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PERMEABILITY ENHANCEMENT METHODS USED IN TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route.This review describes physical and chemical skin permeation enhancement techniques.

INTRODUCTION

All conventional oral dosage forms are required to be administered in multiple doses at a particular time interval in a particular amount for an effective therapy. This multiple administration of the drugs has several drawbacks such as inconvenient administration, chances of overdose if administered prior to time interval, lack of patient compliance, skip of dose by the patient, fluctuation of drug plasma level. So to avoid such complications transdermal drug delivery systems are designed. A transdermal patch is as elfcontained discrete medicated adhesive patch which provides convenient route of administration for a variety of complications of skin and body. The barrier properties of the skin provide a significant challenge to drug permeation. By understanding the mechanisms by which compounds cross the skin, it will be possible to develop means for improving drug delivery through the skin. The average surface area of the skin which covers the body surface of an adult is approximately 2 m^2which receives total one third of blood circulation. Each square cm of the skin contains about 10-70 hair follicles and 200-250 sweat glands. Some of the many factors that influence the rate of delivery of drugs across the skin include, the thermodynamic activity of the drug in the formulation, the interaction of the drug and the formulation with the skin, variations in skin with age, race, anatomical region and disease. The release of the drug from transdermal drug delivery system may follow zero (or pseudo zero order) or first order or both kinetics which maintain the desired drug level for prolonged period.

Skin structure[1]

The skin is largest and most external organ of body. It provides a large surface area for drugapplication, combines with the mucosal lining of therespiratory, digestive, and urogenital tracts to form a capsule which separates the internal body structures from external environment. The pH of the skin varies from 4 to 5.6, Sweat and fatty acids secreted from sebum influence the pH of the skin surface.

Functions of skin [1] [18]

1. Protection – from invasion by microbes, chemicals, physical agents (e.g. mild trauma, UVlight), and dehydration.
2. Reflex action – due to sensory nerves to stimuli
3. Regulation of body temperature – regulate body temperature about 36.8°C (98.4°F) with variation of 0.5°C to 0.75°C.

4. Formation of vitamin D :–7- dehydrocholesterol, fatty substance present in skin, in presence of UV light from sun is converted to vitamin D.
5. Absorption – absorbs some drug with low molecular weight as well as toxic chemicals likemercury.
6. Excretion – excretes sodium chloride in sweat, urea when kidney function is impaired, and aromatic substances (e.g. garlic and other spices)

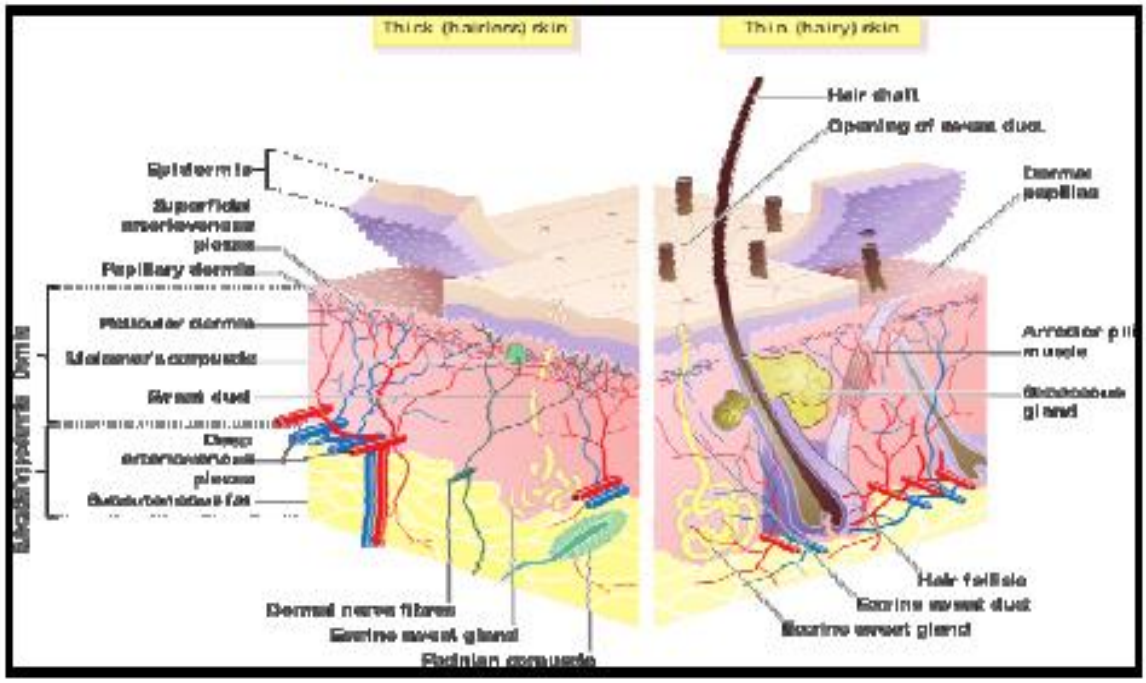
Anatomy and Physiology of skin[1][2][3] [14][17]

Human skin comprises of three distinct but mutually dependent tissues.

A) The stratified, a vascular, cellular epidermis,

B) Underlying dermis of connective tissues, and

C) Hypodermis.



Human Skin (T.S.) Structure[18]

A. Epidermis[1][15] [17][18]

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids.[2] Stratum corneum and the remainder of the epidermis so called viable epidermis cover a major area of skin[17]. The epidermis contains no blood vessels and hence nutrients and waste products must diffuse across the dermo-epidermal layer in order to maintain tissue integrity. Likewise, molecules permeating across the epidermis must cross the dermo epidermal layer in order to be cleared into the systemic circulation. . The source of energy for

lower portions of epidermis is also glucose, and the end product of metabolism, lactic acid accumulates in skin.

The epidermis contains four histologically distinct layers which, from the inside to the outside, are

- Stratum Germinativum (Growing Layer)
- Malpighion Layer (pigment Layer)
- Stratum Spinosum (Prickly cell Layer)
- Stratum Granulosum (Granular Layer)
- Stratum Lucidum
- Stratum Corneum (Horny Layer)

A representation of the 'Brick and Mortar' model of human stratum corneum[1]

Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). A unique feature of mammalian membrane is that phospholipids are largely absent in it. The architecture of horney layer may be modeled as a wall-like structure. In this model, the keratinized cells function as a protein "bricks" embedded in lipid "mortar." The lipids are arranged in a multiple bi layers, and it has been suggested that there is sufficient amphipilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bi layer form. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead Horney cells from the skin surface. As the cells produced bythe basal layer move outward, they alter morphologically and histochemically, undergoingkeratinization to form the outermost layer of stratumcorneum.

B. Dermis[1][2] [16]

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation[4].

C. Hypodermis (Subcutaneous Fat Layer)[1][2]

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and

mechanic protection. It carries principal blood vessels and nerves to skinand may contain sensory pressure organs. For Transdermal drug delivery drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired[4].

Fundamentals of skin permeation[1]

Until the last century the skin was supposed to be impermeable with exception to gases. However, in the current century the study indicated the permeability to lipid soluble drugs like electrolytes. Also it was recognized that various layers of skin are not equally permeable i.e. epidermis is less permeable than dermis. After a large controversy, all doubts about stratum corneum permeability were removed and using isotopic tracers, it was suggested that stratum corneum greatly hamper permeation.

Regional variation in water permeability of stratum corneum[1]

Sr.No.	SkinRegion	Thickness(µm)	Permeation(mg/cm2/hr)	Diffusivity(cm2/secx1010)
1	Abdomen	15	0.34	6.0
2	Volar forearm	16	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13	0.85	12.9
5	Scrotum	5	1.70	7.4
6	Back of hand	49	0.56	32.3
7	Palm	400	1.14	535
8	Plantar	600	3.90	930

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.

Intracellular verses transcellular diffusion

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.

Permeation pathways[1]

Percutaenous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route.

Transcellular

Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds, and endocytosis and transcytosis of macromolecules.

Paracellular

Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient (log k). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants (o/w log k >2) traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs.

Factors influencing transdermal drug delivery[14]

The effective Transdermal drug delivery can be formulated by considering three factors as Drug, Skin, and the vehicles. So the factors affecting can be divided in two classes as biological factors andphysicochemical factors.

A) Biological factors[1][2]

- Skin condition – Acids and alkalis; many solvents like chloroform, methanol damage theskin cells and promotes penetration. Diseased state of patient alters the skin conditions. Theintact skin is better barrier but the above mentioned conditions affect penetration.
- Skin age – The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDSs.
- Blood supply – Changes in peripheral circulation can affect transdermal absorption.
- Regional skin site – Thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect significantly penetration.
- Skin metabolism –Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.
- Species differences – The skin thickness, density of appendages, and keratinization of skin vary species to species, so affects the penetration.

B) Physicochemical factors[1][2]

- Skin hydration – In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectants is done in Transdermal delivery.
- Temperature and pH – The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factorsaffecting drug penetration.
- Diffusion coefficient – Penetration of drug dependson diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.
- Drug concentration – the flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.
- Partition coefficient – The optimal K, partition coefficient is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.
- Molecular size and shape – Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, the effect of molecular size is not known.

Factors affecting permeability [1] [4]

A. Physiological factors:

- Anatomic site of application on the body
- Skin condition and disease
- Age of the patient
- Skin metabolism
- Desquamation (peeling or flaking of the surfaceof the skin)
- Skin irritation and sensitization
- Race

B. Formulation factors

- Physical chemistry of transport

- Vehicles and membrane used
- Penetration enhancers used
- Method of application
- Device used

C. Physicochemical properties of enhancers

- Partition coefficient of 1 or gearter is required
- pH value should be moderate, the flux of ionizable drugs can be affected by changes in pHthat alter the ratio of charged and uncharged species and their Transdermal permeability
- Concentration of penetrant higher than solubility, excess solid drug functions as a reservoir and helps in maintaining constant drugconcentration for prolonged time.

Permeability enhancers[3]:

For many years, clinical investigators and chemical welfare experts have suggested that substances must exist which could temporarily diminish the impermeability of skin. Such materials, if safe and non-toxic, could be used in dermatology to enhance the permeation rate of drugs and even to treat patients systemically by the dermal route. Such materials appear to increase skin permeability by reducing the diffusional resistance of the stratum corneum, by reversibly damaging it, or by altering its physicochemical nature[3]. Ideal penetration enhancers should possess the following properties

(i) Pharmacologically inert

(ii) Inexpensive and cosmetically acceptable

(iii) Nontoxic, nonirritating, and non-allergenic

(iv) Rapid onset of action; predictable and suitable duration of action for the drug used

(v) Reversible effect of the chemical penetration enhancers on the barrier property of stratum corneum

(vi) Chemically and physically compatible with the delivery system

(vii) Readily incorporated into the delivery system[3]

Various technologies have been developed to bypass or modulate the barrier function of the skin& to allow easier passage of drugs into the dermal microcirculation; these can be categorized into:

Physical Approaches

- Iontophoresis .
- Electroporation .

- Microporation.
- Heat.
- Needless injection.
- Medicated tattos.
- Sonophoresis.
- Radio Frequency.
- Magnetophoresis

Chemical Approaches.

- prodrug approaches.
- penetration Enhancer.

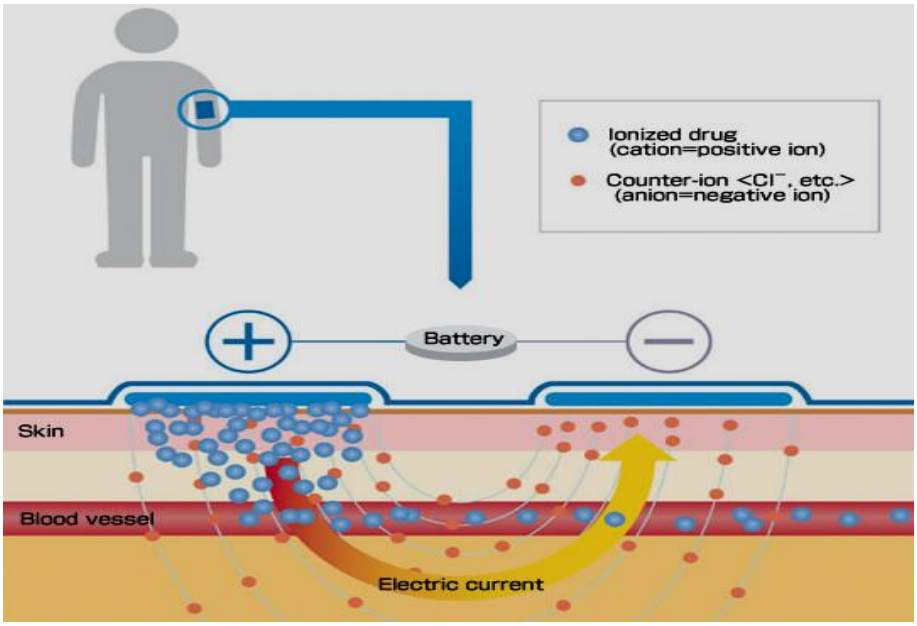
Physical Approaches.

1. Iontophoresis[2][7][8][9][10][11] [14] [15]

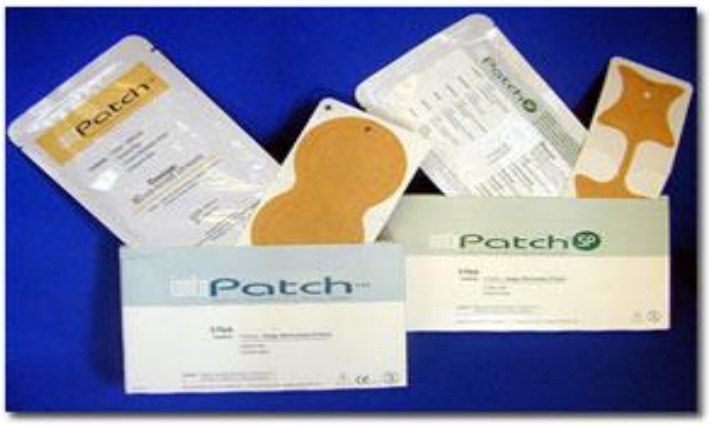
It is a process of enhancing the permeation of topically applied therapeutic agent by the application of electromotive force to drive or repel oppositely charged ions through the dermal layers into the area to be treated, either into the surrounding tissues for localized treatment or into the circulatory system for systemic treatment.The drug is applied under an electrode of the same charge as the drug, and an indifferent counter electrode is positioned elsewhere on the body. The active electrode effectively repels the active substance and forces it into the skin and rough the skin by the application of electric current. Positively charged ions are driven into skin at the anode while negatively charged ions are driven into skin at the cathode. Studies have shown increased skin permeation of drugs at anodic/cathodic electrodes regardless of predominant molecular ionic charge.The limitation of the system isirritation and pain, which limits the dose of the drug. It is currently applied for the rapid deliveryof lidocaine for local anaesthesia[2][8].

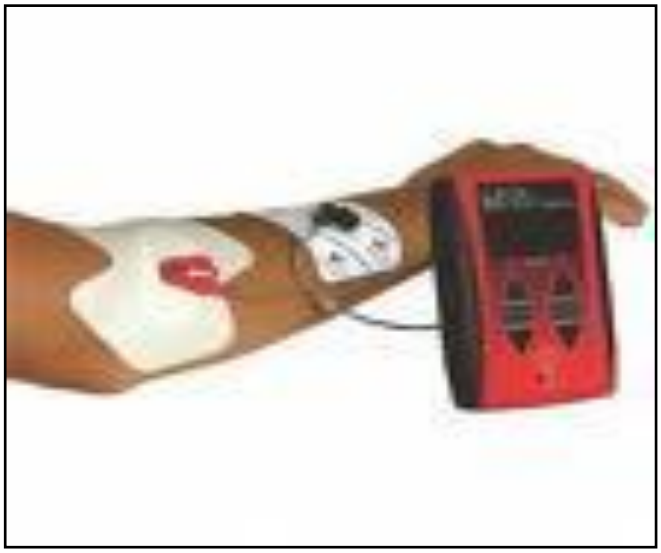
- **Mechanisms.**

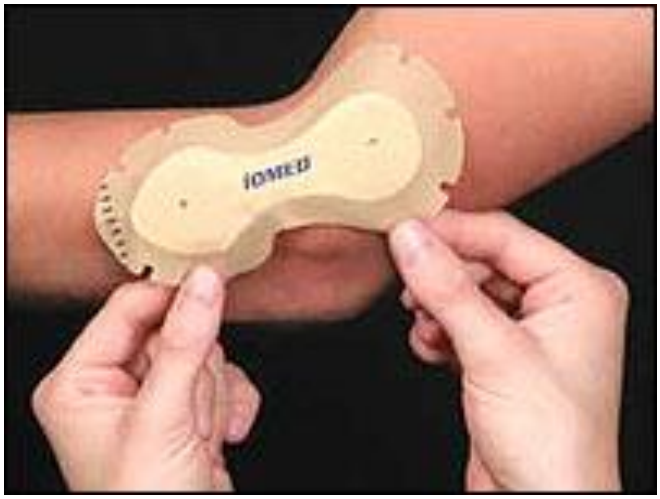
First mechanism proposes that the drug is forced across the skin by simple electronic repulsion of similar charges. Anionic drugs can cross the skin by using a negatively charged working electrode. Similarly, cationic drugs can cross the skin when a positively charged electrode is used.The second mechanism is that the electric current enhances the permeation by inhibiting the skin's ability to perform its protective barrier function.



Iontophoretic Patches





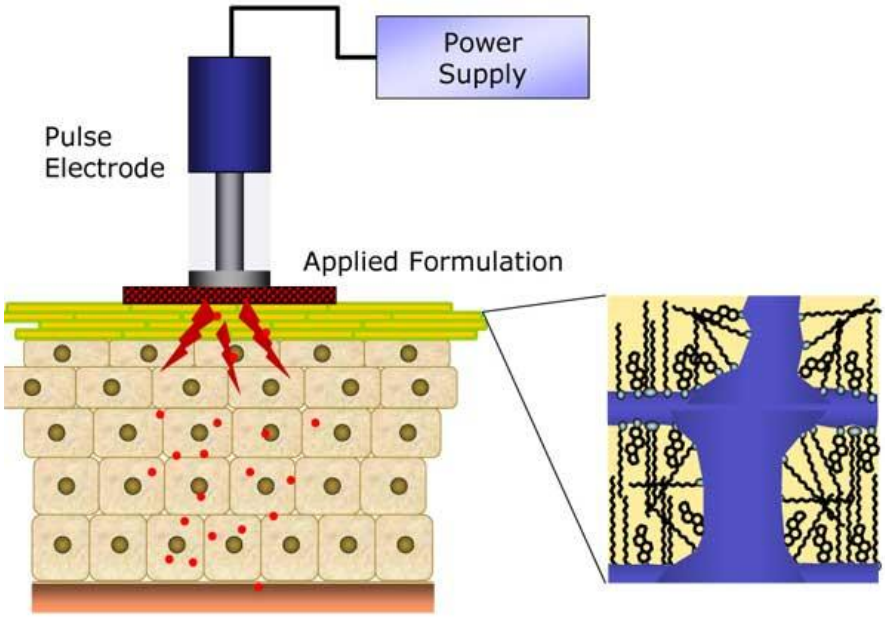


2. Electroporation[8][9][10][11] [14]**.**

Electroporation is another electrical enhancement method. It involves the application of short (microsecond or millisecond), high voltage (50-1000 volts) pulses to the skin. Larger macromolecules have also been delivered by electroporation, including insulin, vaccines,oligonucleotides, and microparticles.A few model compounds such as calcein and LHRHdrugs have also been studied for increased transdermal absorption by electroporation. Electroporation may combinewith iontophoresis to enhance the permeation of peptides such as vasopressin, calcitonin and neurotensin[2].

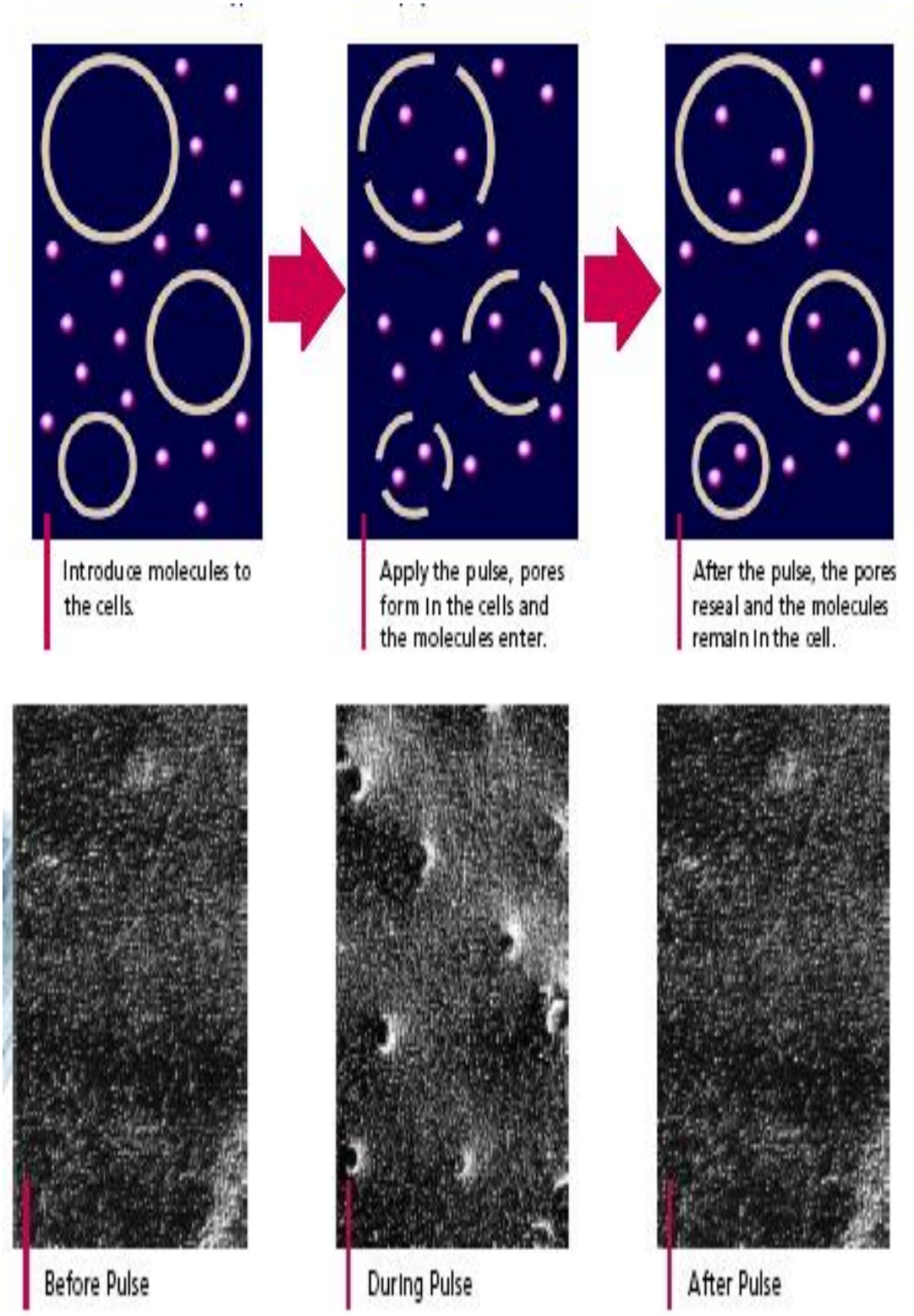
- **Mechanism.**

The mechanism of penetration is the formation of **transient pores**[11]due to electric pulses that subsequently allow the passage of macromolecules from the outside of the cell to the intracellular space via a combination of processes such as diffusion and electrophoresis.



Basic principle of electroporation[11][13]

Short pulses of high voltage current are applied to the skin producing hydrophilic pores in the intercellular bilayers via momentary realignment of lipids .



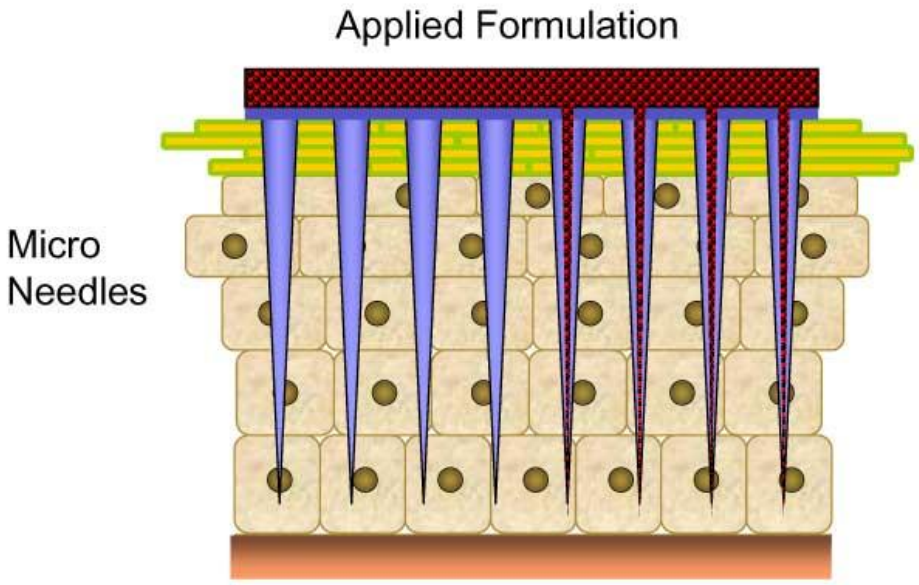
3.Microporation[2][7][8][9][10][11][14]**.-**

One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs was based on the microneedle based method. An array of microscopic needles made frommetal, polymers, silicon or glass can be used to create pathways of microdimension in the skin. The drug can be delivered by variety of mechanisms including:

- directly coating on solid microneedles
- delivering drug through hollow microneedles
- incorporating the drug inside the needleduring fabrication.

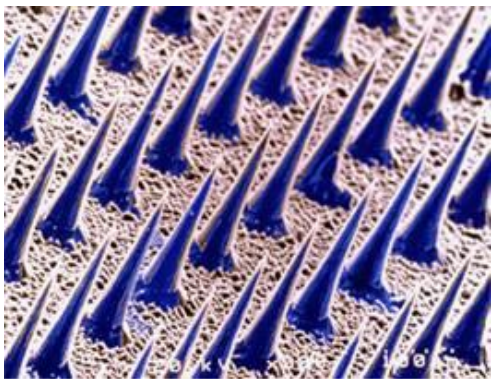
Microporation involves the use of **microneedles** that are applied to the skin so that they pierce only the **stratumcorneum** and increase skin permeability.Microneedles are needles that are 10 to 200 µm in height and 10 to 50 µm in width. . These microneedles of length 50-110 mm will penetrate the stratum corneum and epidermis to deliver the drug from the reservoir and these reservoirs contain drug and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir .

Microneedles do not stimulate the nerves, so the patient does not experience pain or discomfort. They are usually drug coated projections of solid silicon or hollow, drug filled metal needles.

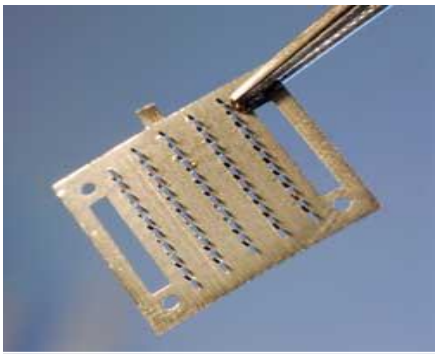


Basic design of µneedle delivery devices[10].

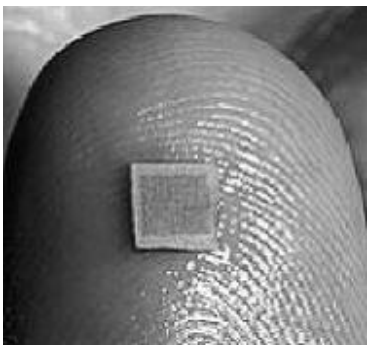
Needles of approximately with or without centre hollow channels are placed onto the skin surface so that they penetrate the stratum corneum and epidermis without reaching the nerve endings present in the upper dermis .



An array of silicon microneedles



An array of stainless steel microneedles



Heat enhances the skin permeation of drugs by increasing body fluid circulation, blood vessel wall permeability, rate-limiting membrane permeability, and drug solubility, thus facilitating drug transfer to the systemic circulation. For example the effect of temperature on in vitro transdermal fentanyl flux was estimated at temperatures of 32° and 37° C. Drug flux approximately doubled over this 5°range.Heat may also cause changes in physiochemical properties of patches, sweating, and increased hydration of skin, thus increasing the permeation of drugs.

❖ Mechanism

When heat is applied, the kinetic energy of drug molecules, proteins, lipids, & carbohydrates is known to increase in cell membrane. Also, drug solubility both in pitch & within the skin may increase with a rise in temperature.

5.Needleless injection[9][10][11]–

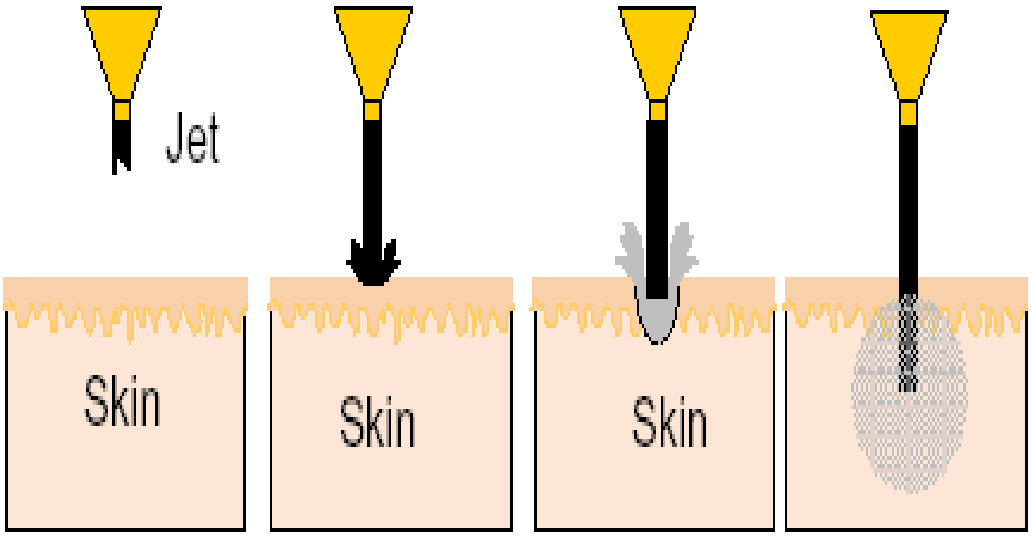
It is a pain free method which involves firing the liquid or solid particles at supersonic speeds through the stratum corneum. Problems with this technique include the high developmental cost for both the device and dosage form and the inability to program or control drug delivery to compensate for intersubject differences in skin permeability.

- Mechanism

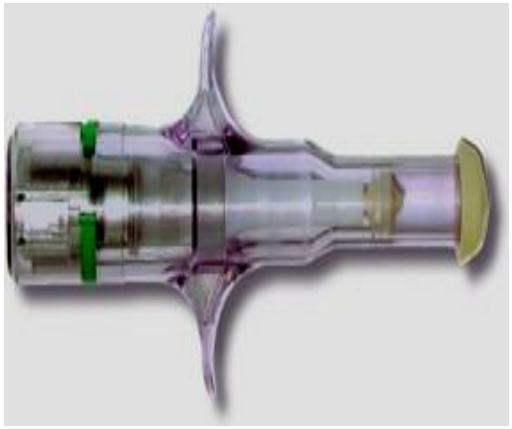
The mechanism involves forcing compressed gas such as helium or nitrogen through the nozzle with the resultant drug particles entrained within the jet flow, reportedly traveling at sufficient velocity for skin penetration[11].

Advantages

- Pain-free delivery — particles are too small to trigger pain [11]
- Improved efficacy and bioavailability.
- Targeting to a specific tissue, such as a vaccine delivered to epidermal cells.
- Accurate dosing and Overcomes needle phobia.
- Safety[11] — the device avoids skin damage or infection from needles or splash back of body fluids.



Needleless Jet Injectors:



6.Medicated tattoos[8][9]**[13] -**

Medicated tattoos are a modification of temporary tattoo. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms[7].It can be applied by wetting with water and pressing against the skin. The tattoo contains a drug layer, a colour design layer, and an adhesive layer that binds to the skin.There is no predetermined duration of therapy.The manufacturer provides a colours chart that can be compared to the colours of the patient's tattoo to determine when the tattoo should be removed.It gives a visual indication as the drug is absorbed into the skin. Upon absorption, the tattoo gradually fades away and is painless to remove with a simple astringent wash containing isopropyl alcohol.The drugs used in medicated tattoos prototypes include acetaminophen, vitamin C.

7. Pressure waves[11]-

Pressure waves generated by intense laser radiation, can permeabilize the stratum corneum as well as cell membrane. Pressure waves is only applied for a very short time(100ns-1μs). It is thought that the Pressure waves form a continuous or hydrophilic pathway across the skin due

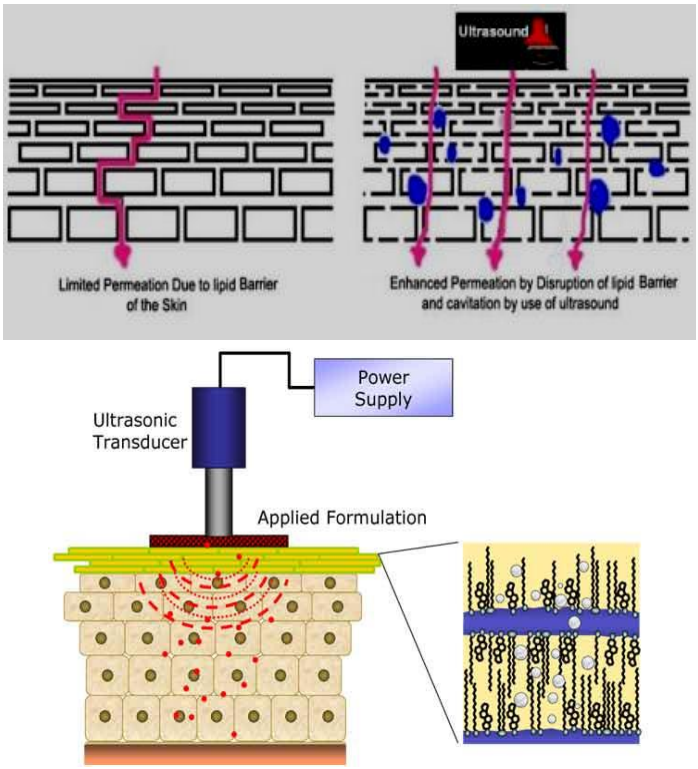
to expansion of lacunae domains in the stratum corneum. A singlepressure waves is sufficient to permeabilise the stratum corneum& allow the transport of macromolecules into the epidermis &dermis.In addition, the drug delivered into the epidermis can enter the vasculature & produce a systemic effect. For example, Insulin delivered by pressure waves resulted in reducing the blood glucose level over many hours. The application of pressure wavesdoes not cause any pain or discomfort & the barrier function of stratum corneum always recovers.

8.Sonophoresis (phonophoresis)[3][**8**][9] [10][11] [14] [15]

Sonophoresis is a technique which involves the use of ultrasonic energy to enhance skin penetration[11] of active substances.This involves rupturing the lipids present in stratum cornea, whichallows the medicament to permeate via biological barrier[7].Transdermal enhancement is particularly significant at low frequency regimens (20kHz< f < 100kHz) than when induced by high frequency ultrasound.Ultrasound parameters such as treatment duration, intensity, pulse length, and frequency are all known to affect percutaneous absorption with frequency being the most important.

Example: Sonophoresis of hypotensive agents and papain has been used in the treatment of eye diseases. Several antibiotics including tetracycline, biomycin, and penicillin have been sonophoretically administered for the therapy of skin diseases.

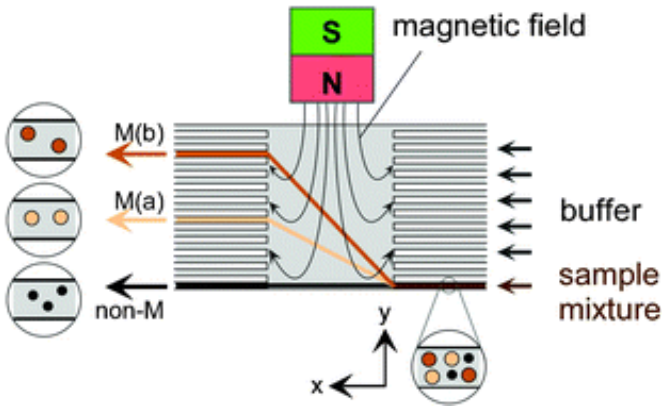
- **Mechanism**
- The mechanism of transdermal skin permeation involves the disruption of the stratum corneum lipids by the formation of gaseous cavities, thus allowing the drug to pass through the skin.



Basic principle of phonophoresis. Ultrasound pulses are passed through the probe into the skin fluidizing the lipid bilayer by the formation of bubbles caused by cavitation .

9.Magnetophoresis[8][9][10][11][12]

The term indicate application of a magnetic field & acts as an external driving force to enhance the drug delivery across the skin.It induce alteration in skin structure so that increase in permeability results[11].Magnetoliposomes consist of magnetic nanoparticles wrapped by a phospholipid bilayer which can be successfully applied for drug delivery systems , magnetic resonance imaging markers for cancer diagnosis,& thermal cancer therapy.



Technique of magnetophoresis[12]

10.Radiofrequency[10][11]

It involves exposure of the skin to a high frequency alternating current off 100KHz that results in the formation of heat-induce microchannels in the cell membrane.The drug delivery rate is controlled by the no. & depth of microchannelsformed[11],which depends on the properties of the microelectrodes in contact with the skin during treatment.. Treatment duration takes less than a secondSkin delivery of testosterone & human growth hormone are in progress by use of this method[19].

Chemical approaches -

Penetration enhancer[3][14] [15] **[16].-**

Incorporation ofsubstances which could temporarily diminish the impermeability of skin, i.e., penetration enhancers facilitates the absorption of drugs by altering the barrier property of the stratum corneum.

A permeation enhancer should be

- pharmacologically inert,
- nontoxic, nonirritating, nonallergic,
- odorless, tasteless, colorless,
- compatible with most drug and excipients,
- inexpensive, and
- Good solvent properties

Different classes of penetration enhancers includes[3]**:**

- Alcohols and polyols (ethanol, propylene glycol).
- Surfactants (Tween, Span, SLS).
- Fatty acids (Oleic acid).
- Amines and amides (Azone, *N* -methylpyrrolidone).
- Terpenes (limonene).
- Sulfoxides (dimethylsulfoxide)
- Esters(isopropylmyristate).

Mechanism:

Permeation enhancers can enhance the skin permeability by mechanisms, including

1. Interaction with intercellular lipids leading to disruption of their organization and increasing their fluidity.
2. Extraction of lipids from the stratum corneum.

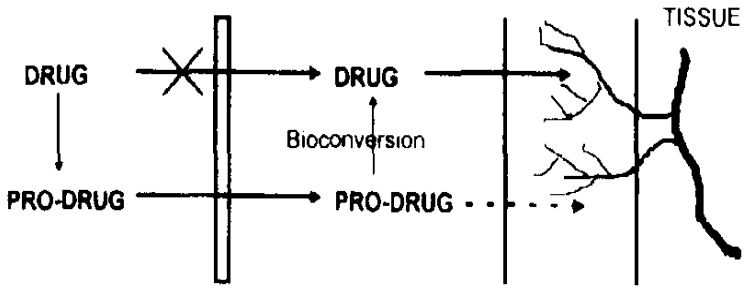
3. Displacement of bound water,
4. Loosening of horny cells,
5. Delamination of stratum corneum.
6. Enhancing solubility and
7. Increasing partitioning into the stratum corneum,
8. Interaction with intercellular protein, and keratin denaturation.

2.Prodrug[14][16]**.-**

Prodrugs are therapeutically inactive derivatives of active drugs.A prodrug undergoes metabolism to produce therapeutically active drug.A prodrug is more lipophilic than the parent drug and has different physicochemical properties.The prodrug approach has been used to enhance the dermal and transdermal delivery of drugs with unfavourable partition coefficients the prodrug design involves addition of a promoiety to increase partition coefficient and also solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimising solubility in the aqueous epidermis[11].

For example: The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S6- acyloxymethyl and 9-dialkylaminomethyl promoieties. The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs, like naltrexone nalbuphine buprenorphin alpha-blockerand other drugs. Different prodrugs were developed for estradiol and "Transdermal Bioactive Hormone Delivery" devices were 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.



Schematic representation of pro-drug approach to increase drug penetration across skin.

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