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REVIEW ARTICLE ON PERMEATION ENHANCERS: A MAJOR BREAKTHROUGH IN DRUG DELIVERY TECHNOLOGY

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ABSTRACT: The human skin serves as an impediment, a thermo regulator and prevents excessive loss of water from the internal organs. Various ways of transferring the drugs have been developed by modifying the barrier properties of the skin. Enhancement in skin penetration by hydration of the stratum corneum, or by use of chemical enhancers acting on the lipids and keratinized structures in the stratum corneum, partitioning and solubility effects is a promising tool in potential clinical applications. Penetration enhancement is a new emerging technology which has the potential to increase the number of drugs taken trans-dermally. Also the drugs with short biological half-life could be easily administered. Among many advantages over other routes the three crucial ones are avoiding metabolism in liver, minimal negative effects and increased bioavailability. Also, the stratum corneum prevents the loss of physiologically essential substances and as a result provides penetration resistance by acting as a protective barrier. This is the rate limiting step in the absorption of the drug percutaneously. In this review article, we present a summary of various advances made in the field of permeation enhancers based on literature survey of various research articles.

INTRODUCTION Permeation enhancers are those substances which promote the absorption of drug through the skin temporarily by transiently enhancing the skin permeability. They are employed to transfer the delivery of drugs which are ionizable (Example: timolol maleate) and impermeable (Example: heparin); to maintain drug levels in blood, to provide higher dose of less potentially active drugs (Example: Oxymorphane), to deliver high molecular weight hormones and peptides and to lessen the lag time of transdermal drug delivery system [1, 2].

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Ideal Characteristics of Permeation Enhancers:

1. These materials should be biocompatible i.e. it should not cause irritation or any allergic response both in the short as well as the long run. Also it should not induce toxicity[3]
2. It should be compatible with the drug being given.
3. It should not exhibit any adverse pharmacological activity inside the body.
4. It should not be expensive and possess good solvent properties.
5. It should not have color, odor and taste.
6. It should be stable chemically as well as physically.
7. The course of action should be reproducible, sustainable and rapid.
8. It should be tested in vitro also.
9. It should not cause leakage of body fluids and endogenous materials (unidirectional flow), and as soon as such substances are removed, the

skin should immediately restore its natural barrier properties.

Ideally, there is no penetration enhancer to possess all the above properties. The major task is to reduce the allergic response. However, substances exhibiting majority of these attributes are used as enhancers. They have been tested in laboratories and clinics.

Pathway of Transdermal Permeation: There are three ways in which permeation occurs. These are mentioned in the table below:

TABLE 1: PATHWAYS OF TRANSDERMAL PERMEATION

Type	Route
Transdermal	Through the SC
Intercellular	Through the skin barrier , SC
Trans-appendage	Via cavities associated with hair roots, sebaceous glands, small muscles and sweat glands

Approaches for permeation enhancement:
There are mainly three approaches for the penetration enhancement [4].

a) Chemical approach
b) Biochemical approach
c) Physical approach

A. Chemical Approach:
Mechanism: Penetration enhancers follow three main routes, they are:

1. Causing disruptions in the highly organized structure of stratum corneum.
2. Interaction with proteins present intercellularly.
3. Improved drug partitionin the stratum corneum with help of co-enhancer (i.e. solvent) [5].

The enhancers act by manipulating either of the three pathways. There are two ways to achieve this, by bringing about a conformational change in the skin proteins or by swelling of the solvent. The fatty acid enhancers for example make the stratum corneum more lipophilic. The purpose of the enhancers is to make the drug more easily soluble on the SC and thus make them diffuse into the skin surface. The equation given below gives the factors which affect rate of drug permeation through the SC for steady state flux [4]. This equation gives a relation between the steady flux, dm/dt, and mass m of the diffusing substance per unit area:

$$dm/dt = D\ Co\ K\ /h$$

Where,
Co- constant drug concentration in donor solution,
K - Partition coefficient of the solute present between the membrane and bathing solution,
D- Diffusion coefficient and
h– Membrane thickness.

Various permeation enhancers have been discovered so far and are being used for decades to benefit mankind, some of the most widely used ones are illustrated below:

I. Alcohols: Alcohols canincrease skin permeation by a various mechanisms such as lipids and protein extraction, stratum corneum swelling and thus improving partitioning of drug into host skin or drug solubility in the formulation [6, 7]. Some examples are:

Polyols: Propylene glycol (PG): Propylene glycol promotes flux of heparin sodium hydrochloride and verapamil hydrochloride and also ketoprofen. At high concentration, propylene glycol stops the flux of ketoprofen. Propylene glycol when combined with azone, enhances the flux of cyclosporine A and methotrexate. PG solvates SC keratin, thus occupying the sites with hydrogen bonding. When PG is combined with azone, large amounts of glycolenter the tissue toincrease intracellular drug diffusion. The drug fluxis directly proportional to length of carbon chain (upto six carbon atoms) in n-alcohols. These alcohols promote extraction of lipids from SC and thus increase absorption. A saturated solution of terpenes in a PG-water co-solvent system was made which enhanced the flux of 5-FU(fluorouracil). The activity of terpenes was related to PG content and the maximum flux was obtained from drugs with 80% PG content. Also, PG increases the partitioning of the drug. PG in conjunction with 5% oleic acid showed an increase in the flux by 10 times.

Short chain glycerides: Short chain glycerides like glyceryl mono-caprylate, enhances partitioning capability of papaverine. Short-chain glycerides have also proved to be good permeation enhancers (e.g., TCP). It is a remarkable hydrophobic system which promotes the absorption of tegafurin combination with ethyl alcohol.

II. Amines and Amides:

Urea promotes drug penetration trans-dermally by:

- Promoting hydration of the SC (Stratum Corneum)
- Formation of diffusive channels with water attraction(hydrophilic) property for drug.

Cyclic urea permeation enhancers consist of a polar parent moiety and a long chain alkyl ester group. Therefore, enhancement occurs via interplay of hydrophilic activity present and the lipid disruption method. They are non-toxic and biodegradable. Other examples include dimethyl acetamide and dimethyl formamide.

III. Cyclodextrines: Cyclodextrins are reportedly biocompatible. In order to increase solubility especially in aqueous solutions they get complexed with lipophilic drugs. The flux across non-hairy skin of rodent (mouse) gets increased thrice when piroxicam forms an inclusion compound with β-cyclodextrin. Carbopol hydrogel's release profile through cellulose nitrate membrane was improved by complexing clonazepam with methyl-β-cyclodextrin. To increase their critical micellar concentration, Cyclodextrinsget complexed with enhancers (quaternary ammonium salts). As a result harmfulness of the enhancers decreases. Absorption results of alprostadil (AP) from β-cyclodextrin complex and O-carboxymethyl-O-ethyl-β-cyclodextrin (CME-β-CD) complex were obtained. These were compared with hair-freeskined mouse. HPE-101 (1-[2-(decylthio) ethyl] azacyclopentan-2 one) was the permeation enhancer used. Former one displayed 10 times lesser flux. Therefore, it was inferred that a complex of CME-β-CD with HPE-101 enhances drug bioavailability.

It was concluded by Lofts son and Masson that there might be a relation between the effect of skin penetration of drug and cyclodextrin concentration that too with flux amount reduced which is commonly observed at high concentrations of cyclodextrins. At higher concentrations of cyclodextrin, it forms a complex with free drug and thus reduces flux.

IV. Fatty acids (FAs): Fatty acids and ester derivatives of these are used as absorption enhancers. Unsaturated FAs are better enhancers than saturated ones. Palmitoeic acid is the most important permeation enhancer. It showed a 640 times increment in hydrocortisone absorption through hairless mouse skin. On the other hand unsaturated FAs are required to stay in their free original form for exhibiting enhancement activity.

V. Pyrrolidones:

N-methylpyrrilidone: Pyrrolidones along with their derivatives are known to have excellent potential as transcutaneous absorption enhancers.

NMP: N-methyl-2-pyrrolidone (NMP) is the most commonly used pyrrolidone known to enhance skin permeation widely. For example, it multiplied the flux of the ibuprofen, an anti-inflammatory drug by 16 times and lux of flurbiprofen by 3 times through numb skin surface. Kim and Chien are two scientists who studied the NMP effect on absorption of certain anti-HIV drugs like zidovudine through the SC. They performed their studies on hairless mouse skin at 37°C. Studies show that ratio of 50:50 of aco-solvent of v/v of1% NMP made in ethanol to tricaprylin (TCP) had no effect on permeation. Various enhancers which were made using 2-pyrrolidone. They at The 1stand 3rd position of the pyrrollidone ring had a small alkyl group and a dodecyl group respectively. Studies showed that a small length alkyl group attached at the first position had a good effect on enhancement property.

1-Propyl and 1-butyl-3-dodecyl-2-pyrrolidone in a 60 wt. % ethanolic solution shows good increase inpermeation of indomethacin through the SC [8].

Azones: Azone forms one of the major classes of surface permeation enhancers. The flux of methotrexate and piroxicam increased when PG was complexed with azone. Azone and PG are a great combination. Azone promotes intercellular transport. PG promotes intracellular transport. Azone and PG act as great permeation enhancers across the stratum corneum through both hydrophilic and lipophilic routes [9]. Azone is known to facilitate the flow through the lipid bilayer. PG facilitates hydrophilic content of the protein region. Azone in combination with PG increases the absorption of hydrophilic drugs considerably.

VI. Sulfoxides: Dimethyl sulfoxide, decylmethalsulfoxide: Dimethyl Sulphoxides (DMSO) is also used as a compound to increase permeation of drugs. It acts as an aprotic solvent as it undergoes intracellular hydrogen bonding rather than forming hydrogen bonds with water. It is widely used in pharmaceutical engineering. As it can dissolve anything and everything therefore, it is also termed as a "Universal Solvent". It does not have any kind of color as well as odor. But it has its own disadvantages. DMSO usage provides concentration dependent effects in a system. For increased efficiency of enhancement, co-solvent concentration of greater than 60% is required. The problem is that at such high concentrations DMSO can cause erythema and it can also damage the surface of stratum corneum. DMSO is widely used as a penetration enhancer to denature skin proteins results in erythema, stinging and burning sensation. Other aprotic solvents are DMAC and DMF. South well along with Barry demonstrated that flux increased 12 times when caffeine penetrated across a human skin treated with DMF, but it was found that DMF causes irreversible damage to skin.

VII. Surface active agents:

Cationic surfactants: Surface active agents are absorbed at interfaces and therefore increase permeation. Cationic surfactants cause a greater penetration than anionic ones. Therefore they damage the skin more.

Anionic surfactants: Anionic surfactants remove the water soluble agents and thus change the barrier function of the stratum corneum. Sodium lauryl sulphate is a prime example for bringing about a change in the SC and thus increasing penetration.

Non-ionic surfactants: Nonionic surfactants are perforated so that they can emulsify sebum. Thus the permeation is increased due to change in the partitioning potential. The permeation enhancement generated by these compounds is because the drug could partition between the different forms of enhancer.

VIII. Terpenes: Terpenes and terpenoids are essential ingredients of essential oils. It is formed of repeating isoprene (C_5H_8) units. They are having great potential as percutaneous permeation enhancers like the essential oils obtained from eucalyptus, ylang-ylang and others act increases the absorbance of 5-flouorouracil.

It is shown in the Differential scanning calorimetry (DSC) studies that, L-Menthol if used as an enhancer can increase the skin permeation of testosterone. In order to do this L-Menthol forms a eutectic mixture with the drug. As a result the initial melting point of 153.7°C drops to 39.9°C. This makes the formulation more soluble thereby increasing its absorption. By making the drug more soluble, Menthol tries to alter the barrier function properties of Stratum Corneum. L-Menthol can be obtained from peppermint oil in plenty quantity.

According to the studies done by Kaplun et al. on rat skin it was found that Eucalyptus was the most active oil. It increased the permeation of 5-fluorouracil by a factor of 60 in comparison to peppermint oil and turpentine oil which produced a 48-fold and 28-fold increase in enhancement.

In the experiments of William et al, highest absorption was obtained with mixtures having 80% PG-content and it was found that activity of terpene depended on PG-content. Terpenes increased lipid disruptions in the SC and high PG-content promoted more drug-partitioning thus, increasing the overall permeation. This was a dual mechanism which was proposed by the studies.

B. Biochemical Approach:

I. Synthesis of bio-convertible pro-drugs:

Prodrugs help to obtain an optimal partition coefficient for entering the skin barrier. After absorption and diffusion to the viable tissues, enzymes convert the prodrug into the active form. Many steroids have been designed using this approach. N-acyl derivatives were formed to increase permeability of 5-fluorouracil to 25 times.S6-acyloxymethyl and 9-dialkylaminomethyl pro-moieties acted as permeation enhancers to 6-mercaptopurine and increased its permeation to up to 240 times. Prodrugs have also been used to increase skin permeability of anti-inflammatory drugs which are non-steroidal like nalbuphine, buprenorphine, β-blockers and others.

II. Co-administration of skin metabolism inhibitors: One of the interventionist approach proposed for permeation promotion through human

skin is to interfere with barrier homeostasis by altering one or all of the processes of bringing together of the lamellar membranes, synthesis, assembly, secretion, processing and activation. Synthesis inhibitor blocks temporarily the synthesis of ceramide, fatty material and cholesterol. This method is now-a-days increasingly experimented to enhance drug permeation of drugs that exhibit poor permeability across normal skin. Fluvastatin increases the octanol/water partition coefficient of lidocaine hydrochloride by 50 times, the in vivo uptake doubled.

C. Physical Approach:

I. Iontophoresis: The mechanism involves diffusion, migration or electro-osmosis of drug through the skin across a concentration gradient. In electro-osmosis bulk of the fluid and counter ions flow in the same direction. Iontophoresis is based on the principle of the motion of this fluid flow without any concentration gradient. Under normal conditions the skin is slightly negatively charged and counter ions form the cations. Following the electro-osmotic principle, flow takes place from cathode to anode. This increases the absorption of cationic drugs by increasing their flux. Originally, continuous DC current was used for iontophoresis, but now-a-days, pulsed waveform of DC is also being used to increase permeation. For example, the flux of TRH (Thyrotropin Releasing Hormone) increased significantly when the process was done using a pulsed DC rather than continuous DC. Also, using pulsed DC has less damaging effects on the skin.

A negatively charged drug is put in-between cathode and the skin surface for its permeation. The cell provides electromotive force to drive the ion towards the anode via the skin. In case of positively charged drug, the electrodes polarities are opposite. After the drug enters the skin it further enters the host circulatory system to reach its target site.

Iontophoresis increases skin permeation as it alters the barrier function the SC [10]. There are certain drugs which are very tough to be given or can only be administered via the parenteral route such as various high molecular weight proteins, peptides and oligonucleotides. Iontophoresis immensely helps in the penetration enhancement of such drugs. The permeation of certain very large molecular weight drugs like insulin has still not been achieved through iontophoresis.

II. Sonophoresis: Sonophoresis is the phenomenon in which the permeability of skin is increased under the influence of ultrasound.

Mechanism of action: According to many scientific studies there are a number of phenomena that take place in the skin when exposed to US (ultrasound). These include:

a) Cavitation effects.
b) Convective transport.
c) Thermal effects.
d) Mechanically occurring effects.

a) Cavitation effects: When a liquid medium is exposed with US then vapor cavities are formed. This process is called cavitation. Pressure variation induced in the medium is the primary cause of cavitation.

Cavitation may be of two types:

1. **Inertial cavitation:** the fast formation, growth and disruption of any bubble.

2. **Stable cavitation:** the gentle periodical movement of bubbles in ultrasonic field.

3. When these bubbles are disturbed and damaged then a shock wave releases which cause changes in the structure of the surrounding cells and tissues[11]. The tissues contain air pockets which are caged in fibrous structures. These air pockets help in cavitation by acting as nuclei upon application of ultrasonic field. The cavitation effects and US frequency are inversely related while intensity of the ultrasonic waves has a direct relation. Cavitation happens when small vapor cavities form a cluster during the negative part of the alternate US pressure cycles, and these clusters grow subsequently in further pressure cycles. Due to cavitation, the lipid bilayer of the SC is altered and aqueous channels develop through the skin for the permeation of drugs.

4. **b) Convective transport:** When porous medium exposed to ultrasound, interference occurs between the incident and reflected US waves. Cavitation bubbles also undergo oscillations due to which different velocities are produced in the fluid.

Many studies show that this method does not provide very good permeation [12].

c) Thermal effects: When US is absorbed the temperature of the absorbing medium rises. This rise in temperature is directly proportional to the intensity of US and the time for which it been exposed. As a result the medium becomes more absorbing as its absorption coefficient increases. In the human aspect, bone has a higher coefficient of absorption than muscle tissues and therefore they face more thermal risk. Ultrasound could have damaging effects on the medium therefore scientists have come up with a safety parameter known as time to threshold (TT). This parameter indicates the time for which the US could be applied on to the tissue if its threshold limit is known.

d) Mechanical effects: Ultrasound causes many variations in the skin such as sinusoidal pressure variation and thus sinusoidal density variations. As it all depends on the US frequency so at frequency above 1 MHz there are no cavitation effects and the density variations occur rapidly and thus the growth of small gaseous nucleus is slowed. But rapid density variations lead to medium fatigue. As a result, disruptions occur in the lipid bilayers and thereby increasing the permeation through it. Therapeutic sonophoresis is considered a good option since this enhanced permeability is only for a short time, but still it is one of the major techniques for transdermal enhancement [12].

III. Thermal Energy: Application of US on skin leads to increase in temperature. Thus there is an increase in skin permeability which leads to drug to enter the systemic circulation. This approach has been mimicked by Zars, lnc. [Salt Lake City, UT, USA]. They developed a mini heating unit CHADD, which gives heat for a certain time at a certain intensity. Full form of CHADD is Controlled Heat-aided Drug Delivery system. Oxidation reaction occurs within the heating unit [13].

IV. Stripping of Stratum Corneum: The dermatologists use various techniques to cause disruption on the topical skin surface for fast penetration of formulations used for the treatment of acne, scars, skin blemishes and hyper pigmentation. One such technique is microderm abrasion which comes under superficial skin resurfacing. During Microscissuining outer surface of the skin is eroded by using sharp microscopic metal granules. This leads to the formation of micro-channels in the skin. Studies have shown that this process can enhance angiogenesis permeation to 100 times [13].

TABLE 2: SUMMARY OF PERMEATION ENHANCERS [17]

Types of Penetration Enhancers	Mechanism of Action	Examples
1.Physical enhancer	These types include increasing the penetration by ultrasonic, magnetic and physical separation	1.sonophoresis 2.electroporation 3.iontophoresis 4.Radiofrequency 5.thermophoresis 6.Needless injection 7.magnetophoresis 8.phonophoresis 9.hydration of SC 10.stripping of SC
2.Chemical enhancers	These include three mechanism 1. By disturbing the ordered structure of SC. 2. By interacting with the proteins (intercellular). 3. by improving drug partition through SC.	1.pyyolidones 2.azones 3.oxizolidinones 4.cyclodextrines 5.sulphoxides and chemicals like dimethyl sulphoxide (DMSO), dimethyl formamide (DMF), dimethyl acetamide (DMAC) 6.Amides and amines 7.fattyacids (capric acid, lauric acid and myristic acid 8. surface active agents
3.Biochemical approach	Performed by changing substances to suitable form	1.synthesis of bio-convertible pro drug 2.coadminisration of metabolite inhibitor of skin

4.Drug vehicle Based	Interaction of enhancers with stratum corneum	Ion pairs and complex coacervates
5. Natural penetration enhancers	Mechanism for terpenes These effects could be increased - 1.Diffusion coefficient 2. partition coefficient 3.solubility of drug 4.extraction of lipids 5.terpenes molecule molecular orientation with lipid bilayer	1.Tarpenes : limonene, linalool 2.Essential oil: neem oil, chenopodium, basil oil
6.Miscellaneous enhancers	Various mechanism	1.phospholipids 2.clofibric acid 3.inhibitors of lipid synthesis

V. Hydration of Stratum Corneum: Stratum corneum has approximately 15-20% water content. The mechanism proposed is that on increasing the water quantity there would be an increase in the permeability of the SC due to the swelling up of SC. This mechanism has yet to be exploited in the laboratory. To achieve this on a daily and economic level the use of occlusion principle could be done thus avoiding the flow of water from the skin surface. For this several ointments, oils, wax, paraffins and other emulsions could be applied. Among these plastic films and oily substances are the most effective [14].

Advantages:

Permeation enhancers provide us the following advantages:

1. Sufficiently high rate of penetration for therapeutic efficiency.
2. It helps to make permeation of unabsorbable drug through skin.
3. Improved penetration of transdermalsurface preparations.
4. No negative effects.
5. These are anti-septic substances.
6. No effect on the zero order skin permeation profile of skin.

Limitations:

1. The concentration of different drugs can be different so same amount of dosage cannot be administered.
2. Several permeation enhancers should strictly not be given at different concentrations at the same time.
3. There is a high risk of side-effects due to these enhancers- For instance; many penetration enhancers cause skin irritation or other allergic
4. reactions. This is due to the fact that chemicals alter the organized lipid structure, cell membrane and components.
5. Many penetration enhancers have limited utility for clinical application because of their toxicity.

Anatomy and Physiology: Anatomically, skin has four different layers of tissue -

1. Stratum corneum (SC)
2. Epidermis
3. Dermis
4. Hypodermis

I. Stratum Corneum: It is also known as the Non-viable epidermis, the outermost skin layer. Stratum corneum is the actual skin barrier to most noxious substances. The thickness of the SC is almost10-20 cell layer thick throughout. Each cell length is - 34-44 μm. Every cell is 25-36 μm in width and 0.5 to 0.20 μm in thickness. The surface area of a cell is 750 to 1200 μm^2.SCcontains 5-15% lipids and 75-85% proteins. Lipids include phospholipids, glyco-sphingolipids, cholesterol sulfate and neutral lipids. Keratin is the main protein found.

II. Viable epidermis: Viable epidermis is present between the SC and dermis skin layers. It is 50-100μm thick. The cell structures in this layer are physicochemically similar with other living tissues. Ton fibrils hold the cells in place. The density of viable epidermis and water is almost comparable. The percentage of water found is 90%.

III. Dermis: The dermis lies just below the viable epidermis layer. Dermis is a structural fibrin. Its cells generally differ from the normal tissue cells in the body. It has a thickness in the range of 2000 μm to 3000μm. The loose connective tissue has a

matrix of fibrous protein rooted in a unclear ground substance.

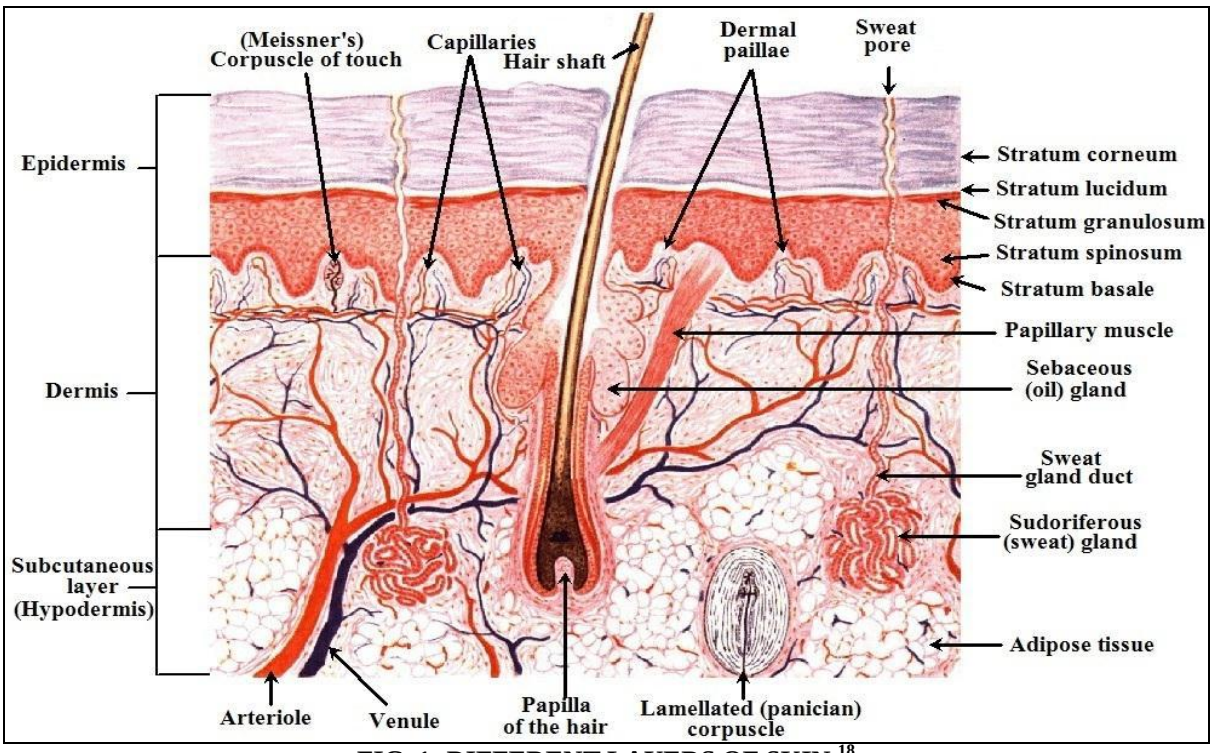

FIG. 1: DIFFERENT LAYERS OF SKIN [18]

IV. Subcutaneous connective tissue: Hypodermis is a subcutaneous tissue. It is made up of a layer of loose connective white fibrous tissue. Blood vessels and lymph vessels along with pores secreting sweat are part of hypodermis only. According to many scientists drugs first enter the systemic circulation after permeation through skin and then reach the hypodermis.

Drug Delivery Devices: Drug delivery systems are the technologies which are developed for the targeted drug delivery as well as controlled release of different drug molecules. Drugs have been used to treat various diseases as well as to enhance the health and support lives. Over the last few decades Bio-medical engineers have contributed their efforts in developing various efficient systems for delivering drugs. These systems are now being deployed to treat hundreds of different diseases such as transdermal drug delivery patches which are used to deliver controlled amount of insulin in the blood stream reducing the pain caused by the use of conventional hypodermic needles.

Some drug delivery devices are:-

I. Microneedlearrays: It is a new alternative way of delivering drug through the skin using micro sized needles that penetrate through the skin but do not reach to the nerves which results in the painless drug delivery through the skin.

II. Iontophoretic patches: These are small patches which is having two electrodes where one can target either positively or negatively charged drug molecules on the application of small amount of current across the electrodes which create small pores in the non-viable epidermis(SC) facilitating the molecules of the medicament to enter the blood stream through blood capillaries.

Novel ways for targeting drugs:

I. Nanosponges: These are small tiny scaffolds made up of polyesters coated with compound that are being targeted to the disease site which results in the effective treatment of that disease. Once they enters the circulation they starts degrading releasing the drug which is maintained in the therapeutic level to carry out desired actions.

II. Liposomes: These are composed of lipid-bilayer structures and therefore can encapsulate both hydrophilic and hydrophobic drugs within them used to target and delivering drugs to the target. These are made up of mainly phospholipids

which are also the active component in the formation of plasma membrane of the animal cells, which are having one polar head facing towards the water region and one non-polar head facing internally.

Recent Advancement in Formulation: The formulations mentioned in this section are still in their developmental stage, but the specific information about the technological parameters and pharmacokinetic data has not been disclosed by the developer. Therefore, the information presented here to illustrate the enhanced drug permeation approach has been taken from the patented literature.

I. Cyclopentadecalactone: It is also referred to as pentadecalactone. It is a type of permeation enhancer marketed by Bentley Pharmaceuticals; Inc. CPEX Pharmaceuticals are also promoting it under the name of CPE-215. Pentadecalactone is currently used in Testim (testosterone gel applied trans-dermally). It is made up of a gel formulation primarily containing ethanol with 8% penta decalactone. Though in its early stages, CPE-215 is currently being tried as a nasal insulin delivery absorption promoter. Nasal bioavailability of insulin was reported to be 10–20%, as compared to subcutaneous injection, and the formulation was well tolerated.

II. SNAC: SNAC is also referred to as salcaprozate sodium and its isomeric name is Sodium N-[8-(2-hydroxybenzoyl) amino]caprylate. It was told by Emisphere's Eligen Technologies that SNAC facilitates absorption by entering into a non-covalent compound with the drug. In the whole procedure tight junctions are not modified by SNAC. In case of proteins, the mechanism involved is protein protection against degradation and a reversible change in protein conformation prior to absorption. It was found that SNAC enhances the cromolyn absorption 8 times by boosting its absorption through the membrane.

This is because cromolynlipophilicity is not at all affected by SNAC. A sub chronic toxicity study was performed on rats. It was found that a quantity of 1,000 mg/kg/day or even greater has no negative effect. Also it is shown that SNAC exposed Caco-2 cells displayed proofs of cell damage due to use of various biologically harmful assays, in addition to lactate dehydrogenase, trypan blue exclusion, mitochondrial dehydrogenase activity, and neutral red binding. Vitamin B12 and calcitonin are currently being made by exploiting the property of SNAC. Several products needed to supply peptide and glucagon-like peptide-1 orally are still under development process. Emishpere's previous efforts to orally deliver insulin and heparin had not achieved success in clinical trials. This success was required for proper investment to lead to continuous development.

III. CNAC: 5-CNAC or 8-(N-2-hydroxy-5-chloro-benzyl)-amino-caprylic acid is an absorption enhancer which originated from Emisphere. It is clinically developed by the Nordic Biosciences in an oral formulation on calcitonin. A lozenge having 200 mg dose of 5-CNAC in combination with 0.8 mg measure of calcitonin allows larger drawing up of calcitonin plus enhanced effects on a bone resorption biomarker as compared to nasal calcitonin. A clinical trial for two weeks with a twice dosage of oral calcitonin with 5-CNAC is known to giving useful reductions in bone resorption biomarkers and cartilage degradation. The absorption is though affected by volume of water consumed with the tablet [15].

IV. GI Permeation Formulations: Merrion Pharmaceutical is a company which focuses on making drug delivery techniques for easy permeation of present oral disintegrating drugs. Their remedy formulations are collectively called as the gastrointestinal permeation enhancement technology (GIPET). This technology mainly involves medium chain fatty acids plus its derivatives. There are several products under development such as alendronate and zoledronic acid (bisphosphonates), a gonadotropin-releasing hormone antagonist, and fond aparinux.

Sodium caprate which is one of the main enhancers is used as a food additive and has been given the safe (GRAS) status. Low-molecular weight heparin achieved an oral bioavailability of 5-9%. Also a 12-fold oral bioavailability of alendronate was increased to approximately 7% by the GIPET formulation approach.

GIPET formulations are seen to be well tolerated in clinical phase 1 and phase 2 studies.

V. Sodium Caprate: Isis Pharmaceuticals used Sodium caprate as a bulking agent to increase the soaking of an antisense oligonucleotide of molecular weight 7701 (ISIS 104838) orally. During the experiments it was seen that when sodium caprate was not used, the oral bioavailability of the antisense oligonucleotide ISIS 104838 could not be detected in rats, dogs, and pigs. Oral ISIS 104838 has also been evaluated in humans in the form of solid formulations with sodium caprate (660 mg total). Two drug release profiles were used. One was delayed release and other one was immediate release. Results showed an average bioavailability of 12% as compared to hypodermic injection and this bioavailability varied between 2% to 27.5% approximately in ten subjects who had fasted for the experiment. Two different release profiles were used to ensure a greater surface area is exposed to the drug and the time of exposure is also increased. These antisense oligonucleotide formulations with sodium caprate could result in an increased therapeutic effect.

VI. Transient Permeability Enhancement Systems: Chiasma is a company that produces formulations under the name of Transient Permeability Enhancer (TPE) system. It is a very good permeation enhancer system. The company has kept their TPE Technology under cover, but their scientists have described the basic property which covers the absorption enhancing formulations. The formulations are a suspension of sodium caprylate and glyceryl triglyceride which is a well-known polymer for matrix formation in any hydrophobic medium. It is utilized in increasing the oral bioavailability of exenatide (a glucagon-like peptide-1 agonist), octreotide (an octapeptide mimicking somatostatin) and other macro-molecules. Presently, Chiasma is doing clinical studies on octreotide acetate in oral form [16].

VII. Formulations for Oral Insulin Delivery: Taking insulin injections is sometimes very painful and also undesirable. Therefore, scientists have been trying to create an oral delivery based system for insulin delivery. This novel system tries to mimics the whole process of insulin secretion from the pancreas. But oral formulations are highly sensitive as they are prone to degradation in the stomach and intestine. Also their absorption through the intestinal membrane is the major issue of concern. Oramed Pharmaceuticals is trying to make an oral insulin formulation. A study of such a formulation was carried out in healthy subjects. The results confirmed that it was well tolerated by the host body showing a decrease in the glucose and c-peptide [20].

Research articles show that this oral product is present in an omega-3 fatty acid in the form of an enteric-coated tablet formulation. The permeation enhancers present in it may range from certain protease inhibitors like a protinin and soybean trypsin inhibitor, EDTA or a bile salt. But the results of an increased bioavailability of insulin as compared to the old perturbation approach are not known. Diabetology Ltd. is another pharmaceutical company which has also formed an oral formulation product, 'capsulin'. It uses "Generally Recognized as Safe (GRAS)"fillers for the purpose of increasing absorption.

TABLE: 3 [19]

Company	Enhancers
Oramed pharmaceuticals	protease inhibitor and omega 3 fatty acids
Nordic biosciences	8-(N-2-hydroxybenzoyl)-amino-caprylic acid
Isis pharmaceuticals	Fatty acid chains, salts and derivatives
Unigene	Combination of protease inhibitor, permeation enhancer, pH modifier, enteric coating
Soligenix	Lipid polymer micelles
Archimedes pharma	Chitosan
Aegis therapeutics	Alkyl glycosides
Generex	Liquid mixed micelle spray
Chiasma	Suspension of sodium caprylate in hydrophobic medium with matrix forming polymers

CONCLUSION: Many existing drugs have to be given via injections which are painful and undesirable as it may be risky also in some cases. Therefore these days skin is a preferred route of drug delivery and it is termed as the transdermal drug delivery system. Drugs entering the systemic circulation have to pass the skin barrier, Stratum Corneum. For this permeation enhancers are required as it is difficult to penetrate though the SC. It is an emerging field with a lot of scope for development. Extensive research going on in this field has manifested the utility of absorption enhancers for increased and easy absorption of drug through the skin. The only drawback is that permeation enhancer is that they tend to produce skin irritation and undesirable patches.

The main focus is to prepare absorption enhancement systems which produce zero to no skin irritation. Their clinical application is limited by the fact that mostly this increased enhancement leads to toxicity. Permeation enhancer can be used as a tool to achieve an effective dosage of the drug to enter therapeutically within the skin. To obtain substances which fully meet the optimal requirements, one approach is to synthesize penetration enhancer by understanding the interaction of enhancer and developing structural activity relationship. This can be done using modern discovery and modelling techniques which aims to produce structures with minimal toxicity and optimal characteristics.

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REFERENCES:

1. Dua K, Penetration enhancer for Transdermal drug delivery system; A tale of the under skin travelers. Advances in natural and applied sciences2009; 1:95-101.
2. Bharkatiya M: Skin penetration enhancement techniques. J Young Pharmacists 2009; 1:110-115.
3. Barry BW, Dermatological formulation: percutaneous absorption. Marcel Dekker, New York, 1983.
4. Singh PB, Choudhury PK, Penetration enhancers for transdermal drug delivery of systemic agents. JPharmRes 2007; 6: 44-50.
5. Barry BW, Lipid-Protein-Partitioning theory of skin penetration enhancement. J Control Release 1991; 15: 237e248.
6. Karande P, Mitragotri S. Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochimicaet Biophysica Acta 2009: 2362-2373.
7. T. Kai, V. H. W. Mak , R. O. Potts, and R. H. Guy, mechanism of percutaneous penetration enhancement: effect of n-alkanols on the permeability barrier of hairless mouse skin: Journal of Controlled Release, 1990 12(3), 103-112.
8. Aoyagi T, Yamamura M, Matsui K, Nagase Y: Preparations of cyclic sulfoxide derivatives and their evaluation as transdermal penetration enhancers: Biological and pharmaceutical Bulletin: 1992 Jul; 40(7): 1961-3.
9. Phillips CA, Michniak BB: Transdermal delivery of drugs with differing lipophilicities using azone analogs as dermal penetration enhancers. Journal of Pharmaceutical Sciences 1995; 84(12): 1427-1433.
10. Green, Philip G. Iontophoretic delivery of peptide drugs. J. Control. Release, 1996, 41(1-2), 33-48.
11. Clarke, L., Edwards, A., Graham, E. Acoustic streaming: an in vitro study. Ultrasound Med. Biol. 30, 559–562, 2004.
12. Mitragotri S, Edwards D.A, Blankschtein D, Langer R, A Mechanistic study of ultrasonically-enhanced transdermal drug delivery, J. Pharm. Sci. 84(6):697–706, 1995.
13. Ritesh Kumar, Anil Philip. Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin Tropical. J Pharma Res 2007; 6 (1):633-644.
14. Heather AE, Benson Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery 2005; 2: 23-33.
15. Leary AC, Dowling M, Cussen K, O'Brein J, Stote RM., Pharmacokinetics and pharmacodynamics of intranasal insulinspray (Nasulin) administered to healthy male volunteers: Influenceof the nasal cycle. J DiabetSci Tech. 2008; 2:1054–6.
16. Leary AC, Dowling M, Cussen K, O'Brein J, Stote R.M. Pharmacokinetics and pharmacodynamics of intranasal insulinspray (Nasulin) administered to healthy male volunteers: Influenceof the nasal cycle. J DiabetSci Tech; 2008; 2:1054–60.
17. Saini S, Chauhan S.K, Agrawal S.S, Recent development in penetration enhancers and techniques in transdermal drug delivery system; Jan-Mar 2014.
18. Raut Vinod S, Nemade S. Lalita, Desai T. Maya, Bonde D. Shailejkumar, Dongare U. Shweta, Chemical Penetration Enhancers: For transdermal drug delivery systems 2014: 33-40; 2248-9207.
19. Aungst J. Bruce, Svensson K. Craig, Absorption Enhancers: Applications and Advances March 2012, 10.1208/s12248-011-9307-4.

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