres without difficulty.

Uses:

Nitroglycerin is used widely in the prophylactic treatment of angina.

Precautions:

Because of different release rates, these systems cannot be used interchangeably by a patient.

Brand names:

- Deponit.
- Nitro-Dur.

3. Transdermal Clonidine:

The first transdermal system for hypertension, Catapres TTS was marketed in 1985.

Characteristics:
The TDDS provides controlled release of Clonidine for 7 days.

Layers:
Catapres TTS is a four-layer patch:

1. Backing of pigmented polyester film.
2. Reservoir of Clonidine, mineral oil, polyisobutylene, colloidal silicon dioxide.
3. Microporous polypropylene membrane.
4. Adhesive layer.

Application Technique of Transdermal Clonidine:
The system is applied to the hairless area of intact skin on the upper outer arm or chest. Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application. Application of new system to a fresh skin site at weekly intervals maintains therapeutic plasma concentration. If the patch is removed and not replaced with a new system, therapeutic plasma clonidine levels will persist for about 8 hours and then decline slowly over several days. Over this period, blood pressure returns gradually to pretreatment level.

Uses:

- It is use for treatment of hypertension.
- Clonidine has also been used for migraine headache.

Side Effects:

- Insomnia.
- Drowsiness.
- Dry mouth.
- Constipation.
- Clonidine may also cause hypotension.

Precautions:
If the patient has local skin irritation before 7 days of use, the system may be removed and replaced with a new one applied on a fresh skin site.

Brand name:
Catapres-TTS

4. Transdermal Nicotine:
Doses:
The commercially available patches contain 7 to 22 mg of nicotine for daily application during the course of treatment ranging from about 6 to 12 weeks.

Layers:
Nicotrol is a multilayer rectangular patch:

1. Outer backing of polyester film.
2. Rate controlling adhesive, nicotine.
3. Disposable liner, removed prior to use.

Application Technique of Transdermal Nicotine:
A nicotine TDDS is usually applied to the arms. The TDDS is replaced daily, with sites alternated.

Uses:

- Nicotine TDDS are used as adjuncts in smoking cessation programs. They have been shown to be an effective aid in quitting smoking when used according to product-recommended strategies.
- Nicotine patches found to be efficient in reducing post-surgical pain.
- Sometimes nicotine patches are used to treat schizophrenia.

Precautions:

- Advise the patient, not to smoke when wearing the system.
- Used TDDSs should be discarded properly, because the retained nicotine is poisonous.

Brand Names:

- Nicoderm CQ
- Prostep
- Habitrol
- Nicotrol

5. Fentanyl transdermal patch:
Duragesic is used in chronic pain management. The patches work by releasing fentanyl into body fats, which then slowly release the drug into the

bloodstream over 48 to 72 hours, allowing for long-lasting relief from pain.

Layers:

Fentanyl is a four layer patch:

1. Backing layer of polyester film.
2. Reservoir of fentanyl, alcohol gelled with hydroxyethyl cellulose.
3. Rate controlling ethylene.
4. Fentanyl containing silicone adhesive.

Application Technique of Fentanyl transdermal patch:

The patch should be applied to a clean, dry area on the upper arm or back. Each patch may be worn continually for 72 hours even while showering or bathing.

USES:

This medication is a narcotic analgesic used to relieve chronic pain.

Adverse Effects:

- Dry mouth.
- Weakness.
- Sweating.
- Dyspepsia (indigestion).

MARKETED SCOPE

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.

The market for drugs delivered transdermally was valued at $5.6bn in 2009 with the majority of these sales being accrued by products utilizing first generation patch technologies. Innovative technologies that are able to deliver drugs with a broader spectrum of characteristics are poised to revolutionize the transdermal drug delivery market and drive significant growth. This report analyses the current state of the transdermal drug market, evaluating its therapeutic uses and the positioning of leading players. The pipeline of transdermal drugs is assessed by therapeutic indication and innovative delivery technologies are discussed at length and benchmarked against one another.

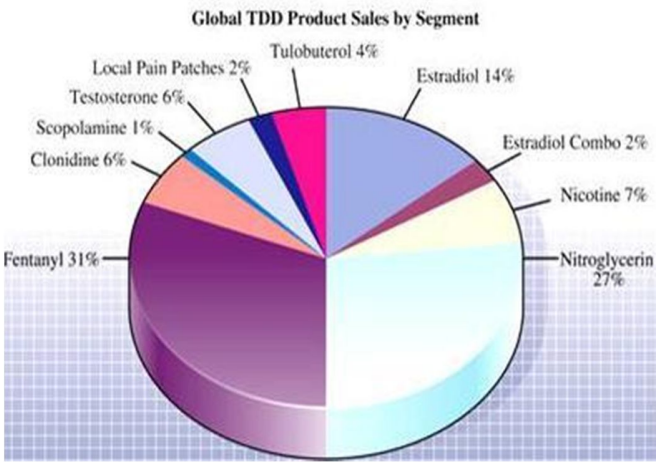

Figure1. Global TDDS Product sales by segment

CONCLUSION

Transdermal drug delivery technologies are becoming one of the fastest growing sectors within the pharmaceutical industry. Advances in drug delivery systems have increasingly brought about rate controlled delivery with fewer side

effects as well as increased efficacy and constant drug delivery.

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