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Review Article

A REVIEW ON PENETRATION ENHANCER FOR SEMISOLIDS

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ABSTRACT

There is considerable interest in the skin as a site of drug application both for local and systemic effect Semisolids dosage forms usually are intended for localized drug delivery. In the past few years, however, these forms also have been explored for the systemic delivery of various drug candidates who's per oral bioavailability is questionable. Several novel drug-carrier systems have been examined that offer enhanced release, controlled release, or a stable environment for the incorporated drug. A recent advance in semisolid dosage form allows modified release as well as flexibility in route of administration. However, the skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. This review describes enhancement techniques based on drug/vehicle optimisation such as Selection of correct drug or prodrug, Chemical potential adjustment, Ion pairs and complex coacervates, Eutectic systems, Hydration, Chemical penetration enhancers, Microneedle array, Stratum corneum ablated, Follicular delivery, Ultrasound, Iontophoresis, Electroporation, Magnetophoresis, Pressure wave, Liposomes and other vesicles, Niosomes, Transfersomes. The mechanism of action of chemical penetration enhancers and their potential for clinical application is described.

Key-Words: *Penetration Enhancers, Stratum Corneum Modification, Semisolid Dosage form, Transdermal Drug Delivery.*

INTRODUCTION

Semisolids serve as carriers for drugs that are topically delivered by way of the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining. Because of their peculiar rheological behaviour, semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site.

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Drug delivery by means of semisolid dosage forms has seen new challenges in the past few years in terms of altered drug-release profiles as well as the enhanced stability of Active pharmaceutical ingredient [1].

Different types of Semisolids

***Ointments:* -** are semisolid preparations for external application to skin or mucous membranes. Function as skin protective and emollients. Ointments are greases with the permissible addition of up to 25% of powder by weight.

Creams: - are semisolid dosages forms that contain one or more drug substances dissolved or dispersed in a suitable base, usually an oil in-water emulsion or aqueous microcrystalline dispersion of long-chain fatty acids or alcohols

that are water-washable and are cosmetically and aesthetically acceptable. [2-3]

Gels:- are semisolid systems that consist of either suspensions of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels can be either water based (aqueous gels) or organic solvent based organogels. [4]

Pastes: **-** are greases containing more than 25% powder by weight are semisolid dosage forms that contain one or more drug substances incorporated in a base with large proportions of finely dispersed solids. are intended for external application to skin, but very thick and stiff.

Jellies: **-** are transparent, non-greasy, semisolid preparation for external applications to skin and mucous membrane.

Poultices: **-** are soft, viscous wet masses of solid substances applied to skin and now outdated.

Suppositories: **-** are intended in other than oral cavity i.e., vaginal, nasal cavity, generally introduced in systemic. [2]

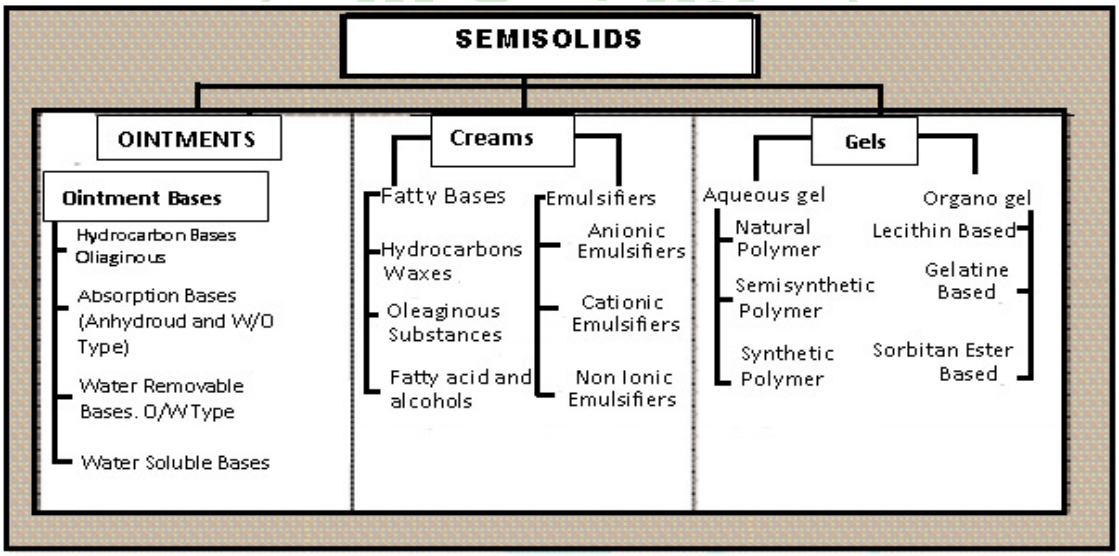

Fig.1: Shows the basic raw materials used in the development of various semisolid dosage forms. [5]

Novel advances in semisolid dosage forms:

Creams: -

a) Creams containing microspheres: -

Albumin microsphere containing vitamin A can be administered by using creams topically. 222 ± 25 µm size of microsphere of vitamin A were produced by emulsion method. The in vitro and in vivo drug release of a microencapsulated and non-microencapsulated vitamin A cream was studied. The in vivo study in six volunteers revealed that these microspheres were able to remain on the skin for a long period of time, and as a consequence they were able to prolong the release of vitamin A. The relative availability of the microencapsulated vitamin A cream, compared with the non-microencapsulated vitamin A cream was 78.2 ± 7.3 %. [6]

b) Cream containing lipid Nanoparticles:-

Occlusion (air- and water-tight trauma dressing) of cream is important criteria since it increases the penetration of topical drugs. This can be achieved by using oils and fats like liquid and semisolid paraffin in large quantities. However, such formulations have the limitations of poor cosmetic properties since they have greasy feel and glossy appearance. The development of a water-in-oil cream containing small particles of solid paraffin was studied. [7]

A high degree of occlusivity was obtained with smooth, flexible films prepared by drying aqueous dispersions of solid paraffin particles with a mean size of 200 nm (nanoparticle dispersion).However, this nano dispersion revealed a rough texture when applied. The development of a water-in-oil cream wherein the aqueous phase was divided into small droplets solved this problem. Nanoparticles were incorporated in the aqueous phase. Hence, the oil phase in which the water droplets were dispersed served as a lubricant for nanoparticles, thereby preventing a rough feel during application. [6, 8, 9]

Gels: -

a) Organogels: -

Sorbitan monostearate, a hydrophobic non-ionic surfactant, gels a number of organic solvents such as hexadecane, isopropyl myristate, and a range of vegetable oils. Gelation is achieved by dissolving/dispersing the organogelator in hot solvent to produce an organic solution/dispersion, which, on cooling sets to the gel state. Cooling the solution/dispersion causes a decrease in the solvent-gelator affinities, such that at the gelation temperature, the surfactant molecules self-assemble into toroidal inverse vesicles. Further cooling results in the conversion of the toroids into rod-shaped tubules. Once formed, the tubules associate with others, and a three-dimensional network is formed which immobilizes the solvent. An organogel is thus formed. [10, 11] structurally, organogel resembles micro emulsion .The basic difference between organogel and micro emulsion is only about their consistency. Micro emulsion is of low viscosity where in organogel viscosity is much higher. Lecithin organogels are emerging as carriers for drug molecules with diverse physicochemical properties including macromolecules. [6]

b) Bioadhesive Gels: -

Bio adhesion is the property whereby some hydrogels adhere to biological tissues, in particular epithelia such as the gastric, buccal, vaginal and rectal mucosa. Chitosan bio adhesive gel was formulated for nasal delivery of insulin. Insulin was released by a zero-order kinetic from the gels. Sodium CMC,HPMC, xanthan gum, Poloxamer 407 and Carbopol 934P normally used as bio adhesive polymer. To increase the drug permeation, penetration enhancers such as the ethylene glycols, propylene glycols,glycerides,non-ionic surfactants and fatty acids were incorporated in the gel formulation. Bio adhesive Gel of Microencapsulated Metronidazole for Vaginal Use was found to be the best because releasing almost 100% of metronidazole over a period of 36 hr. NSAIDS like Ketoprofen and Pranoprofen also successfully delivered using Bio adhesive gel.

Considering in vitro and in vivo studies, the formulated gel could be a useful preparation for controlled delivery of insulin through the nasal route. [12-13]

Advantages of semisolid Dosage forms over conventional Dosage forms

- Avoidance of first pass metabolism,
- Predictable and extended duration of activity,
- Utility of short half life drugs,
- Improving physiological and pharmacological response,
- Provides patient convince.

Challenges for Semisolids

Transdermal route offers several potential advantages over conventional routes, but one of the major problems in transdermal drug delivery is the low penetration rate through the outer most layer of skin. Hence, to improve the percutaneous absorption is the prime objective. [14]

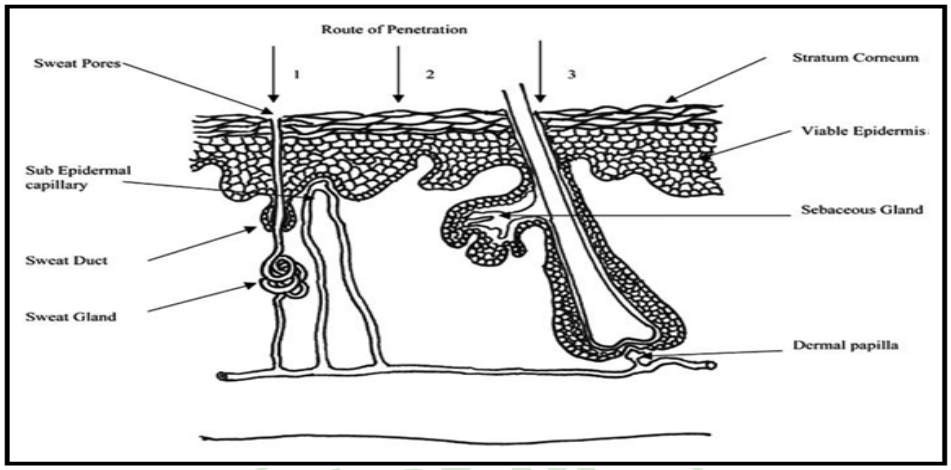

Fig.2:Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles [14]

Drug Delivery Routes Across Human Skin

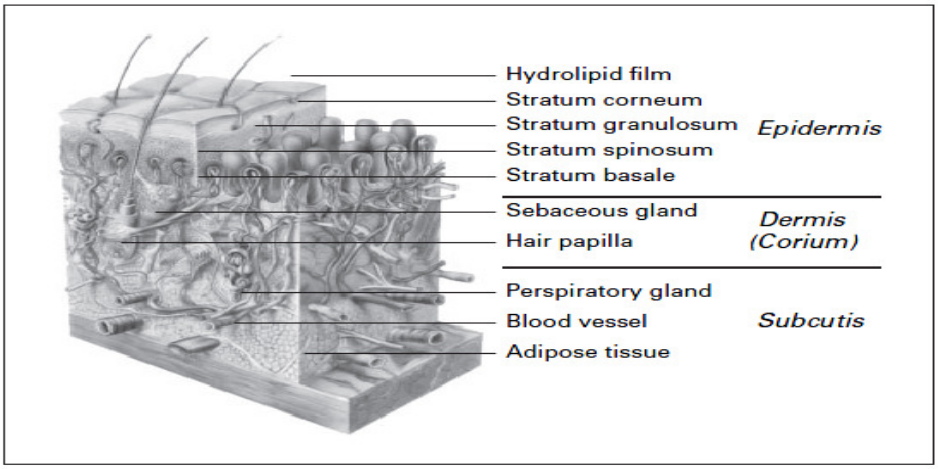

Fig.3: The human skin schematically. [15]

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, *via* the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum . The relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years [13-16] and is further complicated by the lack of a suitable experimental model to permit separation of the three pathways. A follicular shunt route was responsible for the pre-steady-state permeation of polar molecules and flux of large polar molecules or ions that have difficulty diffusing across the intact stratum corneum. However it is generally accepted that as the appendages comprise a fractional area for permeation of approximately 0.1% [17], their contribution to steady state flux of most drugs is minimal. This assumption has resulted in the majority of skin penetration enhancement techniques being focused on increasing transport across the stratum corneum rather than via the appendages. Exceptions are iontophoretic drug delivery which uses an electrical charge to drive molecules into the skin primarily via the shunt routes as they provide less electrical resistance, and vesicular delivery. The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 µm in the dry state to 40

µm when hydrated. [18-19] It comprises a multi-layered "brick and mortar" like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) composed primarily of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulphate and sterol/wax esters. [20]

However it is important to view this model in the context that the corneocytes are not brick shaped but are polygonal, elongated and flat (0.2-1.5 µm thick, 34-46 µm in diameter). The intercellular lipid matrix is generated by keratinocytes in the mid to upper part of the stratum granulosum discharging their lamellar contents into the intercellular space. In the initial layers of the stratum corneum this extruded material rearranges to form broad intercellular lipid lamellae, [21] which then associate into lipid bilayers [22-23], with the hydrocarbon chains aligned and polar head groups dissolved in an aqueous layer**.** As a result of the stratum corneum lipid composition, the lipid phase behaviour is different from that of other biological membranes. The hydrocarbon chains are arranged into regions of crystalline, lamellar gel and lamellar liquid crystal phases thereby creating various domains within the lipid bilayers. [24]

The presence of intrinsic and extrinsic proteins, such as enzymes, may also affect the lamellar structure of the stratum corneum. Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor (NMF), which helps to maintain suppleness.

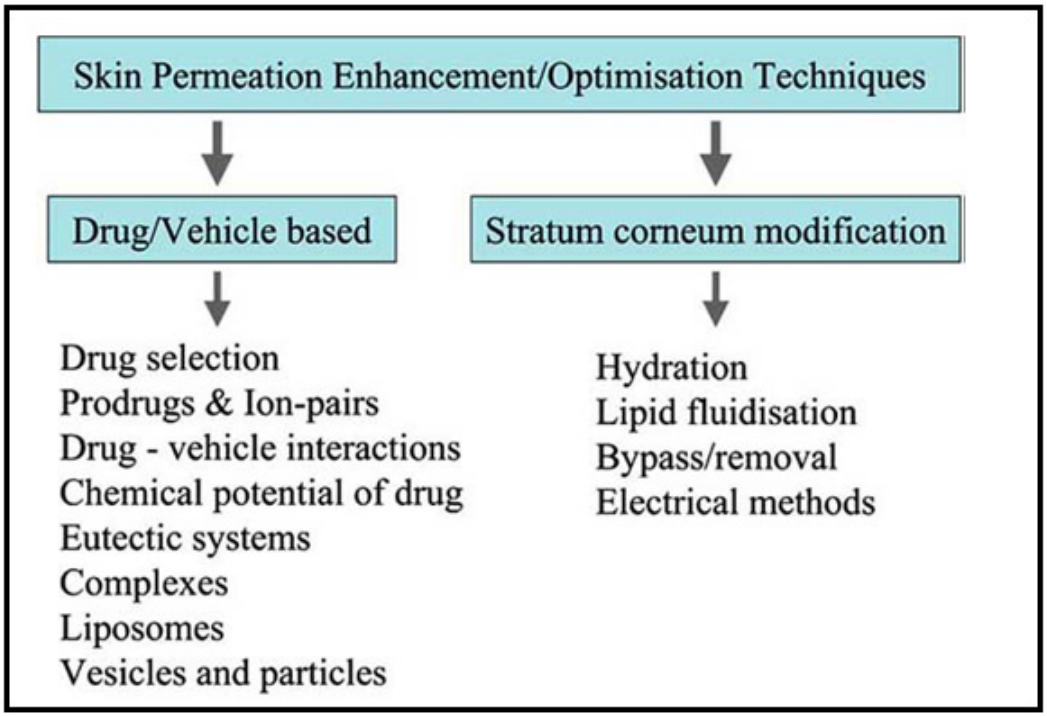

Fig. 4: Techniques to optimise drug permeation across the skin [25]

(I) Drug and vehicle interactions

a) Selection of correct drug or prodrug
b) Chemical potential adjustment
c) Ion pairs and complex coacervates
d) Eutectic systems.

(II) Stratum corneum modification

a) Hydration
b) Chemical penetration enhancers.

(III) Stratum corneum bypassed or removed

a) Microneedle array
b) Stratum corneum ablated
c) Follicular delivery

(IV) Electrically assisted methods

a) Ultrasound (Phonophoresis, Sonophoresis)
b) Iontophoresis
c) Electroporation
d) Magnetophoresis
e) Pressure wave

(V) Vesicles and particles

a) Liposomes and other vesicles
b) Niosomes
c) Transfersomes

(I) Drug and vehicle interactions

(a) Selection of correct drug or prodrug:

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients. The prodrug design strategy generally involves addition of a pro-moiety to increase partition coefficient and hence solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimizing solubility in the aqueous epidermis. The intrinsic poor permeability of the very polar 6- mercaptopurine was increased up to 240 times using S-6- acyloxymethyl and 9-dialkylaminomethyl promoieties.

(b) Chemical potential adjustment:

The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. The diffusion of paraben from saturated solutions in eleven different solvents through a silicone membrane was determined. Due to the different solubility of the parabens in the various solvents, the concentration varied over two orders of magnitude. However, paraben flux was the same from all solvents, as the thermodynamic activity remained constant because saturated conditions were maintained throughout the experiment. Supersaturated solutions can occur due to evaporation of solvent or by mixing of co solvents. 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 antisolvent, the thermodynamic activity of the permeant would increase. [26]

***(c) Ion pairs and complex coacervates*:**

Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ion pairs has been investigated to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralised so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug, which can diffuse within the epidermal and dermal tissues [27]

(d) Eutectic systems:

The melting points of a drug influences solubility and hence skin penetration. According to regular solution theory, lower the melting point greater the solubility of a material in a given solvent, including skin lipids. 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. [28] Number of eutectic systems containing a penetration enhancer as the second components have been reported, for example: Ibuprofen with terpenes [29] and methyl nicotinate [30] propranolol with fatty acids, and lignocaine with menthol. [31]

(II) Stratum corneum modification

(a) Hydration:

Water is the most widely used and safest method to increase skin penetration of both hydrophilic and lipophilic permeants. The water content of the stratum corneum is around 15 to 20% of the dry weight but can vary according to humidity of the external environment. Additional water within the stratum corneum could alter permeant solubility and thereby modify partitioning from the vehicle into the membrane. In addition, increased skin hydration may swell and open the structure of the stratum corneum leading to an increase in penetration, although this has yet to be demonstrated experimentally. For example, Scheuplein and Blank showed that the diffusion coefficients of alcohols in hydrated skin were ten times that observed in dry skin. Hydration can be increased by occlusion with plastic films; paraffins, oils, waxes as components of ointments and water-in-oil emulsions that prevent transepidermal water loss; and oil-in-water emulsions that donate water. Of these, occlusive films of plastic or oily vehicle have the most profound effect on hydration and penetration rate . A commercial example of this is the use of an occlusive dressing to enhance skin penetration of lignocaine and prilocane from EMLA cream in order to provide sufficient local anaesthesia within about 1 hour. Also drug delivery from many transdermal patches benefits from occlusion.

(b) Chemical penetration enhancers (CPEs):

The use of CPEs over the other techniques has certain advantages, including design flexibility of the patch and ease of patch application over a large area (>10 cm2). An ideal penetration enhancer should reversibly reduce the barrier resistance of the SC without damaging the skin cells. According to Finnin *et al*. ideal penetration enhancers should possess the following properties:

- Pharmacologically inert
- Nontoxic, nonirritating, and non-allergenic
- Rapid onset of action; predictable and suitable duration of action for the drug used
- Reversible effect of the CPE on the barrier property of SC
- Chemically and physically compatible with the delivery system
- Readily incorporated into the delivery system
- Inexpensive and cosmetically acceptable

Because the skin provides such a formidable barrier to the delivery of most drugs, a broad range of different chemical additives have been tested to enhance transdermal penetration during the last two decades. Much of the cited literature is found in patents as well as pharmaceutical science literature. Even though many chemical entities have been identified, only a few were introduced in the market due to several limitations, which include their economic feasibility and the toxic effects on skin, which make them undesirable for developing transdermal patches.[26]

Mechanism of chemical penetration enhancement

Penetration enhancers may act by one or more of three main mechanisms

- Disruption of the highly ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, co enhancer or solvent into the stratum corneum.

The penetration enhancer acts by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and nonpolar pathway by altering the multilaminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product. A useful way to consider factors affecting drug permeation rate through the stratum corneum is via the simple equation given below for

steady state flux equation (1). If we plot the cumulative mass of diffusant m, passing per unit area through the membrane A, at long time the graph approaches linearity and its slope its yield the steady flux dm/dt.

$dm/dt = D\ Co\ K\ /h$---------- *(1)*

Where *Co* is the constant concentration of drug in donor solution,

K is the partition coefficient of the solute between the membrane and the bathing solution,

D is the diffusion coefficient and

h is thickness of membrane.

From the above equation, we deduce the ideal properties of a molecule that would penetrating stratum corneum well. These are : [32]

- Low molecular mass, preferably less than 600Da, when D tends to be high.
- Adequate solubility in oil and water so that membrane concentration gradient may be high.
- High but balanced (optimal) K (if too large, may inhibit clearance by viable tissue)
- Low melting point, correlating with good solubility as predicted by ideal solubility theory.

Sulphoxides and similar chemicals

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aprotic solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hydroscopic and is often used in many areas of pharmaceutical sciences as a "universal solvent". DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing of some skin proteins results in erythema, scaling, contact uticaria ,stinging and burning sensation.

Since DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically-related material as a accelerant. Dimethylacetamide (DMAC) and dimethylformamide (DMF) are similarly powerful aportic solvents. However, Southwell and Barry, showing a 12-fold increase in the flux of caffeine permeating across a DMF-treated human skin, concluded that the enhancer caused irreversible membrane damage [21]. DMF irreversibly damages human skin membranes but has been found *in vivo* to promote the bioavailability of betamethasone-17-benzoate as measured by vasoconstrictor assay. DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels. It has been postulated that DMSO denatures the intercellular structural proteins of the stratum corneum, or promotes lipid fluidity by disruption of the ordered structure of the lipid chains. In addition, DMSO may alter the physical structure of the skin by elution of lipid, lipoprotein and nucleoprotein structures of the stratum corneum. Decylmethylsulfoxide (DCMS) is thought to promote permeation enhancement as a result of protein-DCMS interaction creating aqueous channels, in addition to lipid interactions. [32]

Alkanes

Long chain alkanes (C7-C16) have been shown to enhance skin permeability by non-destructive alteration of the stratum corneum barrier.These findings were confirmed in studies in which nonane was investigated as an enhancer], although there must be some destructive solubilisation and biochemical extraction caused by these lipophilic solvents.

Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of -7 ºC and it possesses a smooth, oily but yet non-greasy

feel. Azone is a highly lipophilic material with a log p octanol / water of around 6.2 and it is soluble in and compatible with most organic solvents including alcohol and propylene glycol. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically between 0.1- 5% but more often between 1- 3%]. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone provokes dynamic structural disorder of the intercellular lamellar lipid structure throughout the *stratum corneum* and the creation of fluid domains involving the intercellular lipids, which was suggested by 2H NMR assay. Another mechanism was also proposed based on the alteration of the lateral bonding within *stratum corneum* lipid lamellae]. Azone/PG increase penetration through the stratum corneum by affecting both the hydrophilic and lipophilic routes of penetration. Azone increases the fluidity of the lipid layer, while PG increases the water content of the proteinaceous region and helps azone partition into the aqueous region. A combination of these two helps the penetration of hydrophilic drugs greatly. [33]

Pyrrolidones

N-methyl-2-pyrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch. [34]

The pyrrolidones partition well into human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods. [35]

Urea:

Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism. [36]

Fatty acids and Esters

Percutaneous drug absorption has been increased by a wide variety of fatty acids and their esters, the most popular of which is oleic acid. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. It is of interest to note that many penetration enhancers such as azone contain saturated or unsaturated hydrocarbon chains and some structure - activity relationships have been drawn from the extensive studies of Aungst who employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone Shin et al studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonic surfactant (polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) on the release of triprolidone. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen . Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-flurouracil flux 56-fold through human skin membrane *in vitro* The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a long chain fatty acid with cis- configuration. [33]

Alcohols, fatty alcohols and glycols

A large number of fatty acids and their esters have been used as permeation enhancers. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. Chi et al. reported an increase of 6.5-fold to 17.5-fold in the permeation rate of flurbiprofen through rat skin by unsaturated fatty acids, while no significant increase was observed with saturated fatty acids. Moreover, they have a greater enhancing effect on lipophilic drugs. Addition of oleic acid to an Ethanol: water

(50:50) cosolvent system markedly improved the skin permeation of zalcitabine, didanosine, and zidovudine,whereas addition of the same to ethanol: TCP (50:50) produced no enhancement across hairless rat skin. It was suggested that viscous TCP reduced the thermodynamic activity of oleic acid. Oleic acid was found to be the most efficient enhancer for piroxicam, followed by linoleic acid . Sodium oleate was found to be a better permeation enhancer than oleyl oleate when tested on indomethacin and urea. The fatty acid extract of cod liver oil was found to be as good a permeation enhancer as oleic acid. The most effective transdermal penetration enhancer was palmitoleic acid, which resulted in a 640-fold increase in hydrocortisone flux through hairless mouse skin. Incorporation of pure cod liver oil in a PG vehicle did not improve the hydrocortisone permeability, suggesting that the unsaturated fatty acids have to be in the free form to be able to act as skin permeation enhancers. A 1- hr pretreatment of rabbit abdomen skin with 10% oleic acid in PG greatly enhanced the absorption of piroxicam from its gel. [37]

Surfactants

Surfactants are frequently used as emulsifiers in formulations for dermal application. They are added in order to solubilise lipophilic actives within the formulations. The improvement of the drug solubility can be achieved, for example, by the formation of micelles by the surfactant molecules in the formulation. Surfactants have the potential for the solubilisation of the stratum corneum lipids and thus act as penetration enhancers. Keratin interactions are also thought to explain the penetration-enhancing effects of surfactants. Normally, cationic surfactants are more effective as penetration enhancers than anionic or non-ionic compounds. The potential for skin irritation is connected with the penetration- enhancing effects of the surfactants. Therefore, in formulations for dermal application, mostly non-ionic surfactants are used, which tend to be widely regarded as safe. Surfactants with an analogue structure to the stratum corneum bilayer lipids have low skin-irritating potentials, but also low skin penetration-enhancing effects This is due to surfactant monomer integration into the bilayers instead of micelle formation of the lipids.

Cyclodextrins

Cyclodextrins are biocompatible substances that can form inclusion complexes with lipophilic drugs with a resultant increase in their solubility, particularly in aqueous solutions. However, cyclodextrins alone were determined be to less effective as penetration enhancers than when combined with fatty acids and propylene glycol. [33]

(III) Stratum corneum bypassed or removed

(a) Microneedle array:

Microneedles are applied to the skin so that they pierce only the stratum corneum and increase skin permeability. Microneedles are needles that are 10 to 200 µm in height and 10 to 50 µm in width. 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.

(b) Stratum corneum ablated:

Stratum corneum ablation can be achieved by micro-dermbrasion which use a stream of aluminum oxide crystals and laser-ablation which use high powered thermal pulse to vaporize a stratum corneum**.**

(c) Follicular delivery:

Penetration of topically applied compounds may occur via the stratum corneum as well as via skin appendages, i.e., sweat glands and hair follicles. Initially, skin appendages were not considered to be significant transdermal penetration routes, as evidence suggested that they accounted for only approximately 0.1% of the skin surface area. These calculations, however, did not take into the account that the hair follicles represent invaginations, which extend deep into the dermis with a significant increase in the actual surface area available for penetration. With a rich perifollicular vascularisation and changes in the differentiation pattern along the follicular duct,

the follicle possesses distinct characteristics which favour penetration, and multiple studies suggest that the follicular penetration route may be especially relevant for hydrophilic and high molecular weight molecules, as well as by particle-based drug delivery systems Earliest reports on the participation of hair follicles in percutaneous absorption were based primarily on qualitative, histological studies of dye and stain localization. Later studies led to increasingly quantitative data, characterizing follicular transport as a highly complex phenomenon. Complementary to these findings, Weigmann et al. reported that substances are mainly located in the uppermost cell layers of the stratum corneum, where they are continually depleted due to the physiological process of desquamation. These findings suggest that the stratum corneum only provides a short-term reservoir function. The hair follicles in contrast represent efficient long-term reservoirs (up to 10 days) for topically applied substances, as their depletion occurs only through the slow processes of sebum production and hair growth.

(IV) Electrically assisted methods

(a) Ultrasound(Phonophoresis, sonophoresis):

It is defined as the movement of drugs through intact skin and underlying soft tissues under the influence of an ultrasonic perturbation. It is safe and effective technique for enhancing drug administration in clinical applications when with a proper frequency, power level, and duration.

It increases drug permeation through the skin by disordering the structured lipids in the stratum corneum. Potent chemotherapeutic agent limits the therapeutic window. This window can be expanded by controlling the drug delivery in both, space [selective to the tumour volume and time [timing and duration of release] such that non targeted tissue are not adversely affected. This can be achieved by developing Transdermal drug delivery with the use of ultrasound technique(US) is one of the effective and safe option to treat cancerous tissue. Low frequency US -- less than 1 Mhz medium 1-5 Mhz high frequencies 5-10 Mhz Ultrasonic waves can be carefully controlled and focused on the tumour site. Low frequency US (20 khz) can be used in the transdermal delivery of medium and high molecular weight. Proteins (including insulin, interferon and erythropoietin). Three hours after the US treatment, the skin regained its transport resistance to insulin, indicating that no permanent damage was done by US. [38]

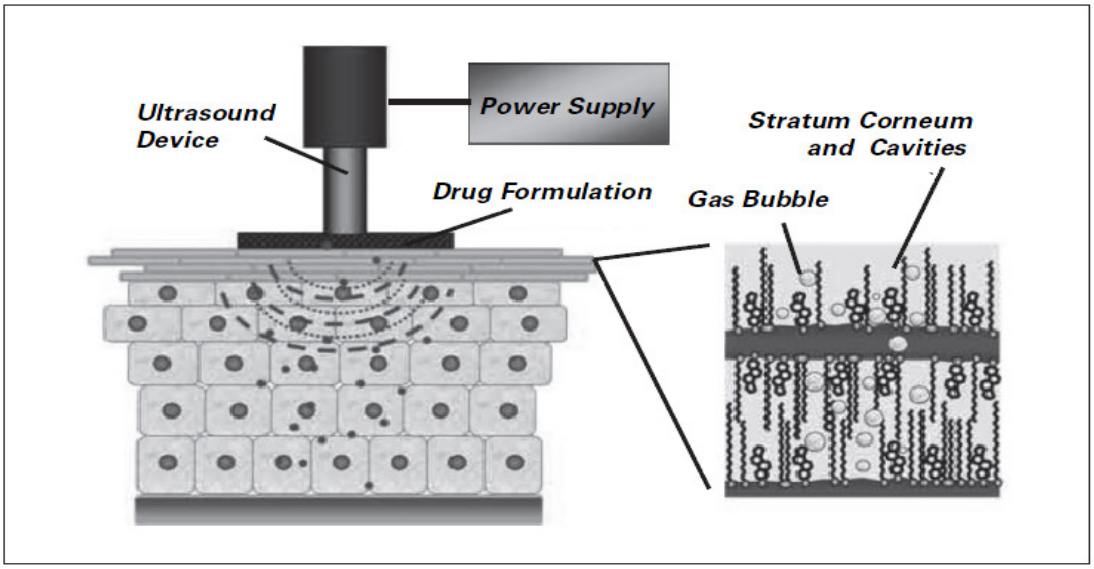

Fig.5: The principle of sonophoresis schematically [39]

(b) Iontophoresis:

Iontophoresis is basically an injection without the needle.

Mechanism:

Repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged active agent and its vehicle Fig 6. One or two chambers are filled with a solution containing an active ingredient and its solvent, also called the vehicle. The positively charged chamber, called the anode, will repel a positively charged chemical, whereas the negatively charged chamber, called the cathode, will repel a negatively charged chemical into the skin. This technique is highly desirable to improve the transdermal delivery of peptide and proteins. By the process of electro migration and electro-osmosis, iontophoresis increases the permeation of charged and neutral compounds like low (lidocaine) and high molecular drugs, such as peptides (e.g. luteinising hormone releasing hormone and insulin). [40]

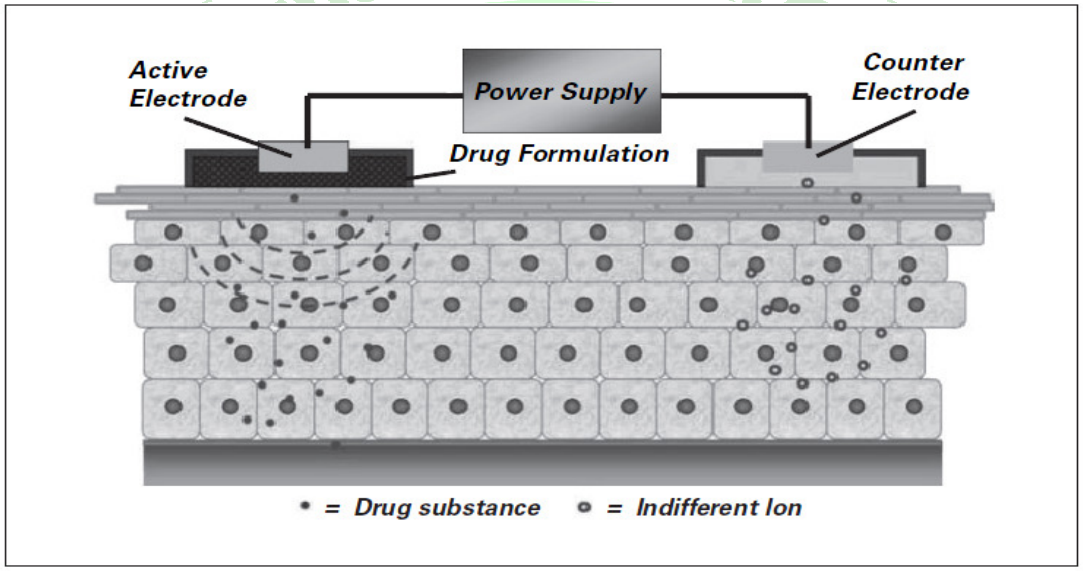

Fig.6: The principle of iontophoresis schematically [39]

(c). Electrophoresis:

Here the membrane of a cell exposed to high-intensity electric field pulses(up to several hundred volts for micro- or milliseconds) can be temporarily, thus becoming highly permeable to exogenous molecules in the surrounding media. The charged molecules were considered transporting through existing shunt routes of the skin at transdermal voltage <100 v. When transdermal voltage was greater than 100v, the transcorneocyte pathway was also accessible to charged molecules as lipid bilayers were electroporated. It is effective, safe, cost-effective, as well as powerfully versatile. E.g. microchip controlled for complex drug delivery patterns. [40]

(d) Magnetophoresis:

The term magnetophoresis was used to indicate application of a magnetic field and acts as an external driving force to enhance drug delivery across the skin. It induces alteration in the skins structure that could contribute to an increase in permeability. 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, and thermal cancer therapy.

(e) Pressure wave:

Pressure waves generated by intense laser radiation, can permeabilize the stratum

corneum as well as the cell membrane. PW 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 single pressure wave is sufficient to permeabilize the stratum corneum and allow the transport of macromolecules into the epidermis and dermis. In addition, the drug delivered into the epidermis can enter the vasculature and 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 waves does not cause any pain or discomfort and the barrier function of the stratum corneum always recovers. The enhancing effect of such a mechanism on caffeine permeation has been reported. [38]

(V) Vesicles and particles

(a) Liposomes and other vesicles:

Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. Liposomes acts by penetrating the epidermis, carrying the drug into skin and those large multilamellar vesicles could lose their external bilayer 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. Thereafter, they may act as penetration enhancers, loosening the lipid structure of the stratum corneum and promoting impaired barrier function of these layers to the drug, with less well-packed intercellular lipid structure forms, and with subsequent increased skin partitioning of the drug. Studies have focused on delivery of agents via liposomes like anti-psoriatic agent via ethanolic liposomes, caffeine for hyperproliferative diseases, catechins, enoxacin. Ethosomes are liposomes with high alcohol content (up to 45%) capable of enhancing penetration to deep tissues and the systemic circulation. It is proposed that the alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate**.** [26]

(b) Niosomes:

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. In fact, if compared with conventional liposomes (phospholipids) niosomes (non ionic surfactant vesicles) offer higher chemical stability, lower costs, and great availability of surfactant classes. Niosomes seems an interesting drug delivery system in the treatment of dermatological disorders. In fact, topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They are thought to improve the horny layer properties; both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids.

(c) Transfersomes:

These are vesicles composed of phospholipids as their 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 squeeze to penetrate the stratum corneum barrier spontaneously. The driving force for penetration into the skin is the "Transdermal gradient" caused by the difference in water content between the restively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis (close to 100%). Studies have been focused on delivery of agents like vaccines, retinyl palmitate, estradiol, copper, zinc, superoxide dismutase, insulin. In some cases the transferosomes drug delivery with some physical enhancement method iontophoresis for estradiol and micro needles for docetaxel. [26]

CONCLUSION

The search for the ideal skin permeation enhancer for semisolids has been the focus of considerable research effort over a last two decades. Although many potent enhancers

have been revealed, in most cases their augmented effects are associated with toxicity, therefore limiting their pharmaceutical application. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will help in the design of enhancers with desirable characteristics and minimal toxicity.

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