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Review Article

ABSORPTION PROMOTER: AN OVERVIEW

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ABSTRACT

Dermal or transdermal route is more convenient route of administration than oral or parenteral route of drug delivery. Outer most layer of the human skin is stratum corneum and it is main barrier for penetration of drug through skin and causes reduction in bioavailability of drug. Most of the drugs don't have ability to cross the stratum corneum for that purpose skin penetration enhancers are developed to improve bioavailability of drug and increase range of drugs which can be given by transdermal or topical route. The present review article include need, different approaches of permeation or penetration enhancement contain drug vehicle based, chemical methods physical methods etc and list of patented penetration enhancers. Drug vehicle based method includes complexes, vesicles etc. Chemical method includes use of different chemicals like surfactants, terpenes, alcohol, urea etc. Physical method includes use of methods like microneedle, use of ultrasonic waves, electroporation etc.

Key words: Penetration enhancers, absorption promoter, absorption enhancers, chemical penetration enhancers, physical penetration enhancers.

INTRODUCTION

Tablet, injection and topical formulations are frequently used as drug delivery systems. Oral route is more convenient and accepted route of drug delivery when repeated or routine administration is required¹. It has advantage like easy and self administration, and drawbacks like poor bioavailability due to hepatic metabolism (first pass), tendency to produce rapid high and low blood level, leading to a need for high and/or frequent dosing, which can be costly and inconvenient.² Skin is one of the useful route for delivery of drug to the system circulation. Increasing numbers of drugs are being added to the list of therapeutic agents having disadvantages like hepatic metabolism and gastric track irritation that can be delivered to the systemic circulation via skin with help of Dermal or by transdermal drug delivery systems.³ Outer most layer of the human skin is stratum corneum and it is main barrier for penetration of drug through skin and causes reduction in bioavailability of drug. Most of the drugs don't have ability to cross the stratum corneum for that purpose skin penetration enhancers are developed to improve bioavailability of drug and increase range of drugs which can be given by transdermal or topical route.⁴

Penetration enhancers are the substances and techniques that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin and thereby increase the permeability of drug through skin. Permeation enhancers are also known as absorption promoter or absorption enhancers.^{5, 6, 7} Penetration enhancers are divided into two type's chemical and physical penetration enhancers. Chemical penetration enhancers are technically simpler and therefore popular technique than physical penetration enhancers. Combinations between chemical penetration enhancers and physical methods such as iontophoresis and phonophoresis have been shown to substantially enhance the skin penetration of several permeants.⁸

NEED OF PENETRATION ENHANCEMENT^{9, 10}

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: $J = dM/S \cdot dt$. 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: $R = hs/Ds \cdot Ks$, $P = Ds \cdot Ks/hs$ 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.

ADVANTAGES OF PENETRATION ENHANCERS^{11, 12}

1. Penetration rate of drug sufficiently high for therapeutic efficiency by using penetration enhancers.
2. It is useful for unabsorbable drugs to facilitate their absorption through skin.
3. It can improve transdermal absorption of topical preparation.
4. It is penetration rate determining factor in transdermal drug delivery system.
5. The terpenes like limonene in propylene glycol solution are effective penetration enhancer for cytotoxic drugs.
6. It also acts as rate limiting factor.

DISADVANTAGES OF PENETRATION ENHANCERS

1. The effective concentration varies from drug to drug.
2. The uses of different penetration enhancer with various concentrations are restricted completely.
3. Physicochemical properties of enhancers are also affecting the side effects in the body.

IDEAL CHARACTERISTICS OF ABSORPTION ENHANCERS^{4, 7, 8, 13, 14}

An ideal absorption enhancer should have following characteristics.

1. Absorption enhancers should show reversible effect on skin, and it should not damage the viable cells.
2. It should be pharmacologically inert, non-allergenic, non-toxic and non-irritating.
3. It should show their effect rapidly and for specific period of time.
4. It should be chemically inert, and chemically stable.
5. It should be compatible with the drug and other additives.
6. It should reduce cost.
7. It should only allow drug molecule to pass through skin and should not allow endogenous material like body fluids, electrolytes etc. to come out through skin.
8. It should be pharmaceutically and cosmetically acceptable.
9. It should have a solubility parameter similar to that of skin

DRUG PERMEATION THROUGH SKIN^{9,14,4}

Drug crosses skin barrier through epidermis and skin appendages. Intracellular space is main route of drug permeation. There are two main routes for drug permeation through skin as shown in Figure 1.

1. Intercellular route
2. Transcellular route
3. Transappendage route
4. By solubilizing the skin-tissue components.
5. Improved partition of the drugs, co-enhancers or cosolvents into the stratum corneum.

PHYSICO-CHEMICAL ASPECTS OF SKIN PENETRATION¹⁵

Passive Kinetic process of drug diffusion through skin involved the concentration gradient from a region of high concentration to a region of lower concentration. Steady state equation can be described by Fick's first law of diffusion. The equation describes rate of transfer (flux, J) of a diffusing substance through the unit area A of the membrane and diffusion coefficient, D to the concentration gradient across the membrane (dc/dx).

$$J = -AD \left(\frac{dc}{dx} \right) \quad (1)$$

The negative sign in eq. (1) is because the diffusion process occurs in the opposite direction to increased concentration. Fick's second law of diffusion, Eq. (2) can be derived from eq. (1) to describe membrane transport under non steady state condition.

$$\frac{dc}{dt} = D \frac{d^2c}{dx^2} \quad (2)$$

By maintaining the sink conditions in the receptor compartment and maximum fixed concentration in the donor compartment, the eq. (2) can be written as

$$J = AD \left(\frac{C_m}{h} \right) \quad (3)$$

Where, C_m is the concentration in the donor-membrane interphase and h is effective diffusional path length. The C_m in the eq. (3) can be used to replace by vehicle membrane partition coefficient (K) as ratio between concentration of permeant in the membrane at the donor-membrane interface and the vehicle in

which applied (C_v). Modified Fick's first law of diffusion describes the steady-state flux across the membrane eq. (4)

$$J_{ss} = ADKc_v/h \quad (4)$$

We can conclude that increased drug flux can be achieved by a change in D, K, and C. the compounds which are skin penetration enhancers should potentially change the solubility or partition behavior of the drug into stratum corneum or its diffusion properties or both. Sometimes change in thermodynamic activity of drug in the formulation manipulate the flux.

DIFFERENT APPROACHES OF PERMEATION/PENETRATION ENHANCEMENT^{8,9}

Following methods shown in Figure 2 can be used for enhancement of penetration through the stratum corneum are given below

A. DRUG VEHICLE BASED

1. DRUG SELECTION⁹

Drug should be selected in such a way that it fits in the criteria of transdermal delivery as follows:

Parameters for Drug selection^{9, 3, 11, 17, 19}

1. Aqueous solubility >1mg/ml
2. Lipophilicity $10 < K_o/w < 1000$
3. Molecular weight <500 Daltons
4. Melting point <200°C
5. pH of aqueous saturated solution 5-9
6. Dose deliverable <10mg/day

2. VESICLES AND PARTICLES¹⁶

2.1. LIPOSOMES³³

Liposomes are lipid vessels or colloidal particles having concentric bimolecular layers that are capable of encapsulating drugs. Liposomes fully enclose an aqueous volume. These are usually formulated from phospholipids and with or without some additives. Cholesterol are included to improve bi-layer characteristics of liposomes; increasing micro viscosity of the bi-layer, reducing permeability of the membrane to water soluble molecules, stabilizing the membrane and increasing rigidity of the vesicles. Liposomes act as absorption promoters by penetrating the epidermis, carrying the drug into skin and those large multi-lamellar vesicles could lose their external bi-layer during penetration and these liposome lipids penetrate into the stratum corneum by adhering onto the surface of the skin and, subsequently destabilizing, and fusing or mixing with the lipid matrix.

2.2. TRANSFERSOMES²⁰

These are vesicles consists phospholipids as main ingredient with 10-25% surfactant and 3-10% ethanol. Liposomes are too large to pass through pores of less than 50nm in size; transfersomes up to 500nm can easily penetrate the stratum corneum barrier of skin.

2.3 ETHOSOMES^{16, 19}

These are liposomes with high alcohol content (up to 45%). Ethosomes are capable to increase penetration into deep tissues and the systemic circulation. It is proposed that the alcohol fluidizes the ethosomal lipids and stratum corneum bi-layer lipids so allowing the ethosomes to penetrate through skin.

2.4. NIOSOMES

These are vesicles are generally prepared from non ionic surfactants. Niosomes are more stable than liposomes also requires low cost for formulation. Niosomes seems an interesting drug delivery system in the treatment of topical disorders. Topical application of niosomes increases the

residence time of drugs in the stratum corneum and epidermis and also reduces the systemic absorption of the drug.

2.5. SOLID LIPID NANOPARTICLES (SLN)

Nanoparticles are colloidal drug delivery systems having a diameter of approximately 200-500nm. SLN have recently been investigated as carriers to enhance drug delivery through skin. Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions comprises solid biodegradable lipids. SLN formulations can use for various application routes (parenteral, oral, dermal, ocular, pulmonar, rectal) have been developed and thoroughly characterized in vitro and in vivo.

2.6 DENDRIMERS

Dendrimers are monodisperse populations that are structurally and chemically uniform. They allow conjugation with numerous functional groups due to the nature of their branches. This dendrimer-drug association increases solubility and transport through biological membranes and sometimes increasing drug stability. Dendrimers interact with lipids present in skin membranes and increases permeation. Dendrimers also act like solubility enhancers, increasing the permeation of lipophilic drugs.

3. PRODRUGS AND ION PAIRS

The prodrug approach has investigated to increase dermal and transdermal delivery of drug. The prodrug design strategy contains addition of a promoiety in structure to increase partition coefficient and thereby solubility and transport of the parent drug in the stratum corneum. When prodrug reaches to epidermis promoiety release the parent drug by hydrolysis thereby optimizing solubility in the aqueous epidermis.

4. CHEMICAL POTENTIAL OF DRUG

The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. Supersaturated solutions can occur due to evaporation of solvent or by mixing of cosolvents. Clinically, The most common mechanism is evaporation of solvent from the warm skin surface, which probably occurs, in many topically applied formulations. In addition, if water is imbibed from the skin into the vehicle and acts as an anti-solvent, the thermodynamic activity of the permeant would increase⁸⁵. Increases in flux of drug up to five to ten folds have been reported from supersaturated solutions of a number of drugs. The potential benefit of supersaturated solutions was first recognized at least three decades ago.

5. EUTECTIC SYSTEMS

The melting point of a drug increases solubility and thereby increases skin penetration. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture: a mixture of two components which, at a certain ratio, inhibit the crystalline process of each other, such that the melting point of the two components in the mixture is less than that of each component alone. The melting point of the drug was depressed to around or below skin temperature thereby enhancing drug solubility.

6. COMPLEXES

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility of lipophilic drug and also increase their stability. Cyclodextrins alone is less effective as penetration enhancer than when combined with fatty acids and propylene glycol.

B. CHEMICAL PENETRATION ENHANCERS^{4, 15,13,2, 21, 25}

1. SULPHOXIDES²²

Sulphoxides like dimethylsulphoxide (DMSO) and decylmethylsulphoxide (DCMS) are used as skin penetration enhancers. DMSO is a powerful aprotic solvent with a high dielectricity constant because of the S-O-bond polarity. The dissolving power of DMSO for salts and polar compounds is very high and because of its dissolving properties DMSO formed solvent-filled spaces in the stratum corneum where the solubility of the drug substances is increased. Above 65% concentration DMSO is able to disrupt lipids of the stratum corneum and increases penetration through skin. A denaturation of intercellular structural proteins of the stratum corneum by DMSO and DCMS has been postulated as an additional reason for the promotion of skin penetration when using sulphoxides as enhancers.

2. ALCOHOLS

Ethanol is the commonly used as penetration enhancer and commonly used in many transdermal formulations and in patches. Alcohol increases the solubility of the drug in the formulation and increases its penetration through skin by extracting lipids and proteins of stratum corneum. Thus increases the penetration of hydrophilic drug substances. Alcohol also increases penetration of lipophilic drug because of their high solubility in lipophilic areas of skin.

3. POLYOLS

Among polyols propylene glycol is the most commonly used co-solvent in topical formulations. Propylene glycol is able to penetrate and thereby can transport lipophilic substances by solvent drag. It shows better penetration for alcohol soluble drug than water soluble. It solubilize keratin within the stratum corneum by competition with water for the hydrogen bond binding sites and the intercalation in the polar groups of the lipid bi-layers by propylene glycol are postulated as mechanisms of action for the penetration.

4. FATTY ACIDS

More frequently used fatty acid as penetration enhancer is oleic acid. Oleic acid molecules at higher concentrations are able to form separate phases within the bi-layer lipids. This lead to permeability defects within the bi-layers and facilitate the permeation of hydrophilic compounds through the stratum corneum.

5. ESTERS

Esters are also frequently used skin penetration enhancers for example Ethyl acetate, methylacetate, Butyl acetate, Methylpropionate, Isopropyl-n-butyrate, Isopropyl-n-decanoate, Isopropylmyristate, Isopropylpalmitate etc.

6. TERPENES AND RELATED SUBSTANCES⁷

These are highly lipophilic compounds having high octanol/water permeation coefficients. Terpenes are nonaromatic ingredients of essential oils and consist of carbon, hydrogen and oxygen atoms only. As penetration enhancers, they interact with intercellular lipids and influence the nonpolar penetration route. Co-solvents like propylene glycol or ethanol have synergistic effects when added to the terpenoids.

7. SURFACTANTS²⁶

Surfactants are frequently used as emulsifiers in formulations. They are added generally use to solubilize lipophilic actives within the formulations. The improvement of the drug solubility can be achieved by the formation of micelles of surfactant

molecules in the formulation. Surfactants have the potential for the solubilization of the stratum corneum lipids and thus act as penetration enhancers. Cationic surfactants are more effective as penetration enhancers than anionic or nonionic compounds. The potential for skin irritation is connected with the penetration-enhancing effects of the surfactants. Therefore, in formulations for dermal application, mostly nonionic surfactants are used, which tend to be widely regarded as safe. Surfactants with an analogue structure to the stratum corneum bi-layer lipids have low skin-irritating potentials, but also low skin penetration-enhancing effects.

8. AZONE

The penetration- enhancing effects of azones is due to an intercalation into lipids of the stratum corneum and the disturbance of the lipid packing order. Presence of Azone derivatives causes decrease in the cholesterol-cholesterol interferences and the cholesterol-ceramide interactions. The fluidity of the hydrophobic stratum corneum regions is increased and also increases permeation.

9. PYRROLIDONES

Pyrrrolidones are able to increase penetration of hydrophilic drugs and lipophilic drug substances for example N-Methyl-2-pyrrolidone (NMP), 2-pyrrolidone (2P) and 2-pyrrolidone- 5-carboxylic acid.

10. UREA

Urea acts as permeation enhancer by facilitating hydration of the stratum corneum by the formation of hydrophilic diffusion channels within the barrier.

11. ALKYL-N, N-DISUBSTITUTED AMINOACETATES

Dodecyl-N, N-dimethylaminoacetate and dodecyl-2-methyl-2-(N,N dimethylaminoacetate) (DDAIP). These substances are water insoluble, soluble in most of the organic solvents and in water and alcohol mixtures. As the length of N, N-dialkyl carbon chain increases decreases the penetration enhancing activity. This is due to the biological decomposition of these enhancers by the skin enzymes to N, N-dimethylglycine and the corresponding alcohols. They enhance skin penetration by the interaction with stratum corneum keratin and the increase in the hydration efficiency resulting from these interactions.

12. VITAMIN E

Vitamin E (α -tocopherol) is also used as skin penetration enhancer. It acts as a penetration enhancer by intercalating within the lipid bi-layer region of the stratum corneum, thus altering the characteristics of the membrane affecting permeability, presumably by disordering gel phase lipids.

C. PHYSICAL METHOD ^{12, 28, 27}

1. IONTOPHORESIS: ^{11, 12, 23, 29, 30}

The iontophoresis increases permeation of solute molecules through tissue by using an electric current. Highly lipophilic nature of skin resists the permeation of water soluble, high molecular weight and charged compounds through the stratum corneum into the systemic circulation as shown in Fig.3. Iontophoresis is external source of energy in the form of an applied direct electric current which is responsible for the movement of ions of drug across the stratum corneum.

2. ULTRASOUND PHONOPHORESIS AND SONOPHORESIS³¹

Another technique attempting to increase permeation involves the use of high or low frequency ultrasound waves. Ultrasound

waves alter the skin porous pathways any of the two mechanisms by enlarging the skin pores or creating more pores shown in Figure 4.

3. MAGNETOPHORESIS: ³²

Magnetophoresis is a novel approach of permeation enhancing. Exposure of a magnetic field causes structural alterations and increase in skin permeability.

4. ELECTROPORATION^{15, 31}

Electroporation increases permeability to ions and macromolecules by exposing the cell to short high electric field pulses. Because of electric field there is breakdown of the cell membrane occurs and form pores in the membrane and hence called as Electroporation (Figure 5).

5. LASER RADIATIONS

Laser radiation involves the direct exposure of skin to a controlled beam of Laser radiations which removes stratum corneum without damaging the underlined epidermis. The permeation of lipophilic and hydrophilic drug molecules can be increased by this technique.

6. RADIO-FREQUENCY

Radio frequency technique involves the exposure of skin to high frequency alternating current (~100 kHz) which produces microscopic passages in the stratum corneum. This whole process is called cell ablation.

7. THERMOPHORESIS

In this technique the skin permeability is increased by increasing the skin surface temperature. Following mechanisms may be involved in increasing the skin permeability in thermophoresis technique;

Increased lipid fluidity which in turn increases drug diffusivity in vehicle and in the skin as well.

Vasodilatation of the subcutaneous blood vessels.

It has been reported that an exposure to low (freezing) temperature may reduce the barrier function of the skin. However, still low temperature hasn't been implemented practically as transdermal enhancing technique.

8. MICRONEEDLE TECHNOLOGY

The microneedles technology consist micron-sized needles made from silicon. Microneedles are fabricated with different range of size, shape and materials. Penetrate the upper layer of skin without reaching the dermis, to be an efficient method to deliver drugs transdermally in an almost painless method. Mechanism of action of microneedles penetrates the stratum corneum and epidermis to deliver the drug from the reservoir as shown in Figure 6. The reservoir may contain drug, solution of drug, gel, solid particulates, enclosed in membrane to separate the drug from the skin and control release of the drug from its reservoir.

CONCLUSION

Skin permeation enhancement technology is a rapidly developing field which would significantly increase permeation of the number of drug through skin; skin is one of the major routes of drug administration. Chemical, Physical etc are different absorption promoters can use to increase absorption of drug through skin with this absorption promoter can reduce the disadvantages associated with parenteral, oral route. Numbers of chemical compounds are evaluated for penetration- enhancing activity, and different modes of action are identified for skin penetration enhancement.

Table 1: Patented penetration enhancers

Sr. No.	Patent No	Title	Inventor, Year
1	US8383149 B2	High enhancer-loading polyacrylate formulation for transdermal applications	Jay Audett et al 2013
2	EP1744714 A4	Transdermal delivery system for use with basic permeation enhancers	Tsung-Min Hsu et al 2009
3	CN101522020 A	Penetration enhancer for plant-compatible concentrates that can be dispersed in water	
4	EP1390024 A1	Isostearic acid salts as permeation enhancers	Mangaraju Gudipati et al 2004
5	EP0857488 B1	Compositions for enhancing skin permeation of drugs using permeation enhancers	Prakash Parab et al 2004
6	EP0913158 B1	Transdermal patch comprising a combination of two or more fatty acids or alcohols as permeation enhancers, a tackifier agent and a cohesion improver to improve adhesion properties	Dario Carrara et al 2003
7	US6299900 B1	Dermal penetration enhancers and drug delivery systems involving same	Barry Leonard Reed et al 2001
8	WO1998018417 A1	Fatty acid esters of lactic acid salts as permeation enhancers	Srinivasan Venkateshwaran et al 1998
9	US5843468 A	Skin permeation enhancer compositions comprising glycerol monolaurate and lauryl acetate	Terry L. Burkoth et al 1998
10	US5601839 A	Triacetin as a penetration enhancer for transdermal delivery of a basic drug	Danyi Quan et al 1997
11	WO1996033678	Triacetin as a transdermal penetration enhancer	Danyi Quan et al 1996
12	US4956171 A	Transdermal drug delivery using a dual permeation enhancer and method of performing the same	Yunik Chang et al 1990
13	US4820720 A	Transdermal drug composition with dual permeation enhancers	Harold F. Sanders et al 1989
14	US4879275 A	Penetration enhancers for transdermal delivery of systemic agent	Gevork Minaskanian et al 1989
15	US4732892 A	L- α -amino acids as transdermal penetration enhancers	Pramod P. Sarpotdar et al 1988
16	EP0268222 A2	Penetration enhancers for transdermal delivery of systemic agents	James V. Peck et al 1988
17	US4762851 A	Pyroglutamic acid esters used as dermal penetration enhancers for drugs	Jose Alexander et al 1988

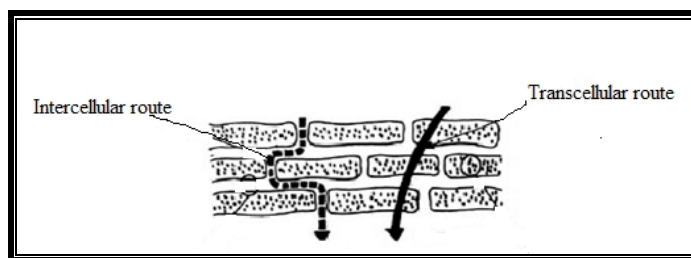


Figure 1: Skin structure and mechanism of penetration through skin⁹

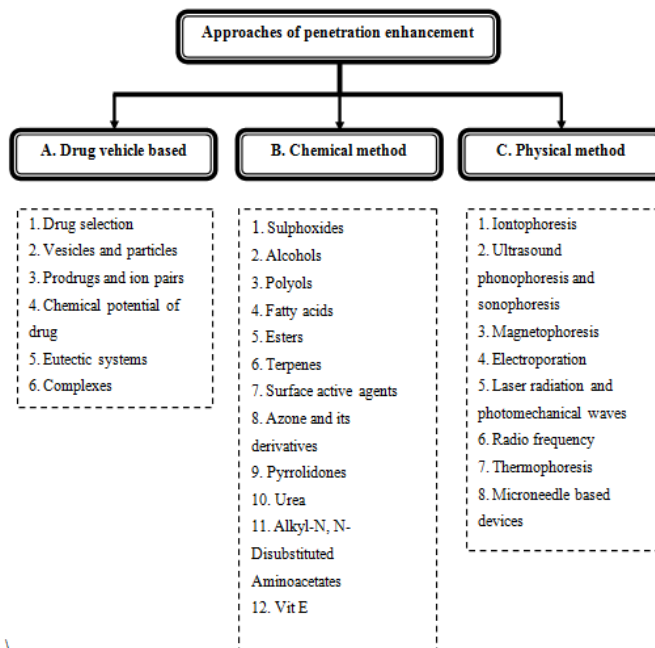


Figure 2: Approaches of penetration enhancement

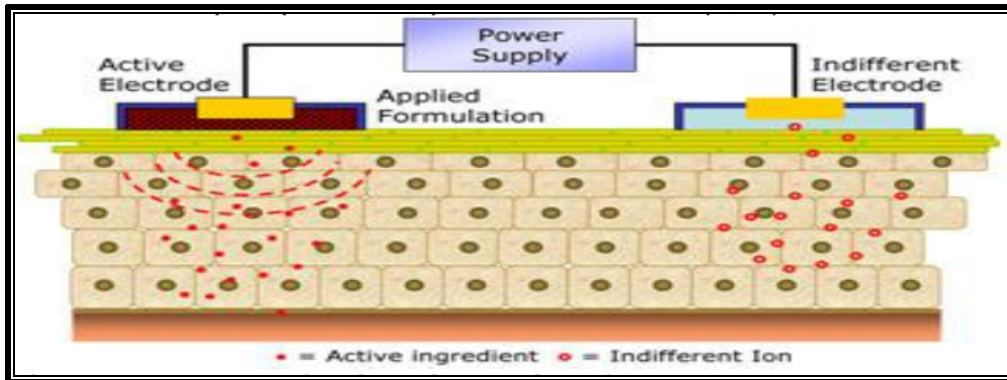


Figure 3: Iontophoresis²⁸

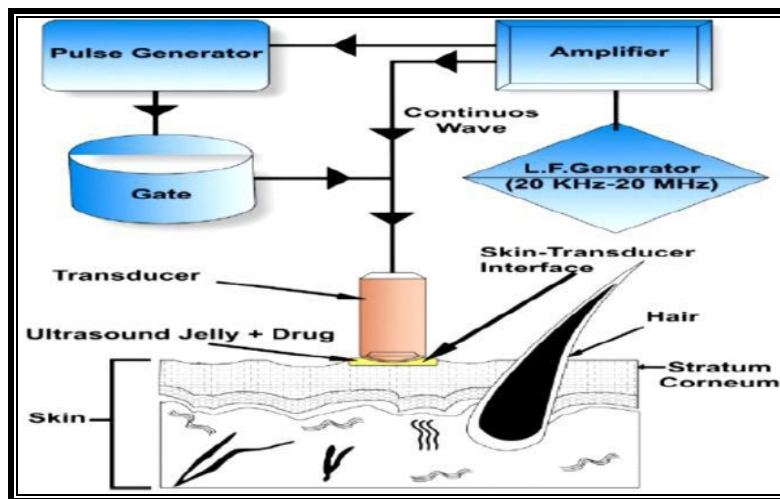


Figure 4: Sonophoresis²³

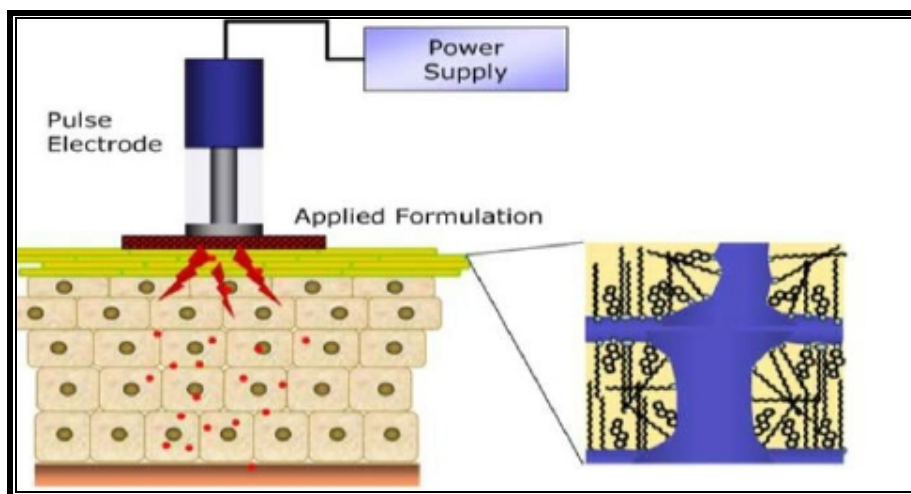


Figure 5: Electroporation²³

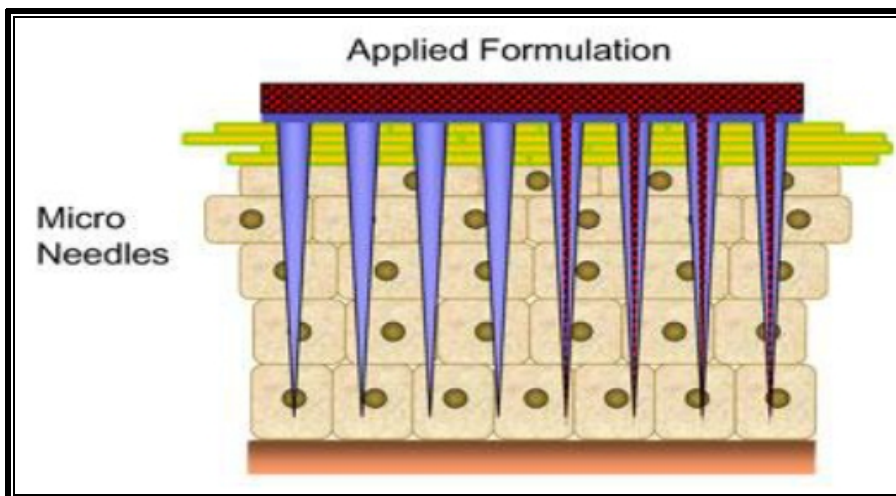


Figure 6: Microneedle technology²⁸

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