Recent in Transdermal Drug Delivery systems

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ABSTRACT

Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form. It delivers a drug through intact skin at a controlled rate into the systemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system. 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. 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 hormone replacement therapy, management of pain, angina pectoris, smoking cessation and neurological disorders such as Parkinson’s disease. Formulated to deliver the drug at optimized rate into the systemic circulation should adhere to the skin for the expected duration should not cause any skin irritation and/or sensitization. Enhancing bioavailability via bypassing first pass metabolism, Minimizing pharmaco-kinetic peaks and troughs, Improving tolerability and dosing Increasing patient compliance in Continuous delivery.

Key words: Transdermal Permeation, Transdermal Patches, Rapid blood level spikes, Iontophoresis.

INTRODUCTION

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 even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, by-passing the gastrointestinal (GI) tract would obviate the GI 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 level spikes and troughs produced by oral dosage forms[1]. These advantages are offered by the currently marketed transdermal 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[2]. 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 to take one pill every day[3].

TRANSDERMAL PATCH

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream[4]. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medication into the patient [5]. A disadvantage to development however, stems from the fact that the skin is a very effective barrier [5]. A wide variety of pharmaceuticals can be delivered by transdermal patches [1]. An adhesive tape with Fludro corticosteroid fludrocortisone impregnated in the adhesive, for the treatment of the skin itself, was developed in the US and sold as Cordran tape [6]. As a steroid fludro corticosteroid is absorbed systemically but this is not the desired action [9]. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979. These patches administered scopolamine for motion sickness [10].

Advantages of transdermal drug delivery systems [9]

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

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

The following are some of the shortcomings of the transdermal delivery system:

- There is possibility of skin irritation due to the one or many of the formulation components.
- Binding of drug to skin may result in dose dumping.
- It can be used only for chronic conditions where drug therapy is desired for a long period of time
- Lag time is variable and can vary from several hours to days for different drug candidates.
- Cutaneous metabolism will affect therapeutic performance of the system.

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pharmacologically inert, nontoxic, nonirritating, nonallergic, odorless, tasteless, colorless, compatible with most drug and excipients, inexpensive, and have good solvent properties. Permeation enhancers can enhance the skin permeability by a variety of mechanisms, including interaction with intercellular lipids leading to disruption of their organization and increasing their fluidity, extraction of lipids from the stratum corneum, displacement of bound water, loosening of horny cells, delamination of stratum corneum, enhancing solubility and increasing partitioning into the stratum corneum, interaction with intercellular protein, and keratin denaturation.

FACTORS AFFECTING TRANSDERMAL PERMEATION

Physicochemical properties of the penetrating molecules

**Partition coefficient**
1. A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability.
2. It may be altered by chemical modification without affecting the pharmacological activity of the drug.

**pH conditions**
1. Applications of solutions whose pH values are very high or very low can be destructive to the skin.
2. With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.

**Penetrant concentration**
1. Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux.
2. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug concentration for a prolonged period of time.

Recent approaches in Transdermal Drug Delivery:

**A) CHEMICAL APPROACH:**
- **Solvents:** Water, alcohols, alkyl methyl sulfoxides (dimethyl sulfoxide), dimethyl acetamide etc
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- **Azone:**
- **Terpenes:** terpenoids and essential oils
- **Bile salts:**
- **Surfactants:**
- **Miscellaneous chemicals:**
- **Prodrug approach**

**B) PHYSICAL APPROACH:**
- **Abrasion:**
- **Microcissuining:**
- **Electroporation:**
- **Iontophoresis:**
- **Pressure waves:**
- **Sonophoresis/phonophoresis:**
- **Microneedle-based Devices:**
- **Needle-less Injection:**
- **Magnetophoresis:**
- **Aquisomes:**
- **Ethosomes:**
- **Solid lipid nanoparticles**

**A) CHEMICAL APPROACH**
This currently represents the most widely studied approach to transdermal drug permeation enhancement. A chemical permeation enhancer should be pharmacologically inert, nontoxic, nonirritating, nonallergic, odorless, tasteless, colorless, compatible with most drug and excipients, inexpensive, and have good solvent properties. Permeation enhancers can enhance the skin permeability by a variety of mechanisms, including interaction with intercellular lipids leading to disruption of their organization and increasing their fluidity, extraction of lipids from the stratum corneum, displacement of bound water, loosening of horny cells, delamination of stratum corneum, enhancing solubility and increasing partitioning into the stratum corneum, interaction with intercellular protein, and keratin denaturation.

**Solvents:**
- **Water:** The water content of human stratum corneum is typically around 15–20% of the tissue dry weight. Soaking the skin in water, exposing the membrane to high humidities or, as is more usual under clinical conditions, occluding the tissue so preventing transdermal water loss can allow the stratum corneum to reach water contents in equilibrium with that of the underlying epidermal skin cells. This, on occlusion, the water content of this outer membrane can approach 400% of the tissue dry weight. Water is the most natural penetration enhancer. Usually, hydration of the stratum corneum is one of the primary measures to increase the penetration of both hydrophilic and lipophilic permeants. Free water within the tissue could alter the solubility of a permeant in the stratum corneum. Also increased skin hydration may swell and open up the compact structure of the stratum corneum, leading to an increase in penetration. But Raised hydration may not always increase drug permeation.

**Alcohols:** These include alkanols, alkenols, glycols, polyglycols and glycerols. Alcohols can enhance skin permeation by a variety of mechanisms such as extraction of lipids and proteins, swelling of the stratum corneum or improving drug partitioning into the skin or solubility of the drug in the formulation. Ethanol increases the permeation of ketoprofen from a gel-spray formulation and triethanolamine salicylate from a hydrophilic emulsion base. Propylene glycol promotes the flux of heparin sodium and verapamil hydrochloride. Its mechanisms of action are probably similar to those suggested above for ethanol. Short chain glycerides, for instance, glyceryl monocaprylate enhances the partitioning of papaverine.

**Sulfoxides and similar compounds:** Dimethyl sulfoxide (DMSO) is the most important compound belonging to this category. DMSO may enhance drug flux by interacting with stratum corneum lipids and changing the intercellular keratin conformation, from a helical to β sheet. It has been used for increasing transdermal permeation of drugs like β-blockers, ephe-drine hydrochloride and azapropazone. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Compounds of category N, N-dimethylamides like N, N-dimethylformamide, promotes drug absorption by increasing both the diffusion and the partitioning of drug. It has been increased the permeation of caffeine and ephedrine hydrochloride. However, Southwell and Barry concluded that the enhancer caused irreversible damage to human skin. Dimethylacetamide has been enhanced the permeation of indomethacin.

**Azone:** Azone was the first molecule specifically designed as a skin penetration enhancer. Azone is regarded as an effective and non-toxic chemical enhancer. It is most effective at low concentrations, being employed typically between 0.1-5%. Azone partitions into a bilayer lipid to disrupt their packing arrangement. Still it may have different effect on the skin based on the solvent system chosen. Azone enhances permeation of wide variety of drugs like indomethacin, urea, methadone, 5-fluorouracil, propranolol hydrochloride.
Terpenes, terpenoids and essential oils

Terpenes and terpenoids are usually the constituents of volatile oil. This category includes a heterogeneous range of members and the effect of specific terpene on skin depends upon its exact physicochemical properties, in particular its lipophilicity. In general smaller terpenes with nonpolar groups are better skin permeation enhancers [16].

L-menthol has been shown to increase the skin absorption of testosterone, ceramides and cholesteryl oleate. Menthol affects skin permeation by forming eutectic mixture with the penetrating compound, thereby increasing its solubility and by altering the barrier properties of the stratum corneum.

Eucalyptol has been shown to increase the flux of indomethacin (lipophilic) and urea (hydrophilic) to a greater extent. Effect of three essential oils (eucalyptus, peppermint, turpentine oil) on the permeation of 5-flourouracil has been studied. Eucalyptus oil found to be the most active. Mode of action of these enhancers may be due to a combined effect of partition and diffusion [32].

Fatty acids and esters

A large number of fatty acids and their esters have been used as permeation enhancers. Variety of mechanisms of action suggested for these chemicals such as partitioning into the lipid bilayers and disrupting their ordered domains [16], improving drug partitioning into the stratum corneum and forming lipophilic complexes with drugs. Unsaturated fatty acids have been found to be more effective than their saturated counterparts [28]. Unsaturated fatty acids: oleic acid and linoleic acid have been found to be more effective as enhancers of midodrine permeation than saturated fatty acids, lauric and decanoic acid [33]. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5 flurouracil flux 56-fold through human skin membrane in vitro [34]. Isopropyl myristate is the most widely studied ester along with several other esters of fatty acids.

Surfactants

Usually, surfactants are added to formulations in order to solubilise lipophilic active ingredients, and so they have potential to solubilise lipids within the stratum corneum. These include Anionic surfactants like sodium lauryl sulphate (SLS), cationic surfactants include cetyltrimethyl ammonium bromide, the nonoxynol surfactants are non-ionic surfactants and zwitter ionic surfactants include dodecyl betaine [14]. Both anionic and cationic surfactants swell the stratum corneum and interact with intercellular keratin. Surfactant activity depends upon the hydrophilic to lipophilic balance, charge and lipid tail length. Anionic and non-ionic surfactants are relatively more widely studied compared to others. Significant enhancement of materials such as chloramphenicol by SLS, and acceleration of hydrocortisone and lidocaine permeation by the non-ionic surfactant Tween 80 have been reported [16].

Bile salts

The potential of sodium cholate, an ox bile extract containing the sodium salts of taurocholic, glycocholic, deoxycholic and cholic acids, and of the free cholic acids (HCOL) to enhance the transcutaneous penetration of progesterone and prednisolone, was evaluated by using excised hairless mouse skin. HCOL was found to increase skin permeability of both steroids by producing structural modifications of the stratum corneum [35].

Miscellaneous

Several other chemical groups have been studied for their ability to enhance drug transport across the skin. Cyclic oligosaccharides such as cyclodextrins form inclusion complexes with a variety of hydrophobic drugs thereby increasing their partitioning and solubility in the stratum corneum. Amino acids, alkyl amino esters and oxazolidinones have also been used successfully as permeation enhancers. Papain and medicinal leech enzymes, relatively new class of chemicals, have been shown to enhance the transdermal delivery of drugs. Macrocyclic ketones with 12 carbon atoms or more have been shown to enhance permeation of drug through skin [16].

Prodrug approach

Drug candidates for topical delivery may lack the requisite physicochemical properties that would allow them to permeate the skin to a clinically useful extent. One way to overcome this obstacle is to make prodrug of the drug with the correct physicochemical properties. Prodrugs are therapeutically inactive derivatives of drugs that undergoes invivo metabolism to produce the therapeutically active drug [13].

Different prodrugs have been developed for estradiol and “Transdermal Bioactive Hormone Delivery” devices are developed based on the results. The release rate of estradiol from Transdermal Bioactive Hormone Delivery is dependent on the chain length of the ester group at the 17th position. Alkyl ester prodrugs of ketorolac having optimum lipophilicity could improve the transdermal delivery of ketorolac. Also, the prodrug approach is a very feasible way to increase the skin permeation of protein/peptide drugs [36].

Although many potent chemical enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. In recent years the emergence of number of physical techniques has expanded the range of drugs that can be delivered transdermally. Promising new technologies involved in enhancing transdermal permeation are [17].

B) PHYSICAL APPROACH

Abrasions

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medications. The observed enhancement of permeability is a result of disruption of the cells of the stratum corneum, causing a reduction of the barrier function of the skin. Upper layers of skin can be simply removed by using chemical peels. Also microdermabrasion uses a stream of aluminium oxide crystals and dermabrasion employs a motor-driven abrasive fraise. Adhesive tape and rotating brush can remove stratum corneum prior to drug application. The prime issues that require consideration include device design and safety, efficacy, ease of handling, and cost-effectiveness, treatment duration and applied pressure on skin permeability [38, 39]. The in vitro permeation of acyclovir through human epidermal membrane using a rotating brush abrasion device was compared with acyclovir delivery using iontophoresis.

Microscissuining: It is a process which creates microchannels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules. Carlisle Scientific is currently in the process of developing a pen-like handheld device called the microscissioneer. A recently developed novel dermal abrasion device (D3S) has shown to increase the penetration of angiotensin into the skin 100-fold compared to untreated human skin [40].

Electroporation

Electroporation or electro permeabilization is a significant increase in the electrical conductivity and permeability of the cell plasma membrane caused by an externally applied electrical field. It involves the application of short (microsecond or millisecond), high voltage (50-1000 volts) pulses to the skin [1]. The mechanism of penetration is the formation of transient pores due to electric pulses that subsequently allow the passage of macromolecules from the outside of the cell to the intracellular space via a combina-
Iontophoresis is a process of transportation of ionic molecules into the tissues by passage of electric current through the electrolyte solution containing the ionic molecules using suitable electrodes. Electrical energy assists the movement of ions across the stratum corneum according to the basic electrical principle of like charges repel each other and opposite charges attract. The drug is applied under an electrode of the same charge as the drug, and a return electrode opposite in charge to the drug is placed at a neutral site on the body surface. Iontophoresis enhances transdermal drug delivery by 3 mechanisms [43]:

1. The ion-electric field interaction provides an additional force which drives through the skin.
2. Flow of electric current increases permeability of skin.
3. Electroosmosis produces bulk motion of the solvent itself that carries ions or neutral species, with the solvent stream.

Electroosmosis produces bulk motion of the solvent itself that carries ions or neutral species, with the solvent stream.

An Iontophoretic device comprises a power source and two electrode compartments as shown in Figure 3. The best suited electrodes to iontophoresis are the Ag/AgCl couple. The drug formulation (D+A-) containing the ionized molecule (D+) is placed in the electrode compartment bearing the same charge; for example, a positively charged drug such as lidocaine would be placed in the anodal compartment. The indifferent electrode compartment is placed at a distal site on the skin. The anodal compartment contains an ionizable drug D+ with its counter-ion A- and NaCl-. Application of an electric potential causes a current to flow through the circuit. At the electrode solution interface, the Ag+ and Cl- react to form insoluble AgCl, which is deposited on the electrode surface. Electromigration transports the cations, including the drug molecule, from the anodal compartment into the skin. At the same time, endogenous anions, primarily Cl-, move into the anodal compartment. In the cathodal chamber, Cl- ions are released from the electrode and electroneutrality requires that either an anion is lost from the cathodal chamber or that a cation enters the chamber from the skin. Shradha R. Baheti, et al: A recent approach towards Transdermal Drug delivery by Physical and Chemical Techniques Parameters Affecting Iontophoresis are physicochemical properties of the drug, buffer Systems, type of electrodes, frequency and strength of current, duration of application, mode of current (direct current/pulsed current).

Advantages [44, 45]:
1. It avoids the risks of infection, inflammation, and fibrosis associated with continuous injection or infusion since it is non-invasive.
2. Iontophoresis enhances the delivery of charged and uncharged polar species via application of a low electric current.
3. Lower quantities of drug used this may lead to fewer side effects.
4. It permits a rapid termination of the action, if needed, by simply by stopping drug input from the iontophoretic delivery system.
5. It is very useful in systemic delivery of peptide/protein based pharmaceuticals, which are very potent, extremely short acting. eg. Thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, interferons, enkaphaline etc
6. Iontophoresis provides predictable and controlled delivery rates through variations of current density, pulsed voltage, drug concentration and ionic strength and reduces dosing frequency.
7. It eliminates gastrointestinal incompatibility, erratic absorption, and first pass metabolism.
8. Self administration of drug is possible.

Disadvantages:
1. An excessive current density may result in pain.
2. It may cause burns due to electrolyte changes within the tissues.
3. The high current density and time of application would generate extreme pH, resulting in a chemical burn and sweat duct plugging.
4. High molecular weight compounds (8000-12000 Daltons) results in a very uncertain rate of delivery.

Dermatologic applications of iontophoresis [46-51]:
Over the last 30 years interest has shifted toward the use of iontophoresis as a drug delivery system for a wide variety of medications [46], ranging from steroids to antibiotics to local anesthetics such as scopolamine, metoprolol, salbutamol, aspirin, diphenhydramine hydrochloride, zidovudine. Iontophoresis has been used for the treatment of patients with ischemic leg ulcers, viral Infections, vitiligo, scleroderma, lymphedema, anesthesia [47]. There are reports of the successful treatment of dermatophytosis with the use of copper sulfate iontophoresis and of sporotrichosis with potassium iodide iontophoresis. M.J. Alvarez-Figueroa, investigated in vitro iontophoretic transdermal delivery of methotrexate across pig skin. P. Santi, investigated diffusive, iontophoretic and electro-osmotic fluxes of verapamil and melatonin [48, 49, 50, 51].

Laser Radiation
This method involves direct and controlled exposure of a laser to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using
this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. A handheld portable laser device has been developed by Norwood Abbey Ltd. (Victoria, Australia), which, in a study involving human volunteers, was found to reduce the onset of action of lidocaine to 3 to 5 minutes, while 60 minutes were required to attain a similar effect in the control group [79]. The enhancement of transdermal drug delivery of lidocaine has been achieved by irradiating 6-μm region mid infrared free electron laser. The flux and total amount penetrated has been enhanced 200-300 fold faster than the control [53]. A significant increase in the permeation of indomethacin and nalbuphine has been observed across skin pretreated with an erbium: YAG laser [33].

Pressure waves
Pressure waves are generated by the intense laser radiation and can permeabilize the stratum corneum and cell membrane, it allows macromolecules to diffuse stratum corneum and facilitate the transdermal drug transport through the skin [14]. The pressure wave is applied for a very short time (100 ns-1μs). It is thought that the pressure waves form a continuous or hydrophilic pathway across the skin due to expansion of lacunae domains in the stratum corneum. The delivery of the drug takes place by diffusion under the concentration gradients. A single pressure wave is sufficient to permeabilize the stratum corneum and allow the transport of macromolecules into the epidermis and dermis [32]. Pressure wave can be generated by optical breakdown, ablation, or rapid heating of an absorbing medium (thermoelastic generation). Among these ablation is the reliable method for generating pressure waves. In ablation the laser radiation causes decomposition of the target material into small fragments, which move away from the surface of the target at supersonic speed. The interactions of the pressure waves with tissue are specific and depend on their characteristics, such as peak pressure, rise time and duration [14].

Advantages:
1. The application of pressure wave did not cause any pain or discomfort.
2. The permeability of the stratum corneum is depending on the duration of pressure wave.
3. The recovery of the barrier function can be easily modulated by changing the characteristics of the pressure wave.
4. Controlled drug delivery possible.
5. Pressure wave can be thought of as a generic technology platform for the drug delivery into many different biological systems (skin, cell, microbial biofilm).
6. Insulin delivered by pressure waves resulted in reducing the blood glucose level over many hours.

Sonophoresis/Phonophoresis [13,33,42,55]
Sonophoresis is the movement of drug molecules through the skin under the influence of ultrasound. Ultrasound is a pressure wave having a frequency of more than 18 kHz. There are three distinct sets of ultrasound conditions based on frequency range and applications:

- High-frequency or diagnostic ultrasound in clinical imaging (3–10 MHz).
- Medium-frequency or therapeutic ultrasound in physical therapy (0.7–3 MHz).
- Low-frequency or power ultrasound for lithotripsy, cataract emulsification, liposuction, cancer therapy, dental descaling and ultrasonic scalpsels (18–100 kHz) [13].

Transdermal permeation enhancement is particularly significant at low frequency regimes (20 KHz < f < 100 KHz) than when induced by high frequency ultrasound. Ultrasound parameters such as frequency, treatment duration, intensity and pulse length are known to affect percutaneous absorption [13]. The mechanism involved in the Sonophoresis may be following

Advantages:
1. Cavitation: Open up the intracellular pathways, allowing substances with high molecular weights a higher degree of penetration.
2. Thermal effects: Reduced the density of lipid in the intercellular domain of the bi-layers [42].
3. Induction of convective transport
4. Mechanical effects: Occurrence of stresses due to pressure variation induced by ultrasound.

Low-frequency ultrasound has been found to enhance transdermal transport of several permeants, including estradiol, salicylic acid, corticosterone, sucrose, aldobetone, water, and butanol. ImRaX Therapeutics (Tucson, AZ) is developing an ultrasound-assisted transdermal system using its SonoRelease technology [55].

Microneedles
It consists of an array of microstructured projections that are applied to the skin so that they pierce only the stratum corneum to create micropores without causing bleeding and increase skin permeability [13]. They are generally one micron in diameter and range from 1-100 microns in length. Microneedles have been fabricated with various materials such as: metals, silicon, silicon dioxide, polymers, glass and other materials [15]. Microneedles used in transdermal delivery can be classified into two categories – solid and hollow microneedles. Solid microneedles have been successfully used in the delivery of proteins, peptides, oligonucleotides and nanoparticles in vitro and in vivo. Hollow microneedles contain a hollow bore offering the possibility of rapid bolus dose drug delivery by pressure driven flow [31].

Factors affecting microneedle based transdermal drug delivery may include insertion force, shape of the needle tip and skin insertion time. The ALZA Corp. has recently commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir or by dry coating the drug on the microporation array [40].

Advantages [56]
1. Microneedles can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.
2. Very small microneedles could provide highly targeted drug administration to individual cells. These are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled.
3. The actual piercing could not be felt unlike when a hypodermic needle is inserted in the skin. This is a very important advancement in the field of medicine, especially in pediatrics where children are usually afraid of needles and refuse to take their medicines.
4. More than one drug can be delivered at a time, thus being advantageous to patients on multi-drug regime, which is difficult to remember and follow.

Disadvantages
1. Microneedles might cause skin irritation and allergy.
2. The dissolvable needles raise concerns because the polymers used to manufacture them may become slightly toxic when in the blood stream.
3. The cost of these patches are little too high.
4. Several new and interesting microneedle concepts have been recently proposed which may find great utility in the future. For example, biodegradable polymer microneedles have recently been fabricated and characterized. The advantage of polymer needles is that they may be produced much more inexpensively (compared to silicon) and they should not pose a problem if they break in the skin since they are biodegradable [9].

Recently Lee et al (2008) has studied on dissolving microneedles for transdermal drug delivery. This study presents a design that encapsulates molecules within microneedles that dissolve within the skin for bolus or
sustained delivery and leave behind no bio hazardous sharp medical waste [58].

Needleless injection

Needle-free injectors are devices that do not use a needle to administer medication. The mechanism involves high pressure to push the medication through the skin to the desired penetration site thus allowing non-invasive and painfree drug delivery [59]. Pressure is produced by using either a gas (carbon dioxide, helium or nitrogen) or a spring device. The pressure forces the medication through a small opening in the device while it is held against the skin. This creates a fine stream of the medication that penetrates the skin. The penetration depth of the drug is dependent upon the amount of pressure used. Devices currently on the market administer the drug to the subcutaneous, intradermal, and intramuscular tissues. Some of the major companies operating in the needle-free delivery markets include Bioject, Injex, Antares, BioValve, Crossject, PenJet, and Aradigm [59].

Advantages
1. Prevention of needlestick injuries.
2. No disposal requirement.

Disadvantages
1. High developmental cost for both the device and dosage form.
2. The inability to program or control drug delivery to compensate for intersubject differences in skin permeability.

Both liquid (Ped-O-Jet, Iject, Biojector2000, Medi-jector and Intraject) and powder (PMED device systems are available. The latter device has been reported to successfully deliver testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin. The PMED device consists of a helium gas cylinder, drug powder sealed in a cassette made of plastic membrane, a specially designed convergent-divergent supersonic nozzle and a silencer to reduce the noise associated with the rupturing of the membrane when particles are fired. Currently, the applications of the device are for delivering insulin, vaccines, growth hormones, and other medications.

Magnetophoresis

It enhances skin permeability by applying a magnetic field. The research data on animal models suggests that skin penetration can be enhanced by applying a magnetic field to therapeutic molecules that are diamagnetic or paramagnetic in nature [40]. Magnetoliposomes consist of magnetic nanoparticles wrapped by a phospholipid bilayer which can be successfully applied for magnetic resonance imaging markers, for cancer diagnosis, and thermal cancer therapy.

Aquasomes:

Aquasomes are spherical 60–300 nm particles used for drug and antigen delivery. It is a successful carrier system as they provide protection and preservation of fragile biological molecules, and surface exposure for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites. These three main types of core materials are mainly used for producing aquasomes: tin oxide, nanocrystalline carbon ceramics and brushite (calcium phosphate dihydrate) [56].

Ethosomes:

A form of Liposomes with high alcohol content which have capability of penetration to deep tissues and the systemic circulation called ethosomes [53,58]. It is due to the presence of alcohol, fluidized the ethosomal lipids and the stratum corneum bilayer lipids.

Niosomes:

Niosomes are obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are similar to liposomes and used as carriers of amphiphilic and lipophilic drugs. Niosomes are excellent vehicle for drug delivery as it is less toxic and improves the therapeutic index of drug by restricting its action to target cells [59].

Solid lipid nanoparticles (SLN):

It is aqueous carriers for enhanced delivery for sunscreens, vitamins A and E triptolide and glucocorticoids [60]. Its enhanced skin penetrating ability is generally due to an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN. A 31% increase in skin hydration has been reported following 4 weeks application of skin enriched cream [61].

Liposomes:

Liposomes are colloidal particles drug delivery system involve concentric biomolecular layers that are capable of encapsulating drugs. The skin delivery of tri-aminolone acetone was four to five times for liposomal lotion than an ointment containing the soybean or egg yolk [62-67]. Recent studies have tried to deliver macromolecules such as interferon, gene delivery, and cutaneous vaccination as liposomes.

Microemulsions:

These systems are transparent mixtures of water, oil, and surfactants. They are thermodynamically stable and optically isotropic. Microemulsion are spontaneously produced in a narrow range of o/w surfactant composition, they are dynamic system with continuously fluctuating interface. Their good dermal and transdermal delivery properties could be attributed to their excellent solubilizing properties [68].

Nanoemulsions:

These are oil in water emulsions with an average droplet size ranging from 100 to 500 nm. They have a very good stability and they do not undergo phase separation during storage. Many studies showed reduced trans-epidermal water loss, which means support to the barrier function of the skin [69]. Nanoemulsion viscosity is very low, which is interesting because they can be produced as sprays. The preparation of nanoemulsions requires high-pressure homogenization. The particles which are formed exhibit a liquid, lipophilic core separated from the surrounding aqueous phase by a monomolecular layer of phospholipids [70]. The concentration range of components of nanoemulsion composed of isopropyl myristate (IPM) as an oil phase, tween 85 as surfactant, ethanol as cosurfactant, water as aqueous phase. The effects of the content of IPM as an oil phase and n-methyl pyrrolidone (NMP) as transdermal enhancer on rat skin permeation of granisetron hydrochloride nanoemulsion were studied in vitro [69].

Micro or nanocapsules: Nanocapsules are submicroscopic colloidal drug carrier systems composed of an oily or an aqueous core surrounded by the thin polymer membrane. It consists of a shell and a space, in which desired substances may be placed. Dispersed polymer nanocapsules can serve drug carriers to achieve controlled release as well as efficient drug targeting. Their release and degradation properties largely depend on the composition. The nanocapsules can be prepared by four principally different approaches: interfacial polymerization, interfacial precipitation, interfacial deposition, and self assembly procedures [70].

CURRENT AND FUTURE PROSPECT:

Transdermal Delivery System for Anti-emetic Medication:

The transdermal delivery system of an anti-emetic hydrophilic adhesive composition of hydrophilic polymer and anti-emetic agent, a patch containing one or two hydrophilic layer of the composition, generates hydrophilic amicro-channels in skin of a subject using the patch or composition [71].

Transdermal Buprenorphine to treat Pain in Sickle Cell Crisis: A specific dosage regimen of buprenorphine achieves pain relief from painful episodes due to sickle cell disease. The dosage used in the form of BTDS transdermal patch [72].
Transdermal Delivery of Non-Steroidal Anti Inflammatory Drugs: Therapeutically effective amount of a non-steroidal anti-inflammatory drug; which is a safe skin-tolerant ester sunscreen ester; and at least one volatile liquid. The invention also provides a method for administering at least one systemic or locally acting non-steroidal anti-inflammatory drug to an animal.

Transdermal delivery system for neurobehavioral disorder: Methyphenidate and amphetamine based stimulants are first line pharmacotherapies for attention-deficit hyperactivity disorder, a common neurobehavioral disorder in children and adults. A number of long-acting stimulant formulations have been developed with the aim of providing once-daily dosing, employing various means to extend duration of action, including a transdermal delivery system, an osmotic-release oral system, capsules with a mixture of immediate and delayed release beads, and prodrug technology.

Transdermal delivery system for Dopaminergic treatment: Continuous dopaminergic treatment is considered to prevent or delay the occurrence of dyskinesia in patients with Parkinson’s disease (PD). Rotigotine is a non-ergoline dopamine-receptor agonist for the treatment of PD using a transdermal delivery system providing stable plasma levels.

Transdermal delivery system for rheumatic diseases: Temoxicam is a non steroidal anti-inflammatory drug (NSAID) widely used in the treatment of rheumatic diseases and characterized by its good efficacy and less side effects compared to other NSAIDs. Its oral administration is associated with severe side effects in the gastrointestinal tract. Transdermal drug delivery has been recognized as an alternative route to oral delivery, pharmacokinetics in rabbits, and efficacy in asthmatic rats were evaluated.

Transdermal adhesive patches (capsaicin) treat neuropathic pain: Capsaicin dermal patch is an adhesive patch containing a high concentration (8% w/w) of synthetic capsaicin. It is indicated in the Europ for the treatment of peripheral neuropathic pain in non-diabetic adults using a single 30-or 60-minute application repeated every 90 days, as required, and in the US for the treatment of neuropathic pain associated with post therapeutic neuralgia.

Transdermal silicone based patch (dopamine): The nonergoline dopamine agonist rotigotine is delivered transdermally using a silicone-based patch, which promotes unidirectional drug flow from the transdermal system to the skin. Pharmacokinetic data show stable steady-state plasma concentrations over 24 h, maintained with once-daily patch administration.

Transdermal delivery system (isradipine) for hypertension: Isradipine (ISDP) is an effective calcium channel blocker used in the treatment of hypertension. It undergoes extensive first pass metabolism, and bioavailability through the oral route is only about 15 to 24%. Hence, attempts have been made to develop a matrix type controlled transdermal drug delivery system for ISDP. Corresponding values for the cumulative amounts of drug permeated across the rat skin for the above matrix films was evaluated. It was concluded that drug release from matrix films followed Higuchi model and the mechanism of drug release was diffusion mediated may be suitable for the development of a transdermal drug delivery system of ISDP.

CONCLUSION: A lot of work has been done related to transdermal patches. Recently new researches are going on to introduce newer drugs via this system. Various devices used to increase the absorption rate and penetration of the drug is also being studied. However, due to certain disadvantages like large drug molecules cannot be delivered, large dose cannot be given, the rate of absorption of the drug is less, skin irritation; etc, the use of TDDS has been limited. But day to day increments in the invention of new devices and new drugs that can be administered via this system, the use of TDDS is increasing rapidly in the present time.

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