International Journal of Advanced Pharmaceutical Sciences, Volume 1, Issue 04, Page 01-25
ISSN:2456-8147

Study of Novel Emulsion Technique

*Dinesh Sharma ,M Nayak, *Dept of Pharmaceutics, Kalinga University, Raipur, Chhattisgarh, India

An open access journal

Supporting Information:

Received: 07 April 2018
Accepted: 27 April 2018
Published: 05 May 2018

Competing Interests:
The authors have declared that no competing interests exist.

Corresponding author address

Dinesh Sharma
*Dept of Pharmaceutics, Kalinga University, Raipur, Chhattisgarh, India

ABSTRACT

The aim of the present review is to study nanoemulsion gel. Various components of nanoemulsion gels are studied. The aim of the present work is to create at of nanoemulsion gel. The nano emulsion gels are having various advantages. The nanoemulsion gels are prepared by various polymers. The various methods of preparation is also studied. There are many advantages of nanoemulsion gels over conventional dosage form. Emulsion system helps to enhance absorption of two immiscible media. The gelling agents used in preparation helps for greater contact time. Permeation enhancers are also used for better topical action. Therefore it is useful for enhancing action of analgesic , antifungal as well as anti -inflammatory .

Keyword- Nanoemulsion gel, classification, skin

INTRODUCTION

The term "Nanoemulsion" is refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. It is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant and co-surfactant. The dispersed phase consist of small particles or droplets, with a size range of 5 nm-200 nm, and are having very low oil/water interfacial tension. Because size of the droplet is less than 25% of the wavelength of visible light, these are transparent. Nanoemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a cosurfactant or co-solvent is used in addition to the surfactant, the oil phase and the water phase[1]

Types of Nanoemulsions

Three types of Nanoemulsions are most likely to be formed depending on the composition

O/W Nanoemulsion

Wherein oil droplets are dispersed in the continuous aqueous phase

W/O Nanoemulsions

Wherein water droplets are dispersed in the continuous oil phase

Bi-continuous Nanoemulsions

Wherein microdomains of oil and water are interdispersed within the system.

In all three types of Nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants[1,2].

Components of Nanoemulsion

Main three components of Nanoemulsions are as follows:

- Oil
- Surfactant
- Co-surfactant

Nanoemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy Nanoemulsions are based on low interfacial tension. This is achieved by adding a cosurfactant, which leads to spontaneous formation of a thermodynamically stable Nanoemulsion. The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the Nanoemulsions transparent liquids[1,2] in principle, Nanoemulsions can be used to deliver drugs to the patients via several routes, but the topical application of Nanoemulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin. Nanoemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions and gels. Mobility of drugs in Nanoemulsions is more facile[2] as compared to the Nanoemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin.[1] The superior transdermal flux from Nanoemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin.[1] Nanoemulsions may affect the permeability of drug in the skin. In this case, the components of Nanoemulsions serve as permeation enhancers. Several compounds used in Nanoemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum. For example, short chain alkanols are widely used as permeation enhancers. It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum.[1]

The surfactants used to stabilise such systems may be:

(i) Non-ionic

(ii) Zwitterionic

(iii) Cationic

(iv) Anionic surfactants

A combination of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the Nanoemulsion region.

Examples:

(i) Non-ionic includes Polyoxyethylene surfactants such as Brij 35 (C12E35) or sugar esters such as sorbitan monooleate (Span 80).

(ii) Zwitterionic surfactants include Phospholipids are a notable example and exhibit excellent biocompatibility.

(iii) Cationic surfactants include Lecithin preparations from a variety of sources including soybean and egg are available commercially and contain diacylphosphatidylcholine as its major constituent[1]. Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants, with hexadecyltrimethyl ammonium bromide

(CTAB) and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known.

(iv) Anionic surfactant include sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o Nanoemulsions. Attempts have been made to rationalise surfactant behaviour in terms of the hydrophile-lipophile balance (HLB), as well as the critical packing parameter (CPP). Both approaches are fairly empirical but can be a useful guide to surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3–6) surfactants are favoured for the formation of w/o Nanoemulsions whereas surfactants with high HLBs (8-18) are preferred for the formation of o/w Nanoemulsion systems. Ionic surfactants such as sodium dodecyl sulphate which have HLBs greater than 20, often require the presence of a cosurfactant to reduce their effective HLB to a value within the range required for Nanoemulsion formation. In contrast, the CPP relates the ability of surfactant to form particular aggregates to the geometry of the molecule itself. In most cases, single-chain surfactants alone are unable to reduce the oil /water interfacial tension sufficiently to enable a microemulsion to form, a point made in a number of pertinent microemulsions reviews. Medium chain length alcohols which are commonly added as cosurfactants, have the effect of further reducing the interfacial tension, whilst increasing the fluidity of the interface thereby increasing the entropy of

the system. Medium chain length alcohols also increase the mobility of the hydrocarbon tail and also allow greater penetration of the oil into this region [3, 4].

Table 1.1: List of oils used in Nanoemulsions

Name	Chemical name
Captex 355	Glyceryl Tricaorylate/Caprate
Captex 200	Propylene Dicaprylate/Dicaprate Glycol
Captex 8000	Glyceryl Tricaprylate (Tricaprylin)
Witepsol	90:10 % w/w c12 Glyceride tri: diesters
Myritol 318	c8/c10 triglycerides
1sopropyel myristate	Myristic acid isopropyl ester
Oleic acid	Elainic acid

Table 1.2: List of Surfactants used in Nanoemulsions

S.NO	Solubilizing agents, surfactants, emulsifying agents adsorption enhancers
1	Capryol 90
2	Gelucire 44/14, 50/13
3	Cremophor RH 40
4	Imwitor 191, 308(1), 380, 742, 780 K, 928, 988
5	Labrafil M 1944 CS, M 2125 CS

6	Lauroglycol 90
7	PEG MW > 4000
8	Plurol Oleique CC 497
9	Poloxamer 124 and 188
10	Softigen 701, 767
11	Tagat TO
12	Tween 80

Table 1.3: List of Co-Surfactant used in Nanoemulsions.

S.NO	**Co Surfactant**
1	TranscutolP
2	Glycerin,Ethylene glycol
3	Propylene glycol
4	Ethanol
5	Propanol

ADVANTAGES OF NANOEMULSION OVER OTHER DOSAGE FORMS

- Increase the rate of absorption.
- Eliminates variability in absorption.
- Helps solublize lipophilic drug.

- Provides aqueous dosage form for water insoluble drugs.
- Increases bioavailability.
- Various routes like tropical, oral and intravenous can be used to deliver the product.
- Rapid and efficient penetration of the drug moiety.
- Helpful in taste masking.
- Provides protection from hydrolysis and oxidation as drug in oil phase in O/W Nanoemulsion is not exposed to attack by water and air.
- Liquid dosage form increases patient compliance.
- Less amount of energy requirement.
- Nanoemulsions are thermodynamically stable system and the stability allows self-emulsification of the system[1.]

DISADVANTAGES OF NANOEMULSION BASED SYSTEMS

- Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
- Limited solubilizing capacity for high-melting substances.
- The surfactant must be nontoxic for using pharmaceutical applications.
- Nanoemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon Nanoemulsion delivery to patients[1].

GELS:

The term gel represents a physical state with properties intermediate between those of solid and liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity. It is therefore recommended that the term should be restricted to those systems that satisfy the following criteria, which are similar to suggested by Herman[5].

- They are coherent colloidal system of at least two components (the gelling agent and a fluid component).
- They exhibit mechanical properties characteristic of the solid state.

- Each component is continuous throughout the system.

The term "gels" is broad, encompassing semisolid of a wide range of characteristics from fairly rigid gelatin slabs, to suspension of colloidal clays, to certain greases. A gel can be looked upon as being composed of two interpenetrating phase (the gelling agent and a fluid component).

Gels are semisolid, being either suspensions of small inorganic particle or large organic molecule interpenetrated with liquid. In the first case, the inorganic particles, such as bentonite, from a three-dimensional "house of cards" structure throughout the gel. This is a true two-phase system, as the inorganic particles are not soluble but merely dispersed throughout the continuous phase.

Large organic molecules tend to exits in solution as randomly coiled flexible chains. These molecules are either natural or synthetic polymers, tends to entangle with each other because of their random motion. It is interaction between the units of the colloidal phase, inorganic or organic, that sets up the "structural viscosity" immobilizing the liquid continuous phase. Thus gels exhibit characteristics intermediate to those of source liquid and solids[6].

Classification:

Gels are classified according to the following ways:

I. According to source of gelling agent:

a. Natural gels

b. Synthetic gels

II. According to the liquid medium entrapped:

a. Hydrogels

b. Organogels

III. According to their cross linkage:

a. Chemical gels

b. Physical gels

IV. According to the chemical nature of gelling agent:

a. Organic gels

b. Inorganic gels

Most natural gums such as acacia, carrageenan, and xanthan gum, are anionic polysaccharide that yields natural gels. Number of cellulose derivatives have been synthesized and used as gellants (e.g. sodium carboxymethylcellulose, hydroxyethylcellulose, carbopol, hydroxyl propyl cellulose etc.) that yield synthetic gels. The nature of the solvent also determines whether the gel is a hydrogel (i.e. water based) or an organogel (i.e. with nonaqueous solvent).Thus, bentonite magma and gelatin gel hydrogels and dispersions of metallic stearates in oil are examples of organogels. A hydrogel is a polymeric material that exhibits ability to swell in water and absorb a significant fraction of water (2000 times the polymer weight) within its structure without dissolving in water. A wide variety of natural of both plant and animal origin, materials prepared by modifying naturally occurring structures, and synthetic polymeric material are hydrogels[6].

Organic gel typically contains polymers such as carbomer, polyethylene glycol, etc. as gel formers. These are further subdivided according to the chemical nature of the dispersed organic molecules. In case of inorganic gels, the chemical nature of gelling agent is inorganic e.g. bentonite magma. Solid gels the with low solvent concentration are known as xerogels. These are often produced by evaporation of the solvent, leaving the gel framework behind. E.g. gelatin, tragacanth.

Uses[6]:

In the pharmaceutical and cosmetic industry, nanoemulsion gels are having following uses.

- Gels are used as delivery systems for orally administered drugs.
- It also used to deliver topical applied drug directly to the skin, mucus membrane or the Eye.
- As long acting forms of drug injected intramuscularly.
- In tablet granulation, protective colloids in suspensions, thickeners in oral liquid, and suppository bases gels are used as binder.
- In cosmetics like shampoos, fragrance products, skin and hair care preparations.

- The bulk property of swelling is of particular interest for "swelling implants" which can be implanted in a small dehydrated state via a small incision and which then swell to fill a body cavity and/or to exert a controlled pressure.

SKIN:

In human body the skin is one of the most extensive and readily accessible organs . The skin cover an area of about 2 square meter and weigh 4.5-5kg, about 16% of total body weight of the average human being. It also receives 1/3rd of the total blood supply. Thickness of the human skin ranges form 0.5mm on the eyelids to 4mm on heels.

It separates the underlying blood circulation network from the outside environment and serves as barrier against physical and chemical attacks, it also acts as thermostat in maintaining body temperature and shields the body from microorganisms[7].

Anatomy of the skin:

The skin is a multi-layered organ and anatomically contains many histological layers. It is an anatomical barrier between the body and its environment. Skin is contributes to about 16-18% of normal body weight. It is composed of three primary layers such as.

- Epidermis
- Dermis
- Hypodermis or subcutaneous fat layer

A) Epidermis:

It is the most superficial layer of the skin and is composed of stratified squalors epithelial cells, which varies in thickness in different parts of the body. It is thickest on the palm of the hand and soles of the feet. In the epidermal layer there are no blood vessels or nerve ending. The epithelial cells are joined together mainly by highly convoluted interlocking bridge, which are responsible for the unique integrity of the skin.

Keratinocytes, melanocytes, Langerhans cells and Markel's cells are the main type of cell which make the epidermis. This layer helps the skin to regulate body temperature. The outermost layer of the epidermis consists of 25to30 layers of dead cells.

The Epidermis is divided into five anatomical layers.

a) Stratum corneum
b) Stratum lucidum
c) Stratum granulosum
d) Stratum spinosum
e) Stratum basale

The stratum corneum is the outermost layer of the epidermis and consist of thin, non-nucleated, dead cells where the protoplasm is replaced by keratin[8].

B) Dermis:

This layer lies just below the epidermis. The dermis is 1/8th of centimeter thick and constitutes the main the mass of the skin. The thickness of the dermis ranges from 2000µm-3000µm. It consists of matrix. Loose connective tissue, composed of fibrous protein embedded in an embedded in an amorphous ground substance. Collagen imparts extensibility and imparts extensibility and imparts elasticity to the dermis.

Beneath the dermis the dermis the fibrous tissue opens out and merges with the fat containing subcutaneous tissue. The upper portion of the dermis is formed into ridges or papillae projecting into the epidermis.

The dermis of the skin consists of the following structures.

1. Blood vessel
2. Lymph vessel
3. Sensory nerve ending
4. Sweat glands and their ducts.

5. Hair root, hair follicles and hairs

6. Sebaceous gland

The dermis is structurally divided into two areas: a superficial area adjacent to the epidermis, called the papillary region, and a deep thicker area known as the reticular region[7,8].

C) Papillary region:

The papillary region is composed of loose areolar connective tissue. It is named for its fingerlike projection called papillae that extend toward the epidermis. In the palms, fingers, soles, and toes, the influence of the papillae projecting into the epidermis forms contours in the skin's surface, these are called friction ridges. Friction ridges occur in patterns that are genetically determined and are therefore unique to the individual, making it possible to use fingerprints or footprints as a means of identification.

D) Reticular region:

The reticular region lies deep in the papillary region and is usually much thicker. It is composed of dense irregular connective tissue, and receives its name from the dense concentration of collagenous, elastics, and reticular fibers that weave throughout it. These protein fibers give the dermis its properties of strength, extensibility, and elasticity. Also located within the reticular region are the roots of the hair, sebaceous glands, sweat glands, receptors, nails, and blood vessels.

E) **Hypodermis:**

It is composed of loose, textured white fibrous connective tissue in which fat and elastic fibers are intermingled. Water content is about 30%. The thickness is variable but much thicker than the dermis. It is richly supplied with blood and lymph vessels. The base of the hair follicle, the secretory portion of sweat gland, and cutaneous nerves are also present in this layer. The main cell types are fibroblasts, macrophages and adipocytes the hypodermis contains 50% of body fat). Fat server as padding and insulation for the body.

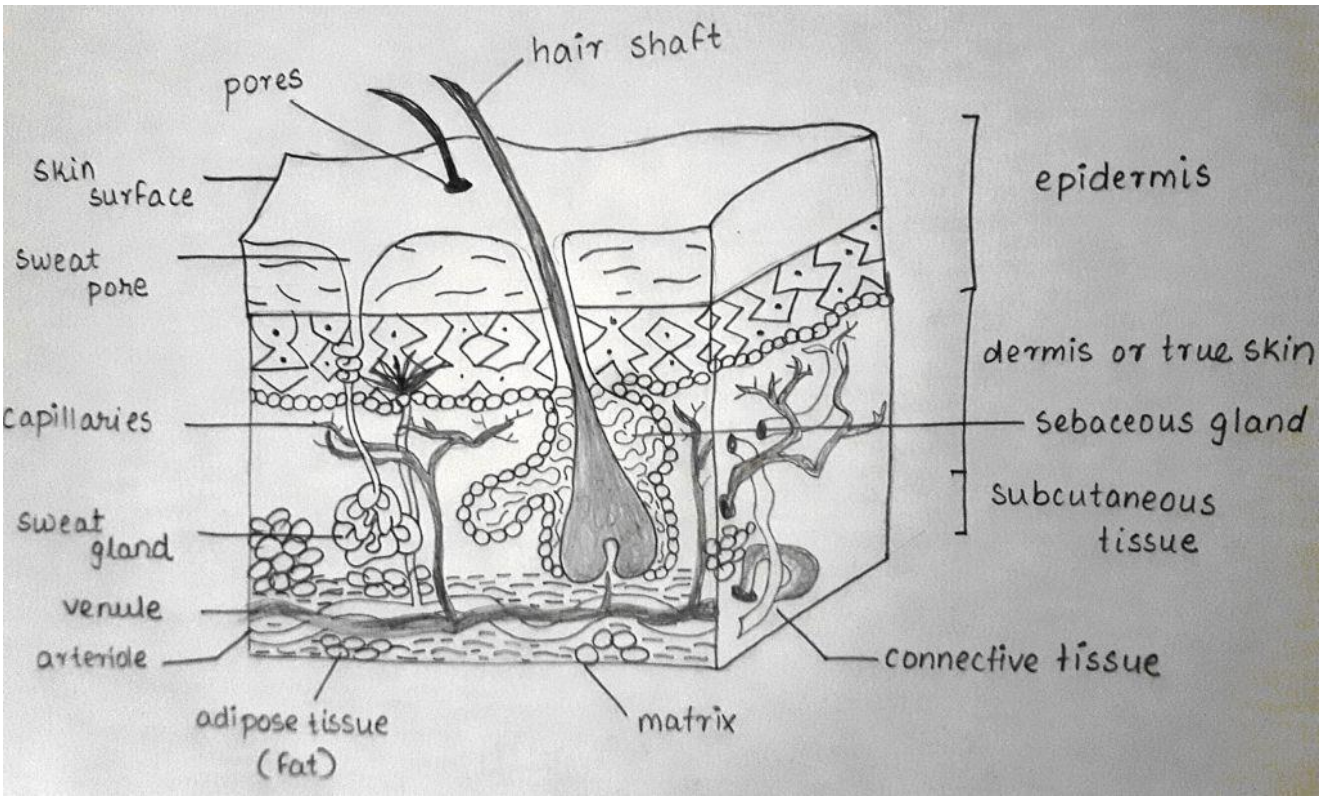

Fig 1.1: Longitudinal section of the skin

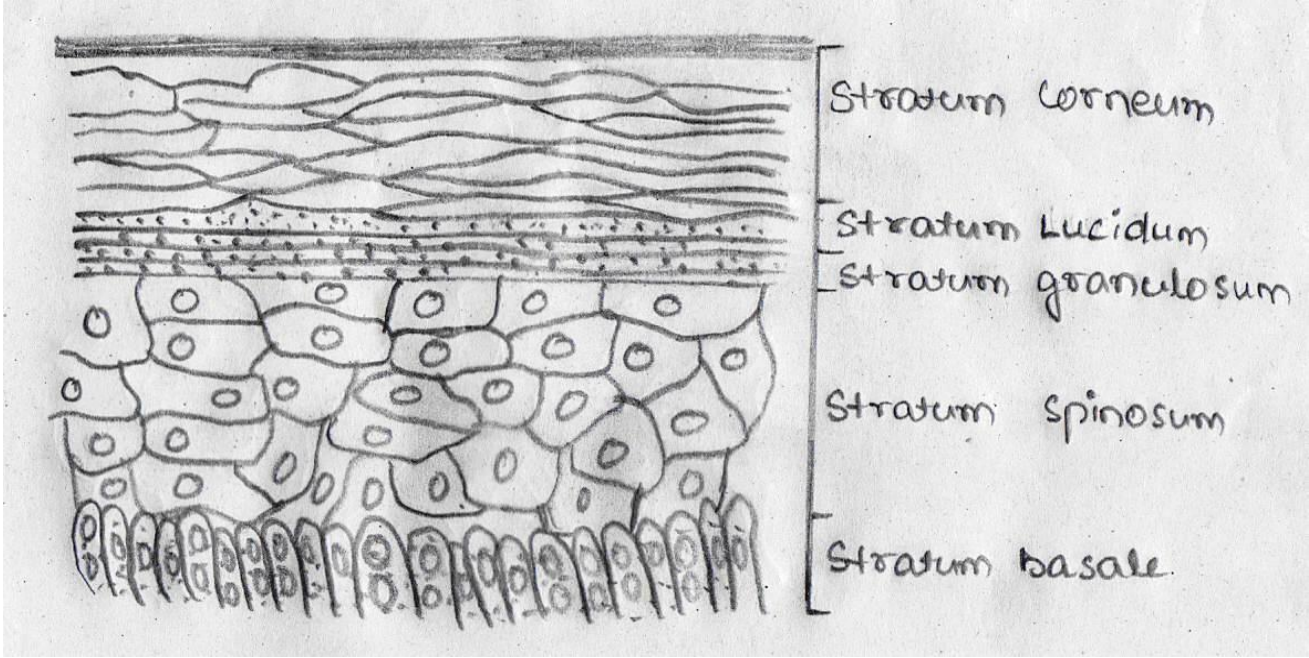

Fig 1.2: Anatomy of the skin

Percutaneous absorption:

Percutaneous absorption is defined as penetration of substances into various layer of skin and permeation across the skin into the systemic circulations. This is a step-wise process and can be divided into three parts.

- Penetration is the entry of a substance into a particular layer
- Permeation is the penetration from one layer into another, and is different both functionally and structurally from the first layer
- Absorption is the uptake of a substance into systemic circulation[1].

Routes of drug permeation:

A) Transappendageal route:

Transport substances via sweat glands and the hair follicles with their associated sebaceous glands. The route is considered to be of minor importance because of their relatively small area[9].

B) **Transepidemal route:**

The transepidermal route across the continuous stratum corneum comprises transport via intracellular and intercellular spaces. Both polar and non-polar substances diffuse via transcelluar and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated stratum corneum, whereas the non polar molecules dissolve and diffuse through the no aqueous lipid matrix of the stratum corneum[9].

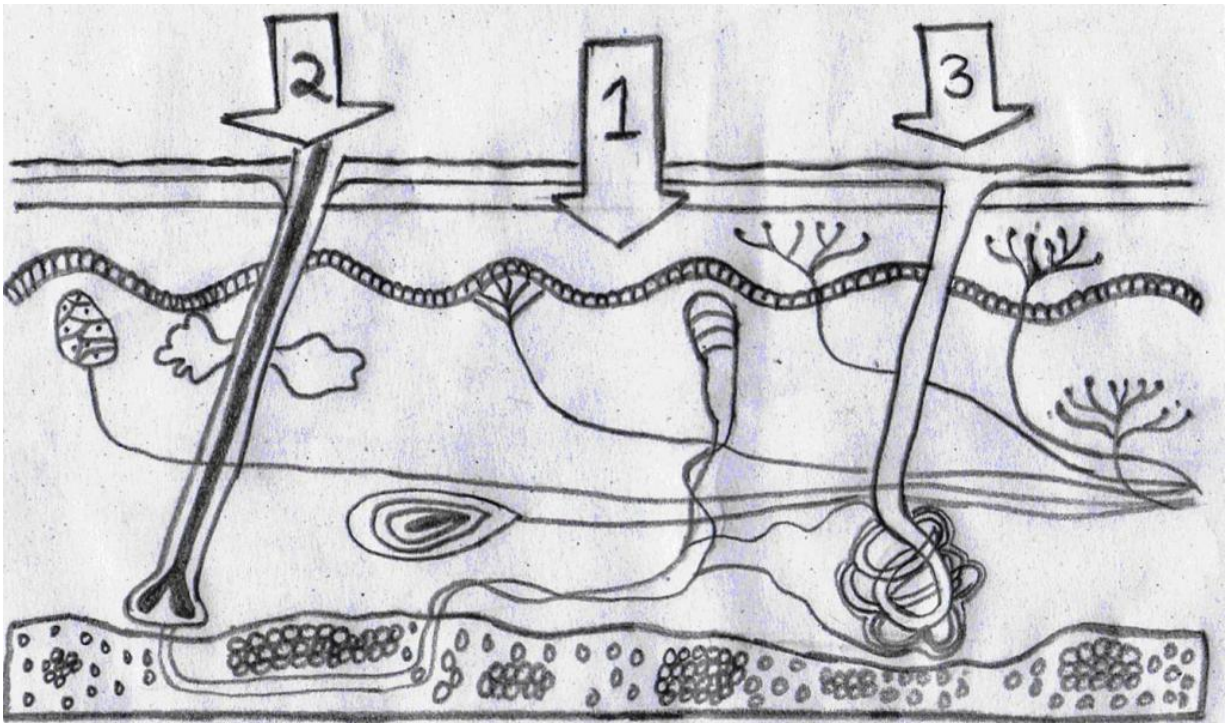

Fig 1.3:Routes of Drug permeation (1) across the intact horny layer, (2) through the hair follicles with the associated sebaceaous glands, or (3) via the sweat glands.

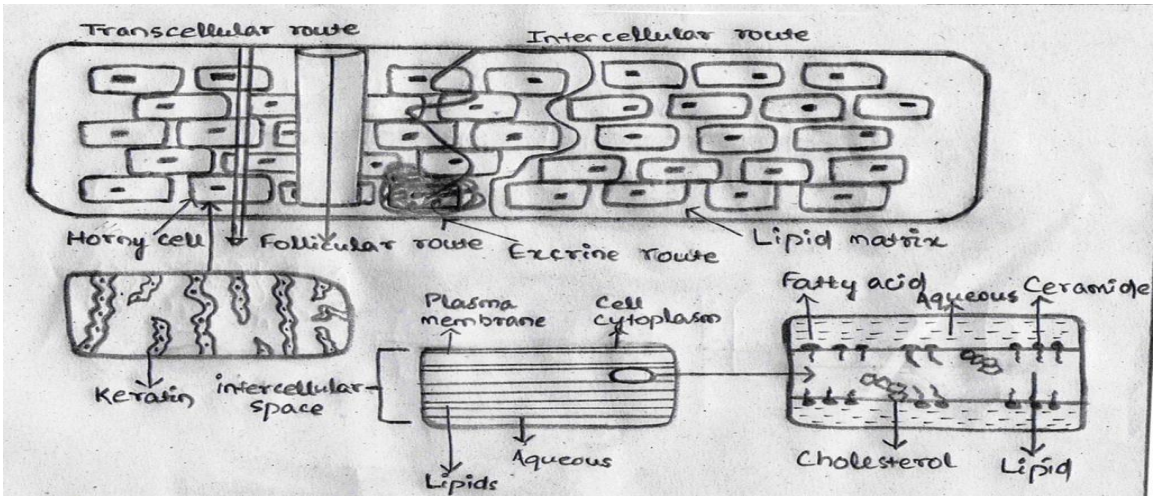

Fig 1.4: Permeation route through stratum corneum

When a drug is placed onto the skin surface it will first partition into the stratum corneum. The major route of penetration is through the intercellular channels, which contain a complex mixture of structured lipids. The partitioning behavior of the drug is therefore an important determinant in this first step of the absorption process. Also the solubility characteristics of the penetrant in the lipids of the stratum corneum should be taken into account. The solubility may be influenced by the components that diffuse out of the formulation into the skin. The second stage for the molecule is diffusion thought the structured lipids. Molecular weight, size, shape and polarity also influence diffusion rate.

Factors affecting transdermal permeability:

The principle transport mechanism across mammalian skin is by passive diffusion through primarily the transepidermal route at steady state or through transappendageal rout at initially, non steady state. The factors, which affect the permeability of the skin mainly the stratum corneum, are classified into following categories[6, 7].

Physicochemical Properties of the Penetrant Molecule:

1. Partition co-efficient:

Drug possessing both water and lipid solubilities are favorably absorbed through the skin. Transdermal permeability coefficient shows a linear dependence on partition co-efficient. Varying the vehicle may also alter a lipid/water partition co-efficient of a drug molecule. The partition co-efficient of a drug molecule may be altered by chemical modification without affecting the pharmacological activity of the drug[6].

2. pH condition:

The effect of pH is mainly on the rates of absorption of acidic and basic drugs, unchanged form of drug has better penetrating capacity. Transport of ionizable species from aqueous solutions shows strong pH dependence.

3. Drug concentration:

Transdermal permeability across mammalian skin is a passive diffusion process and this depends on the concentration of penetrant molecule on the surface layer of the skin.

Physicochemical Properties of the Drug Delivery System:

1. The affinity of the vehicle for the drug molecules:

It can influence the release of the drug molecule from the vehicle. Solubility in the vehicle will determine the release rate of the drug. The mechanism of drug release depends on whether the drug is dissolved or suspended in the delivery system and on the interfacial partition co-efficient of the drug from the delivery system to skin tissue.

1. **Composition of drug delivery system:**

Composition of drug delivery system may affect not only the rate of drug release but also the permeability of the stratum corneum by means of hydration.

2. Enhancement of transdermal permeation:

Release of the drug from the dosage from less due to the dead nature of the stratum corneum. Penetration enchancers cause the physicochemical or physiological changes in stratum corneum and increase the penetration of the drug through the skin. Various chemical substances found to possess drug penetration enhancing property.

Physiological and Pathological Condition of the Skin:

1. Skin age:

Fetal and infant skin appears to be more permeable than adult skin. Percutaneous absorption of topical steroids occurs more rapidly in children than in adults. Water permeation has shown to be same in children.

2. Lipid film:

The lipid film on the skin surface is formed by the excretion of sebaceous glands and cell lipids like sebum and epidermal cell which contain emulsifying agent may provide a protective film to prevent the removal of natural moisturizing factor from the skin and help in maintaining the barrier function of the stratum corneum[6].

3. Skin hydration

Hydration of stratum cornenum can enhance can transdermal permeability. The rate of penetration of salicylic acid through skin with dry and hydrated corneum was measured when the tissue were hydrated, the rate of penetration of the most water soluble esters increased more than that of the other esters.

4. Skin temperature:

Raising skin temperature result in an in an increase in the rate of skin permeation. Rise in skin temperature may also increase vasodilatation of blood vessels, which are in contact with skin leading to an increase in percutaneous absorption.

5. Cutaneous drug metabolism:

After crossing the stratum corneum barrier, some of the drug reaches the general circulation in active from and some of this in inactive from or metabolic form, because of the presence of metabolic enzymes present in the skin layers. It was reported that more than 95% of testosterone absorbed was metabolized as it present through the skin.

6. Species differences:

Mammalian skin from different species display wide differences in anatomy in such characteristics as the thickness of stratum comeum, number of sweat gland and hair follicles per unit surface area.

7. Pathological injury to the skin:

Injuries to the skin can cause the disturbance in the continuity of stratum corneum and leads to increase in skin permeability.

Approaches to overcome the barrier [9]:

A number of approaches have been used to overcome the barrier function of stratum corneum. These include physical and chemical methods.

1) **Physical methods:**

a) Iontophoresis
b) Sonophoresis
c) Thermal modulation
d) Stripping of stratum corneum
e) Hydration of stratum corneum

Physical enhancement techniques have been studied that involve the use of an energy source to overcome the barrier properties of the skin. Iontophorosis and electroporation have been used typically for delivery of large molecular weight compounds. Low frequency sonophoresis has been demonstrated. Among all these methods chemical permeation enhancers are widely used for the permeation of drug across the skin since. the physical methods causes painful destruction of the skin with high current setting.

2) **Chemical methods**:

a) Delipidization of stratum corneum

b) Synthesis of lipophillic analogues

c) Use of sorption promoters

Chemical Penetration Enhancers [5]:

Agents capable of modifying the barrier to penetration presented by the skin are called as "penetration enhancers" or the chemical penetration enhancers are the substances which reversibly reduce the barrier resistance of the stratum corneum without damaging the viable cells

Properties proposed for an ideal penetration enhancer are:

- They should be nontoxic, non-irritating and non-allergic.
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
- The penetration enhancers should work unidirectionally i.e should allow therapeutic agents into the body while preventing the loss of endogenous material from the body.

- When removed from the skin barrier properties should return both rapidly and fully.
- The penetration enhancers should be appropriate for formulation into diverse topical
- preparations, thus should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin 'feel'.
- Pharmacologically inert.

The activity of penetration enhancers may be expressed in terms of an enhancement ratio (ER). ER = Drug permeability coefficient after enhancer treatment/Drug permeability coefficient before enhancer treatment. Barry and co-workers devised the lipid-protein-partitioning (LPP) theory to describe the mechanisms by which enhancers' effect skin permeability.

Mechanism of action of penetration enhancers are:

- Disruption of highly ordered structure of stratum corneum lipids.
- Interaction with intracellular proteins.
- Increase the thermodynamic activity of the drug by acting as a cosolvent.
- Increase the partition coefficient of the drug to promote its release from the vehicle into the skin.
- Promote penetration and establish drug reservoir in the stratum corneum.
- Those that impact diffusion across the stratum corneum and those that alter partitioning into the stratum corneum. The former class generally comprises a long alkyl chain capable of intercalating with the long chains of the intercellular lipids, in addition to a polar head group that is capable of interacting with the lipid polar head group.

Although the transdermal preparation in the market are mostly transdermal patches in which drug is present in a matrix or in a rate controlling membranes, the newer types of carriers used for the drugs offer newer possibilities for dermal and transdermal drug delivery. These carrier systems include vesicular systems, nanoparticles and liquid crystalline systems.

Classification of Penetration enhancers[5]:

Based on conceptual diagram, penetration or permeation enhancers or accelerants have been classified, according to their organic and inorganic character into three areas.

Area-1: In this enhancers are solvents
Area-2 Enhancers for hydrophilic compounds
Area-3 Enhancers for hydrophobic compounds

1) **Solvents:** Hydrophilic solvents like Dimethyl sulfoxide (DMSO),N-methyl-2-pyrrolidone, Dimethyl formamide (DMF), Dimethyl acetamide (DMA),Glycerol, polyethylene glycol can be used to solubilize drugs. These solvents can affect the penetration of the drug through the skin by allowing the stratum corneum to swell and solubilize or partially leaching of the epidermal lipids.

2) **Azones:** Chemically it is 1-dodecylazacycloheptane-2-one.wasfound to be absorbed in very low amounts. It increases the release rate of drugs like steroids, antibiotics, antifungals from polymer matrix. The use of azone as a penetration enhancer with various concentration is restricted completely as above 10% azone causes skin irritation.

3) **Alcohol and Glycols:** Of the various alcohols studied as skin penetration enhancers, ethanol is most widely used. It increases the flux of levonorgestrol by six folds and estradiol by 40 folds through the rat skin. Propylene glycol can significantly enhance the permeability of human skin to lipophilic compounds.

4) **Fatty acids:** Percutaneous absorption of drug had been increased by a variety of long chain fatty acids, the most popular of which is oleic acid. The alkyl esters of fatty acids can also act as a penetration enhancer.

5) Surfactants: Surfactants permeation promoting activity is due to action to decrease the surface tension to improve the wetting of the skin and to enhance the distribution of drugs. Hydrophilic head groups such as in sodium lauryl sulfate are very effective in altering the penetration of polar molecules, but alcohols which have low hydrophilicity are ineffective. The more hydrophilic surfactants interact strongly with the keratin and alter transport and the less

hydrophilic surfactants (long chain alcohols) interact weakly and do not alter the transport of polar molecules. Anionic surfactants like sodium lauryl sulfate and cationic surfactants irritate the skin strongly, swells the stratum corneum, however nonionic surfactants are harmless. The degree of enhancing activity is strongly depending on the surfactant structure and concentration.

6) Phospholipids: Many studies have employed phospholipids as vesicles to carry drugs into and through human skin. A few studied have used phospholipids in a non-vesicular form as penetration enhancers. For example theophylline was enhanced through mouse skin by 1% phosphatidylcholine in PG. Phospholipids could act as a penetration enhancer by following mechanisms. Firstly, phospholipids may exert a direct influence on permeability characterstics, secondly phospholipids is incorporated within the viable cells via intercellular lipids in the stratum corneum and form a lipophilic route for the permeability of drugs, thirdly an exogenous phospholipid disrupts the lamellar structure of the stratum corneum and increases lipid fluidity of stratum corneum.

7) **Pyrrolidones:** N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2P) are the most widely studied enhancers of this group. It had been used as permeation promoters for numerous molecules including hydrophilic and lipophilic permeates. In terms of mechanisms of action, the pyrrolidones partition well into human corneum stratum. Within the tissue they may act by altering the solvent nature of the membrane and pyrrolidones have been used to generate ‘reservoirs’ within skin membranes for sustained release of permeant.

PRINCIPLES OF DRUGE PERMEATION THROUGH SKIN:

Drug permeates the skin through passive diffusion that can be described by Fick’s First and second laws of diffusion[10, 11]. The primary theory underlining the permeation of a drug across a barrier is that the rate of transfer of a diffusing permeate per unit area a cross section at steady state (flux, f) is proportional to the amount of permeant M at steady that crosses a barrier of unit area S over unit t, as shown in Eq.1.

$$J = dM / S.dt \quad (1)$$

Fick's first law expresses the flux in terms of concentration gradient (eq.2), in which D is the diffusion co-efficient of the diffusing permeate, C is its concentration gradient across the barriers and x is the thickness of the barrier though which the substance permeates.

$$J=-dc / dx \qquad (2)$$

The diffusion coefficient illustrates that the ability of the permeate to pass through the barrier is a function of system variables such as pressure, temperature, solvent, nature of the barrier and permeate. The negative sign indicates that the flux is in the direction of decreasing the concentration, i.e., down the concentration gradient[10].

Coefficient (P) describes the rate of diffusion of a permeant in terms of linear velocity as length per unit time (eq.3).

$$P= D.K/=h\ dm/Cd.S.dt \qquad (3)$$

The plot cumulative amount of the permeant M that passes per unit area through the membrane as a function of time, the obtained slope of the linear portion of the curve represents zero-order rate of drug delivery, i.e., the flux f while the x- intercept of the slope is the lag time (t_L). This is a measure of the time required for the permeant to establish a uniform concentration gradient within the membrane separating the donor from the receptor compartment.

Penetration enhancers may be incorporated into formulation in order to improve drug flux through membrane (stratum corneum). The flux is governed by the diffusion coefficient of the drug in the vehicle, the partition coefficient between the formulation and the stratum corneum and the membrane thickness. The flux J of is actually proportional to a gradient of thermodynamic activity rather than concentration. The activity will change in different solvents and the diffusion rate of a solvent at a definite concentration may vary widely depending upon the solvent employed. The thermodynamic activity of a drug may be held constant (a=1) in a delivery form by using saturated solution in the presence of excess solid drug.

Unit activity ensures constant release of the drug at a rate that depends on the membrane permeability and the geometry of the dosage form illustrates some of the properties that may be manipulated on application of a penetration enhancer to the skin. Thus an effective penetration

enhancer may increase the diffusion coefficient of the drug in the stratum corneum (i.e. disrupt the barrier nature of the stratum corneum), may act to increases the effective concentration of the drug in the vehicle (for example acting as an anti-solvent), could improve partitioning between the formulation and the stratum corneum or, less likely, by decreasing the skin thickness.

FACTORS INFLUENCING THE SUITABILITY OF A DRUG FOR

TRANSDERMAL DRUG DELIVERY:

- Potency of the drug:- the daily systemic dose should be ≤ 20 mg
- Molecular size:- the drug should have a molecular weight of < 500 Daltons.
- Lipophilicity :- the logP should be in the range 1-3.
- Melting point:- should be < 200 ◦C.
- Hydrogen bonding groups:- should be ≤ 2.
- Irritation:- the drug should not be directly irritated to the skin.
- Immunogenicity:- the drug should not stimulate an immune reaction in the skin.

  A predictive rule of thumb is that the maximum flux of drug through the skin should decrease by a factor of 5 for an increase of 100Da in MW, and decrease by a factor of 10 for an increase of 100 ◦C in melting point. It has been generally accepted that the highly organized crystalline lipid lamellae play an essential role in the barrier properties of the stratum corneum. Many techniques have been aimed to disrupt and weaken the highly organized intercellular lipids in an attempt to enhance drug transport across the intact skin or to increase the driving force for permeation of drugs across this skin barrier.

Conclusion:

Novel nanoemulsion gel with suitable viscosity is required for transdermal application. various polymers are used to increase the viscosity thereby enhancing it's efficiency. Permation rate is studied for better biological therapeutic action. Nanoemulsion gels is

better prepared for better action. Future research on nanoemulsion gels is necessary for better therapeutic bioavailability. This area of study has got brighter future

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