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"A REVIEW ON RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEM"

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Abstract
Transdermal drug delivery offers an attractive alternative to the conventional drug delivery methods of oral administration and injection.The delivery of drugs into systemic circulation via skin has generated much attention during the last decade. Drugs administered through these systems escape first-pass metabolism and maintain a steady state scenario similar to a continuous intravenous infusion for up to several days. However, the stratum corneum acts as a barrier that limits the penetration of substances through the skin. Different approaches of penetration enhancement are used such as Ultrasound (sonophoresis) and Iontophoresis are both promising technologies.The rationale behind using this technique is to reversibly alter the barrier properties of skin, which could possibly improve the penetration of drugs such as proteins, peptides and other macromolecules to increase the systemic delivery of high molecular weight compounds with controlled input kinetics and minimum inter-subject variability. Transdermal biology delivery, as well as standard drugs, is becoming increasingly popular as the method provides countless benefits. It decreases pain, biohazardous waste and infection danger. Mostly, needle-free drug delivery generally increases patient compliance. The review presents mainly the routes of penetration through skin and the physical approach of penetration enhancement to optimise the transdermal delivery system and future trends in the field of cutaneous vaccination and gene delivery.

Keywords: Transdermal drug delivery, Skin penetration enhancer, Stratum corneum, Iontophoresis, Sonophoresis.

Introduction

TDDS has become one of the most widely investigated routes of noninvasive drug delivery into the body through the skin, unlike conventionally used direct administration routes that make use of needle-based injections. TDDS has significantly influenced the delivery of various therapeutic agents, especially in pain management, hormonal therapy, and treatment of diseases of the cardiovascular and central nervous systems.[11]

Transdermal delivery includes passive diffusion through the skin of a drug substance and subsequent absorption by the systemic distribution capillary system. The primary resistance to drug diffusion through the skin occurs in the stratum corneum (SC) through a lipid pathway consisting of highly ordered lipid bilayers situated between dead disk-like cells called "keratinocytes". This pathway's physicochemical nature explains that stratum corneum will easily diffuse only lipophilic drugs. Transdermal delivery that traditionally uses a patch containing drug substance pressed onto the skin is non-invasive, convenient and painless and can prevent gastrointestinal toxicity (e.g., peptic ulcer disease), gastrointestinal degradation (e.g., insulin-like polypeptides) and first-pass hepatic metabolism. Few drugs can penetrate the skin at rates that are sufficient to produce therapeutic plasma levels using traditional methods of transdermal delivery; these drugs are either of relatively low molecular weight (< 250 Da), such as Nicotine and nitroglycerin, or of higher molecular weight (> 250 but < 500 Da), such as fentanyl, estradiol, and testosterone, have a high therapeutic potential and are therefore effective at low delivery rates.[10]

In order for transdermal drug delivery systems to be effective, the drug must obviously be able to penetrate the skin barrier and reach its target in required concentration. Significant effort has been devoted to developing strategies to overcome the impermeability of intact human skin. These strategies include passive and active penetration enhancement and technologies to bypass the stratum corneum.[6]

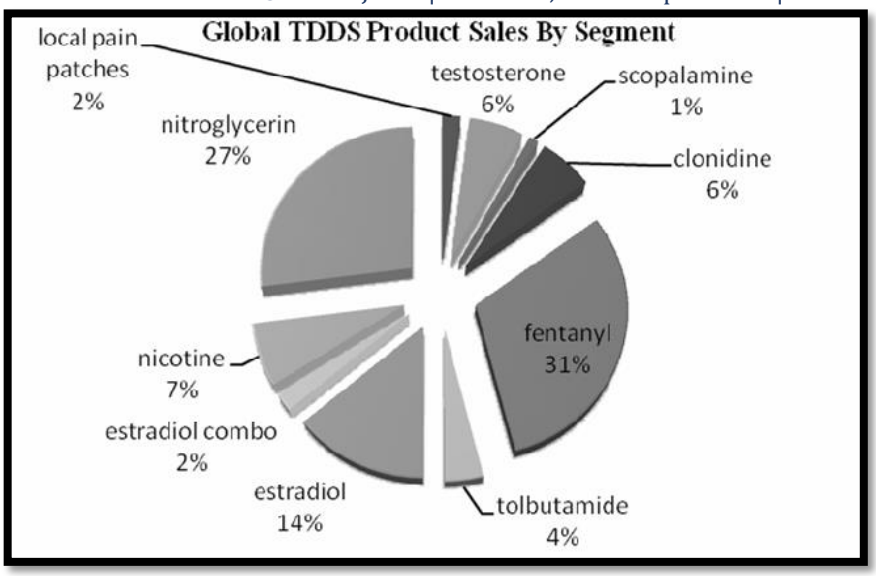

Figure 1: Global TDDS Product Sales

Advantages of TDDS[9]

- Stable and controlled blood level
- Long duration of action (ranging from few hours to one week)
- Suitable for administration of drugs having :
  - Very short half life example : nitro-glycerine
  - Narrow therapeutic window
  - Poor oral availability
- Drug action can be terminated
- No interference with gastric and intestinal fluids
- Number of doses get reduces which improve patient compliance
- Unwanted side effects get minimized
- Self-medication is possible
- Brain targeting is possible by Transdermal drug delivery system .

Disadvantages of TDDS[9]

- We cannot formulate all types of drugs as Transdermal drug delivery system
- Drugs which are irritant to skin
- Difficult to administer large dose i.e. more than(10mg/day)
- Drugs undergoes protein binding in skin are not suitable .

The skin site for transdermal administration

The skin, as the largest organ of the body, account for more than 10% of body mass and receives about one third of the blood circulating through the body , serves as a protective layer of the underlying tissues such as muscles, ligaments and internal organs, shielding it from exogenous molecules as well as from mechanical and radiation-induced injuries. The skin also plays a role in immunology and metabolism, regulates body temperature, serves as an excretory organ through sebaceous and sweat glands and contains sensory nerve endings for the perception of touch, temperature, pain and pressure. The skin varies in color, thickness and presence of nails, hairs and glands between the different regions of the body, although all types of skin have the same basic structure.[12]

The skin can be considered to have four distinct layers of tissue.[12]

1. Non-viable epidermis (stratum corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

1.Non-viable epidermis (stratum corneum)

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Stratum corneum consists of lipid (5-15%) including phospholipids, glycolsphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

2.Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50- 100 µm. The density of this region is not much different than water. The water content is about 90%.

3.Dermis

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histological in normal tissue. Dermis thickness range from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amorphous ground substance.

4.Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and coetaneous nerves.

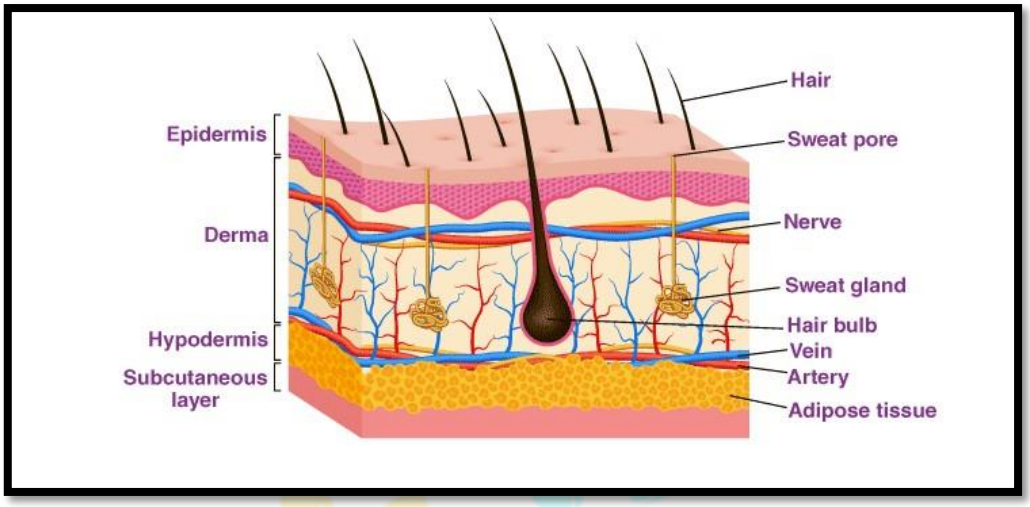

Figure 2: Structure of Skin

Penetration enhancers:[9]

Penetration enhancers are the substances used to increase permeation of skin mucosa. Penetration enhancer increases the absorption of penetrant through the skin which is also known as absorption promoter or absorption enhancers. Penetration enhancers used to increase the permeability of drug through skin.

The penetration enhancers may show their effect any one or combination of the following mechanisms.

- By disrupting the structure of stratum corneum lipids.
- By interacting with intercellular proteins.
- By improving drug partitioning, co-enhancer or solvent into the stratum corneum.
- Dissolution of drug in its vehicle.
- Diffusion of drug from vehicle to surface of skin.

Need of penetration enhancement:[9]

Penetration enhancement is the most critical factor in transdermal systems, so as to improve flux. Flux (J) can be defined as the amount (M) of material flowing through unit cross section (S) of a barrier in unit time (t).

Flux can be given by: J=dM/S.dt

Each phase of the membrane can be characterized in terms of diffusional resistance(R), which usually is the function of thickness (hs) of the phase, the permeant diffusion coefficient (Ds) within the phase, and the partition coefficient (Ks) between the membrane phase and external phase.

It can be expressed as:

$$R=hs/Ds.Ks ,$$
$$P= Ds.Ks/hs$$

Where P is permeability coefficient.

The permeability coefficient is related to membrane flux (J) as given J=APs (Cp-Cr), where Cp-Cr is the difference in permeant concentration across the membrane and A is the area of application.

Approaches to penetration enhancement:

Newer dosage forms and drug delivery systems providing excellent improvement in drug therapy are termed novel drug delivery systems (NDDS). These are termed 'novel' because of recent development with satisfactory results in the field of drug delivery. The primary objective of NDDS is to ensure safety and to improve efficacy of drugs as well as patient compliance. Some of these novel advanced transdermal technologies include[2] (Fig:).

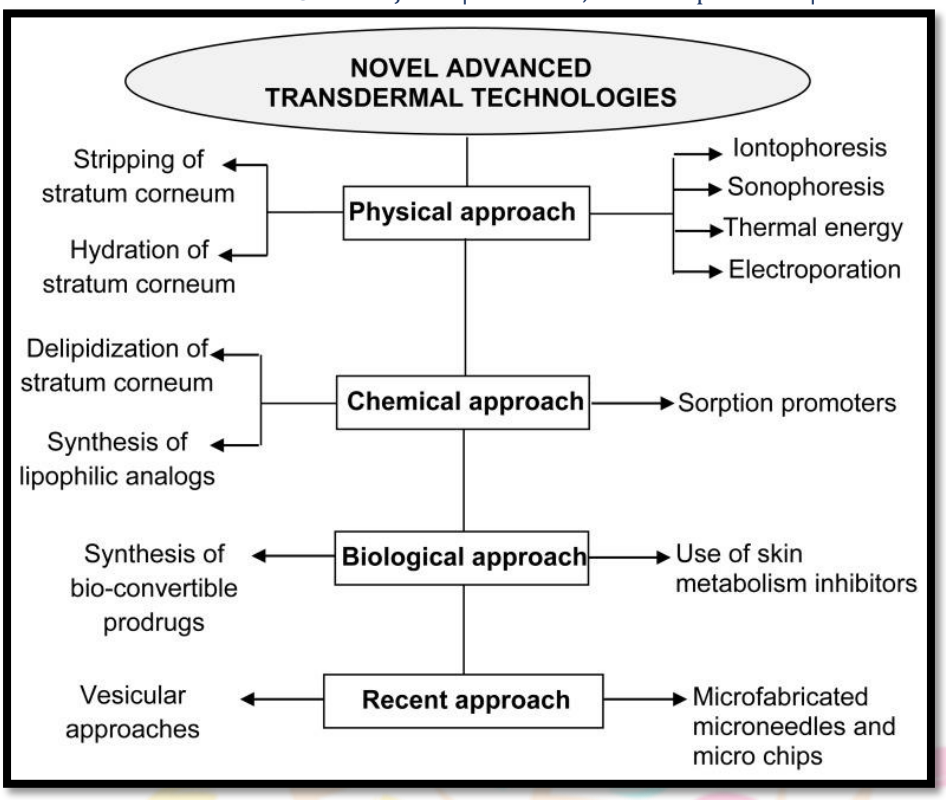

Figure 4: Novel Advanced Transdermal Technologies

Novel advanced transdermal technologies

A) Physical approach

a) Iontophoresis

Ionotophoresis is the process of enhancing the permeation of topically applied therapeutic agents . The principle of iontophoresis technique is based on that the like charges repels each other and opposite charge attract. Thus during iontophoresis, if delivery of positively charged drug, the charged drug is dissolved in the electrolyte surroundings the electrode of similar polarity i.e. Anode. An application of electromotive force, the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body.[9]

Principle of iontophoresis:

The Iontophoretic technique is based on the general principle that like charges repels each other and opposite charge attract. Thus during iontophoresis, if delivery of positively charged drug is desired, the charged drug is dissolved in the electrolyte surroundings the electrode of similar polarity, i.e. anode. An application of electromotive force the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body. Communication between the electrodes along the surface of the skin has been shown to be negligible. When cathode is placed in the donor compartment of the Franz diffusion cell to enhance the flux of an anion, it is termed cathode iontophoresis and for anodal iontophoresis the situation would be reversed. If any neutral molecules are present at the anode at this time the can be transported through the skin along with the water. Such water movement often results in pore shrinkage at the anode and pore swelling at cathode.[14]

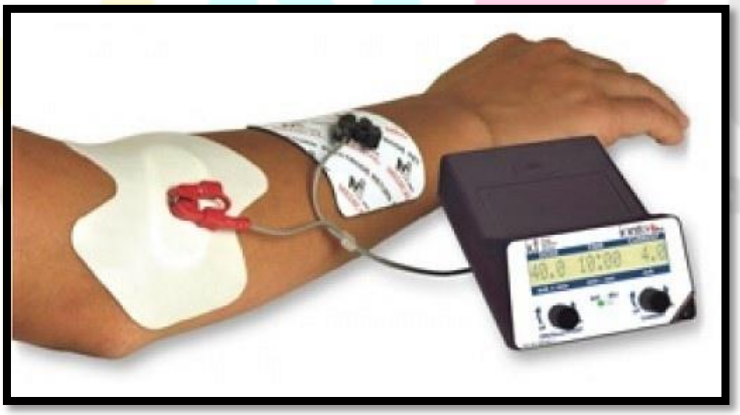

Figure 5: Iontophoresis Treatment

Merits of iontophoretic system[2]

- It is a non-invasive technique that could serve as a substitute for chemical enhancers.
- It eliminates problems like toxicity problems, adverse reaction formulation problems associated with presence of chemical enhancers in pharmaceuticals.
- It may permit lower quantities of drug compared to use in TDDS, and this may lead to fewer side effects.
- Permit a rapid termination of the modification, simply by stopping drug input from the iontophoretic delivery system.
- Self-administration is possible.

Demerits of iontophoretic system[2]

- Arrangement to protect electric shock needed.
- An excessive current density usually results in pain.
- Treatment is somewhat costly.

Mechanism of iontophoresis technique

Major mechanisms of enhancing drug flux through skin are:

- Iontophoresis (electrorepulsion, electromigration or Nernst plank effect)
- Electroosmotic flow
- Damage effect (current induced increase in skin permeation)

Iontophoresis enhances drug delivery across the skin by two principal mechanisms: electrorepulsion and electroosmosis. Electrorepulsion is the direct effect of the applied electric field on a charged permeant. The second mechanism, electroosmosis, results from the fact that the skin supports a net negative charge at physiological pH.

For effective delivery via iontophoresis, the positively charged chamber, termed anode, will repel a positively charged chemical, while the negatively charged cathode, will repel a negatively charged chemical into the skin. In the presence of an electric field, electromigration and electroosmosis are the dominant forces in mass transport.

These movements are measured in units of chemical flux, commonly µmol/cm2 h. This technique is based on the general principle that like charges repel each other. Thus, during iontophoresis, if delivery of a positively charged drug (D+) is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode in this example. On application of an electromotive force the drug gets repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body. Communication between the electrodes along the surface of the skin has been shown to be negligible, i.e. movement of the drug ions between the electrodes occurs through the skin and not on the surface. When the cathode is placed in the donor compartment of a Franz diffusion cell to enhance the flux of an anion, it is termed **cathodal iontophoresis**, and for **anodal iontophoresis** the situation would be reversed. Iontophoresis uses a low current, and patients' have little or no sensation during the procedure.[2]

Consider delivery of negatively charged drug across the biological membrane, it is placed between negative electrode (cathode) and skin. The drug ion is then attracted through the skin towards the positive electrode by an electromotive force provided by the cell. Once the drug has passed through outer barrier of the skin, it reaches to its site of action by rapidly going into the circulation. The electric circuit is completed by the movement of endogenous counter ions from within the skin. Mechanism of Iontophoretic transport of drug across the skin involves diffusion, migration or eletroosmosis. Eletroosmosis is the bulk flow of fluid occurring in the same direction as the flow of counter ions when the voltage difference is applied across the charged. This flow involves motion of fluid without concentration gradient.[14]

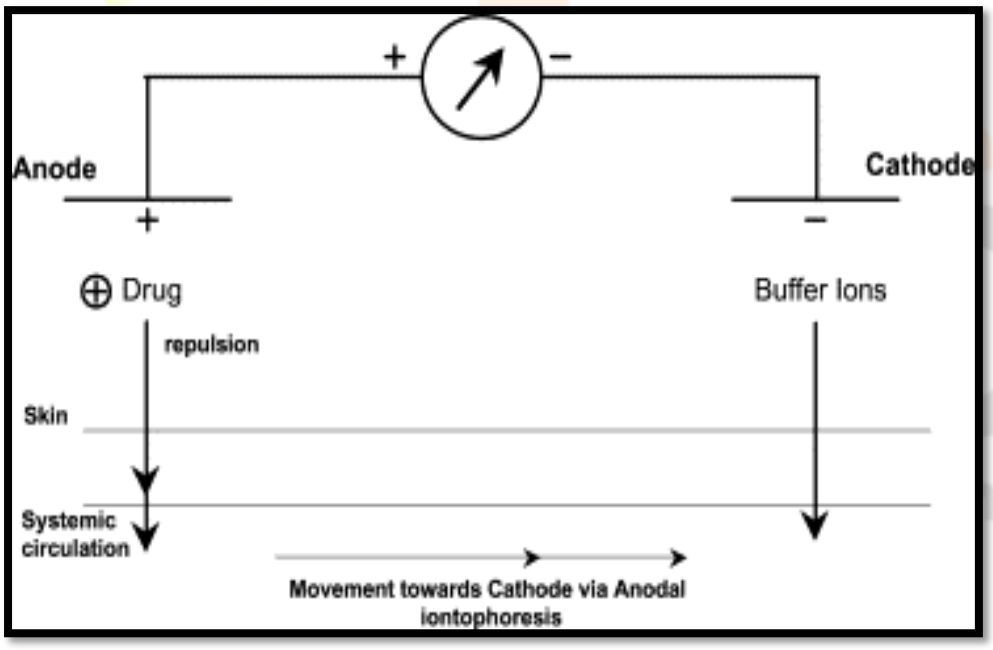

Figure 6: Iontophoretic mechanism

Factors affecting iontophoresis

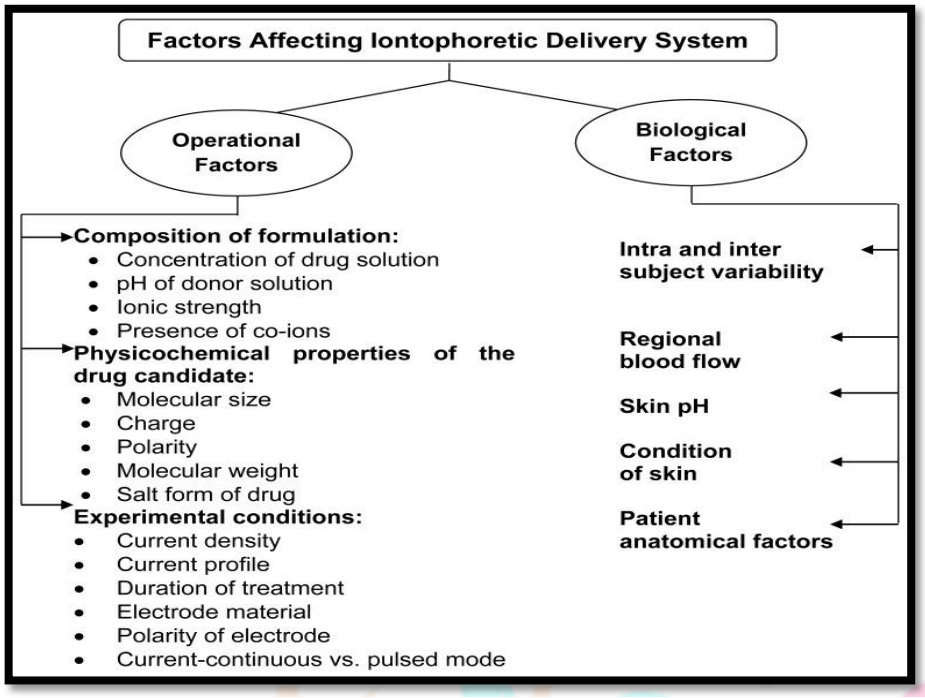

Figure 7: Factors Affecting Iontophporic Delivry system

Contraindication[16,17]

- Epilepsy , Seizures
- Pacemakers
- Heart Diseases
- Metal Implant
- Pregnancy
- Recent Wounds , Skin Grafting or Scar.

Applications of iontophoresis:[14]

Treatment of hyperhydrosis
Non-invasive monitoring of glucose Electro osmosis
Dentistry
Ophthalmology
Diagnostic applications.

b) Sonophoresis

Sonophoresis is the movement of drug molecules under the influence of ultrasound through the skin. This method utilizes less than 100 kHz low-frequency pressure waves. Ultrasound application to the skin can interfere with the bilayer of the stratum corneum lipid. As a result, drug molecules can more easily permeate the skin. It is a process that increases the absorption of topical compounds in the epidermis, dermis and skin appendages exponentially (transdermal delivery). Sonophoresis occurs because ultrasound waves in the skin epidermis stimulate micro-vibrations and increase the overall kinetic energy of molecules that make up topical agents.[10]

Advantages of Sonophoresis[10]

- Improved penetration of drugs (selected drugs) by passive transport.
- It allows strict control of transdermal rates of penetration.
- Reduced dosing frequency and compliance with patients.
- Reduction of drug plasma levels fluctuations.
- Evicting first-pass hepatic removal and gastrointestinal irritation.
- Replaces oral administration when the route is inappropriate as in the case of vomiting, diarrhea.
- Easy termination of the delivery of drugs in the event of toxicity, by ending ultrasound.

Disadvantages of Sonophoresis[10]

- Stratum corneum must be intact for effective drug penetration.
- It may take time to administer it.
- Minor tingling, irritation and burning have been reported (these effects can often be minimized or eradicated with appropriate adjustment to the results).

Mechanisms of action

It is important to identify the different effects of ultrasound exposure on human tissue to understand the mechanisms of sonophoresis. Upon exposure to ULTS, various phenomena may occur in the skin.This includes:

a) cavitation effects
b) thermal effects
c) convective transport induction
d) mechanical effects.[15]

1) Cavitation Effects[4]

Cavitation is the result of the pressure changes associated with the propagation of a compressional wave (which is the only wave that can propagate for large distances through soft tissues). This may lead to structural disordering of the stratum corneum lipids, due to oscillations of the ultrasoundinduced cavitation bubbles near the keratinocyte lipid bilayer interfaces. Cavitation bubbles also generate shock waves upon collapse and this may also contribute to the structuredisordering effect. The diffusion of permeants through a disordered bilayer phase would naturally be higher than that through normal bilayers.

2) Thermal Effects[3]

The increase in the skin temperature resulting from the absorbance of ultrasound energy may increase the skin permeability coefficient because of an increase in the permeant diffusion coefficient. A temperature increase of 10˚C causes a twofold increase in the estradiol skin permeability. Because the typical skin temperature increase in case of therapeutic sonophoresis is ~7˚C, it can be concluded that thermal effects are a non-significant phenomenon as they cannot explain the 13-fold increase in estradiol skin permeability.

Convective Transport[3]

Fluid velocities are generated in porous medium exposed to ultrasound due to interference of the incident and reflected ultrasound waves in the diffusion cell and oscillations of the cavitation bubbles. Fluid velocities generated in this way may affect transdermal transport by inducing convective transport of the permeant across the skin, especially through hair follicles and sweat ducts. Experimental findings suggest that convective transport does not play an important role in the observed transdermal enhancement.

Mechanical Effects[3]

Ultrasound is a longitudinal pressure wave inducing sinusoidal pressure variations in the skin, which, in turn, induce sinusoidal density variation. At frequencies greater than 1 MHz, the density variations occur so rapidly that a small gaseous nucleus cannot grow and cavitational effects cease. But other effects due to density variations, such as generation of cyclic stresses because of density changes that ultimately lead to fatigue of the medium, may continue to occur. Lipid bilayers, being self-assembled structures, can easily be disordered by these stresses, which result in an increase in the bilayer permeability this increase is, however, non significant and hence mechanical effects do not play an important role in therapeutic sonophoresis. Thus cavitation induced lipid bilayer disordering is found to be the most important cause for ultrasonic enhancement of transdermal transport.

Contraindications[7]

- Infection
- Cancer
- Heart problems/pacemaker
- Implants (metal, silicone, saline)
- Pregnancy.

Applications of sonophoresis[7]

- Ultrasound helps treat elbow tennis and tendon problems.
- Sonophoresis is used to treat damaged skin.
- The painful condition of the muscle responds to non-invasive ultrasound treatment.
- Hormone ultrasound delivery with topical anesthesia rapidly decreases intravenous cannulation pain.
- Low-frequency ultrasonic gene delivery.
- Ultrasound for calcific shoulder tendinitis.
- Dolphin therapy and sonophoresis model.

c) Thermal energy[6]

The skin surface temperature is usually maintained at 32°C in humans by a range of homeostatic controls. The effect of elevated temperature (non-physiological) on percutaneous absorption was initially reported by Blank et al. Recently, there has been a surge in the interest of using thermoregulation as a means of improving the delivery profile of topical medicaments. Previous in vitro studies have demonstrated a 2–3-fold increase in flux for every 7–8°C rise in skin surface temperature. The increased permeation following heat treatment has been attributed to an increase in drug diffusivity in the vehicle and an increase in drug diffusivity in the skin due to increased lipid fluidity. Vasodilation of the subcutaneous blood vessels as a homeostatic response to a rise in skin temperature also plays an important role in enhancing the transdermal delivery of topically applied compounds. The in vivo delivery of nitroglycerin, testosterone, lidocaine, tetracaine and fentanyl from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery.

d) Electroporation[9]

Electroporation is the phenomenon in which cell membrane permeability to ions and macromolecules is increased by exposing the cell to short high electric field pulses. The mechanism for electroporation by two pathways, through pores formed in the multiple lipid bilayer connecting corneocytes and through appendage cells. The efficacy of transport of drug depends on the electrical

parameters and the physicochemical properties of drugs. In electroporation the transdermal delivery of the drug molecule is increased by the application of a high voltage (100 volts) in the form of direct currect (DC).

B) Chemical approach

Sorption promotors/chemical enhancer

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells.[18,19] Some of the more desirable properties for penetration enhancers acting within the skin have been given as :[20]

- They should be non-toxic, non-irritating and non-allergenic
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body.
- The penetration enhancers should work unidirectionally, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.
- They should be cosmetically acceptable with an appropriate skin feel.

Penetration enhancers may act by one or more of three main mechanisms :[20]

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, coenhancer or solvent into the stratum corneum.

C) Recent approach

Microneedle[8]

The microneedle drug delivery system is a novel drug delivery system, in which drugs are delivered to the circulatory system through a needle. This represents one of the most popular methods for transdermal drug delivery and is an active area of current research. This involves a system in which micron-sized needles pierce the superficial layer of the skin, resulting in drug diffusion across the epidermal layer. Because these microneedles are short and thin, these deliver drugs directly to the blood capillary area for active absorption, which helps in avoiding pain. Scientists have attempted to use multiple techniques for appropriate optimization and geometric measurements required for effective insertion of microneedles into human skin, which also represents the broad objective of research on microneedles.

Future trends[3]

Vaccination

In recent years, the potential for exploiting the skin for purposes of vaccination has received a great deal of attention. Transcutaneous immunization provides access to the immune system of the skin, which is dominated by densely distributed and potent antigenpresenting cells (Langerhans cells). Langerhans cells have been shown to play essential roles in the induction of Tcell-mediated immune reactions against a wide variety of antigens. In order for this technique to be practical, the vaccine, which is generally a large molecule or complex, has to penetrate the stratum corneum barrier. Normally, skin is not permeable under these conditions. One common strategy is to use an adjuvant, which is a compound used to enhance the immune response to vaccine compounds. Glenn et al. found that applying cholera toxin to the surface of the skin stimulates an immune response to vaccine compounds such as diphtheria or tetanus toxoids. Another strategy is to use physical enhancers such as ultrasound. Ultrasound can be used to enhance skin permeability to both the adjuvant and the vaccine, and hence to facilitate their delivery to the target cells.

Gene therapy

Another future application for ultrasound as a topical enhancer, which seems to show promise, lies in the field of topical gene therapy. Gene therapy is a technique for correcting defective genes that are responsible for disease development, most commonly by replacing an 'abnormal' disease-causing gene with the 'normal' gene. A carrier molecule (vector) is usually used to deliver the therapeutic gene to the target cell. Topical delivery of the vector–gene complex can be used for target cells within the skin, as well as for the systemic circulation. The identification of genes responsible for almost 100 diseases affecting the skin has raised the option of using cutaneous gene therapy as a therapeutic method. The most obvious candidate diseases for cutaneous gene therapy are the severe forms of particular genodermatoses (monogenic skin disorders), such as epidermolysis bullosa and ichthyosis. Other applications might be healing of cutaneous wounds such as severe burns and skin wounds of diabetic origin. Topical gene therapy acquires the penetration of a large complex to or through the skin. Ultrasound pretreatment of the skin will increase its permeability and permit the delivery of the carrying vector.

Conclusion:

Since1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. In order to overcome the skin's barrier function , the physical enhancements penetration enhancer more effective . These approaches are very useful for the drugs having low permeable property , low soluble drugs and for the drugs having short biological half life. To overcome the problems of other techniques physical techniques has been found to be more effective as well as acceptable. Transdermal technology ensures as much as 95% of a supplement reaches the cells where it is needed. Doctors around the world are calling Transdermal delivery "The delivery system of the future" and found fantastic alternative to pills and tablets. Although iontophoresis provides many benefits and seems to be more effective than any other techniques, there is need for further research and judicious use of technology with microelectronics devices and to make it available for commercial application.

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