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A Review on Topical gel with emphasis on Permeation enhancer excipient

Susmita Sudhir Mandal[1*], Dinesh M. Sakarkar[1]

Maharashtra Institute of Pharmacy, Bramhapuri, MH, India, Pin code-441206,

E-mail id: susmita23mandal@gmail.com, Mob no.9370883318

Abstract: Topical medication administration is a localized drug delivery system anywhere in the body by means of ophthalmic, rectal, vaginal and skin as topical routes. Skin is the one of the universal and administration and is main route of topical drug delivery system. The human skin serves as an impediment, a thermo regulator and prevents excessive loss of water from the internal organ. Enhancement in skin permeation by hydration of the stratum corneum, or by use of chemical enhancers acting on the lipids and keratinized structure in the stratum corneum, partitioning and solubility effect is a promising tool in potential clinical application. Permeation substances or excipients is a new emerging technology which has the potential to increase the number of drug taken transdermally. 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 protective barrier. This is the rate limiting step in the absorption of the drug percutaneously. In this review article, we present a topical formulation on with emphasis given various advances made on permeation enhancers based on literature survey of various research articles.

Keywords : Topical gel; Drug delivery; Permeation enhancer; Nonoemulgel; DSC (Differential scanning colorimetry); SC (Stratum corneum); PG (Propylene glycol); DMSO (Dimethyl sulfoxide; DC (Direct Current); US (Ultrasound); LRN (Lornoxicam).

Introduction

Topical delivery is an attractive route for local and systemic treatment. The delivery of drugs onto the skin is recognized as an effective means of therapy for local dermatologic diseases. It can penetrate deeper into skin and hence give fine absorption.

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In the formulation of topical dosage forms, efforts are being made to utilize drug carriers that ensure adequate localization or penetration of the drug within or through the skin in order to enhance the local and minimize the systemic effects, or to make sure that adequate per-cutaneous absorption. The most frequently used approach is to include the penetration enhancers in the formulation. In addition to penetration enhancers, there are studies available in which physical methods such as iontophoresis is used in improving the skin delivery of drugs. Topical preparation avoids the GI-irritation, avoids the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations act directly at the site of action. [1]

Topical gel preparation has remains one of the most popular and important pharmaceutical dosage forms. As a result, the therapeutics effects of the drugs are achieved effectively whereas the systemic side effects can be avoided or reduced. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. The release of the drug from topical preparations depends on the physicochemical of the vehicle and the drug employed. Examples: Drug commonly prepared in topical gel form includes gastrointestinal (GI), non-steroidal anti-inflammatory drugs (NSAID) and the antibacterial, antifungal, local anesthetic and antihistaminic agents. [2]

Drug delivery through skin has been a promising concept for a long time because skin is easy to approaches a large surface area with vast exposure to the circulatory and lymphatic networks and the route is non-invasive. Transdermal gel preparations are advised for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. Gels often provide a quick release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments. They are highly biocompatible with a lower risk of inflammation or adverse reactions, easily applied and do not need to be removed.[3] In this case, the active ingredient(s) stay on the skin surface or penetrate through the epidermal layers and may reach the dermis, but not absorbed into the blood circulation, this category is usually defined as topical drug delivery system. [4, 5]

Topical herbal gels are transparent or translucent semisolid dosage forms which consist of one or more herbs in defined quantities to produce specific therapeutic effect. These gels are applied to skin, rectus, vagina etc. In this modern century, herbal products are gaining huge popularity by leaps and bounds worldwide as synthetic drugs have constraint of adverse effects.

Topically applied dermal and transdermal delivery systems could replace needles required to administer many of the new biologics-based drugs and vaccines, in addition to other significant advantages such as avoiding first-pass hepatic metabolism, gastric degradation and frequent dosing. The topical drug delivery system is generally used where the others system of drug administration fails or it is mainly used in pain management, contraception, and urinary incontinence. Over the last decades the treatment of illness has been accomplished by administrating drugs to human body via. Various routes namely oral, sublingual, rectal, parental, topical, inhalation etc. [6]

The administration of a pharmaceutical dosage form to the skin for the treatment of a cutaneous condition or a cutaneous manifestation of a general disease with the purpose of confining the drug's pharmacological or other activity to the skin's surface is known as topical delivery. Chemicals entering into and through the skin are assumed to pass through the stratum corneum, which has long been thought to be the most critical barrier. The presence of stratum corneum on the surface, on the other hand, makes it selective towards previously delivered drugs or delivery methods. Humans have long been troubled by diseases and ailments of the body and mind.

On the other hand, dedicated research by scientists all over the world has made it possible to treat, prevent, and remove many of humanity's ailments. Pharmaceutical research has advanced steadily throughout time and it is now essential to keeping people well and preventing disease. The use of biomolecules such as medications, proteins and other bio- molecules to cure diseases has advanced dramatically in recent decades. They could only be employed in a limited way at first due to the limitations of drug delivery via. Hazardous circumstances in the body.

Some of the major benefits provided by topical drug delivery include improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to the maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. The primary advantage of adopting a topical administration method is that it bypasses first-pass metabolism. Another benefit of topical formulations is that

they avoid the risks and drawbacks of intravenous therapy, as well as the numerous conditions that affect absorption, such as pH variations, enzyme presence and gastric emptying time.

Topical distribution is dominated by semi-solid formulations in all its forms, but foams, sprays, medicated powders, solutions, and even medicated adhesive systems are also used. When other means of medication administration fail, the topical drug delivery system is used to treat pain, contraception, and urinary incontinence. In recent decades, drugs have been administered to the human body through a variety of channels, including oral, sublingual, rectal, parental, topical, inhalation, and others. Externally used topical and internally used topical for local activity are the two types of topical medicine delivery systems. It's self-evident that you can get through the skin barrier.

The topical drug delivery system is affected by physiological factors such as skin thickness, hydration, inflammation, and pH, lipid content, densities of hair follicles and sweat glands, blood flow, and physicochemical factors such as partition coefficient, molecular weight, and degree of ionization. The application of a drug-containing formulation to the skin to treat cutaneous disorders (e.g., acne) or cutaneous manifestations of a general disease (e.g., psoriasis) with the goal of limiting the drug's pharmacological or other effect to the skin's surface or within the skin is referred to as topical drug delivery. [7]

Topical action may or may not require intracutaneous injections. Pharmaceutical dosage forms utilized in topical drug delivery systems include semisolids, liquid preparations, sprays, and solid powders. The most commonly used semisolid formulations for topical medicine administration are gels, creams, and ointments. Topical therapies function by affecting the afflicted region directly. A gel is a cross-linked two-component, three-Dimensional network of structural elements. The structural ingredients that make up the gel network can be inorganic particles or organic macromolecules, such as polymers. [8]

Topical delivery includes two basic types of products, i.e., internal and external topical. Internal topical with local activity that are applied orally, vaginally or in the rectal tissues to the mucous membrane. External topical are sprayed, or otherwise spread on the cutaneous tissues to cover the affected area. Due of pharmaceutical penetration into the underlying tissue, topical therapies are most commonly used for localized effects at the application point. Although some medication may be absorbed inadvertently, it is normally in small amounts and has minimal impact. [9, 10]

Table No. 1: Different type of topical gel dosage forms

Topical Gel Products	Indications	Adverse Effects
Diclofenac sodium 1% gel	Acute Musculo-skeletal Pain	Ulcerative colitis, Crohn disease.
Methanol 5% Gel	Neuralgia	Hypertensive reaction
Sufentanil Gel	Chronic pain	Difficulties in breathing, tightness in chest, swelling of mouth, seizers.
Benzoyl peroxide gel 2.5%	Acne	Painful irritation of skin, including burning, blistering, itching, severe redness, swelling.

Table No. 2: Pathways of transdermal permeation

Types	Routes
Transdermal	Through the Subcutaneous (SC)
Intercellular	Through the skin barrier, SC, via. Cavities associated with hair.
Trans - appendages	Roots, sebaceous glands, small muscles and sweat gland.

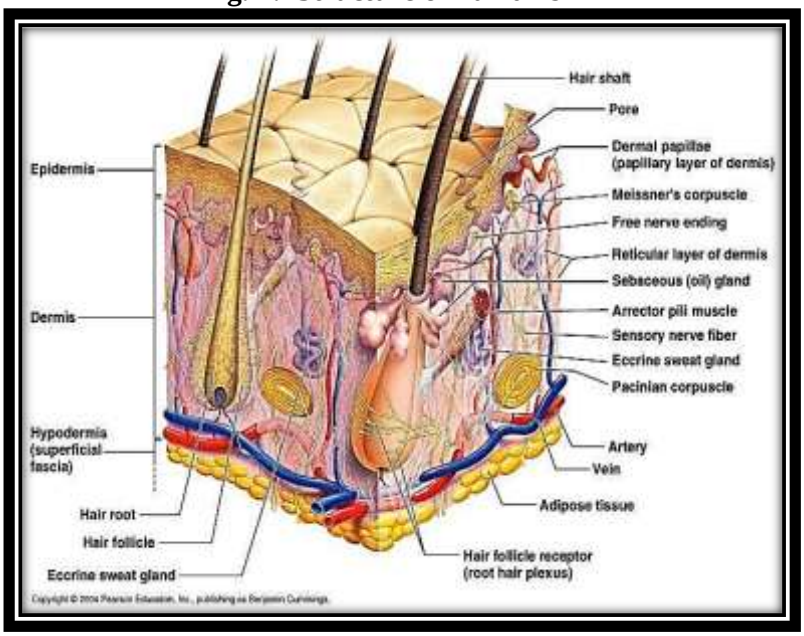
Gel as pharmaceutical dosage form

The term 'Gel' was introduced in the late 1800 to name some semisolid material according to their physiological characteristics rather than molecular composition. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels are a substantially dilute cross-linked system, which exhibits no flow when in the steady-state. They consist of a two component semi-solid system rich in liquid. Their one characteristic feature is the presence of continuous structure providing solid like properties. Gels have become a premier material used for drug delivery formulations due to its biocompatibility, network structure, and molecular stability of the incorporated bioactive agent. [11]

Anatomy and physiology of skin

Human skin is made up of three tissues: the stratified, vascular, cellular "epidermis," the underlying dermis of connective tissues, and the hypodermis. A microscopic section of the epidermis reveals the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinatevum. The human body has two systems that protect it from harmful organisms found in the environment. The internal defense system destroys microorganisms and germs that have already infiltrated the body. Microbial germs are kept out by the body's external defense mechanism. The skin is the largest external defense mechanism. Skin not only protects the outside of the body, but it also serves additional purposes. It serves as a mechanical barrier between the inner workings of the body and the outside environment. It depending on the environment, the skin temperature varies between 30°C and 40°C.

Fig. 1: Structure of human skin



Epidermis

The absence of blood vessels is the epidermis most distinguishing feature. The capillaries of the dermis give nutrients. The epidermis, or top layer of skin, is a stratified, squamous, keratinizing epithelium. The multilayer envelop of the epidermis varies in thickness, depending on cell size and then number of cell layers, ranging from about 0.8 mm on palm and soles down to 0.66 mm on eyelids. [12]

Cells that exist in the epidermis are

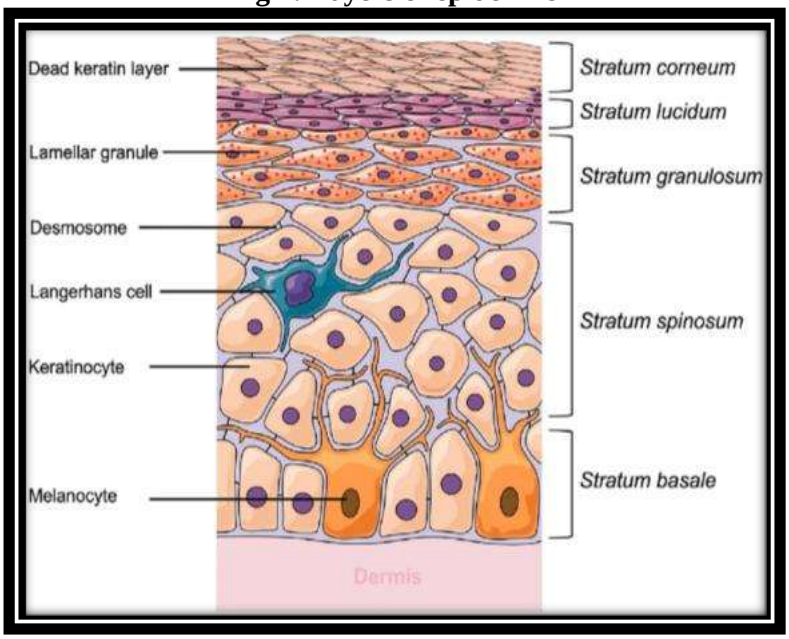
(a) Keratinocytes: These are responsible for the skin's barrier properties, account for more than 90% of the total.

(b) Melanocytes: These are the pigment artisan cells and found in the basal layer of epidermis.

(c) Langerhans cells: These are vital immunological cells and can be found in the mid dermis as well.

(d) Merkel cell: These cells are found in the elementary layer of epidermis and the one of amine outrider and decarboxylation system. [13]

Fig 2: Layers of epidermis



Epidermis composed of five layers these are -

(a) Stratum germinatum (Basal Layer): These are nucleated, columnar, 6micro wide connected by cytoplasmic intracellular bridges. They mechanically support and control the passage of the cells.

(b) Stratum spinosum (Prickle cell layer): The cell produced by the basal layer move outward. The polygonal cell called prickle cells because they interconnected by fine prickles.

(c) Stratum granulosum (Granular layer): These are granular layer of the epidermis. The keratinocytes approaches surface, manufacturing the basic staining particles.

(d) Stratum lucidum: The palm and soles are anatomically distinct, poorly staining hyaline zone forms a thin, translucent layer, this region known as stratum lucidum.

(e) Stratum corneum: Outermost layer of epidermis and it consist of 70% proteins, 15% lipids and only 15% water.

Dermis

The next layer of the dermis skin is a thick layer of fibrous and elastic tissue that gives it flexibility and strength. This layer is primarily composed of collagen, elastin, and fibrillin. The dermis contains nerve endings, an interfibrillar gel of glycosaminoglycan, salt water, lymphatic cells, sweat glands, oil glands, hair follicles, and blood vessels. The dermis is a vascularized collagen-rich connective tissue that contains mucopoly-saccharides (also known as the ground material). Blood vessel found in dermis provides nutrition's for both dermis and epidermis. Dermis also plays a major role in temperature regulations. Dermis has a thickness of 3-5 mm.[14]

Cell types found in dermis are

(a) Fibroblasts: collagen producing cells

(b) Macrophages: Scavenger cells

(c) Mast cells: Responsible for immunological reactions and interaction with eosinophils.

Hypodermis

The hypodermis is the deepest layer of the skin. It is the layer that connects the body's underlying tissues, such as muscles and bone, to the skin. Although they are coated in the epidermis, sweat glands, sebaceous glands, and hair follicles all have their origins in the dermis. On the skin's surface, sweat glands release a dilute salt solution. The skin is cooled by the evaporation of this mild salt solution, which is important for body and skin temperature regulation. Sweat glands are present all over the body. Hair follicles secrete sebum, an oily liquid that is then deposited on the skin's surface. Sebum is a water-resistant layer that keeps hair and skin from drying out.

Fig. 3: A Diagrammatic representation of cross section human skin showing Different cell layer & appendages

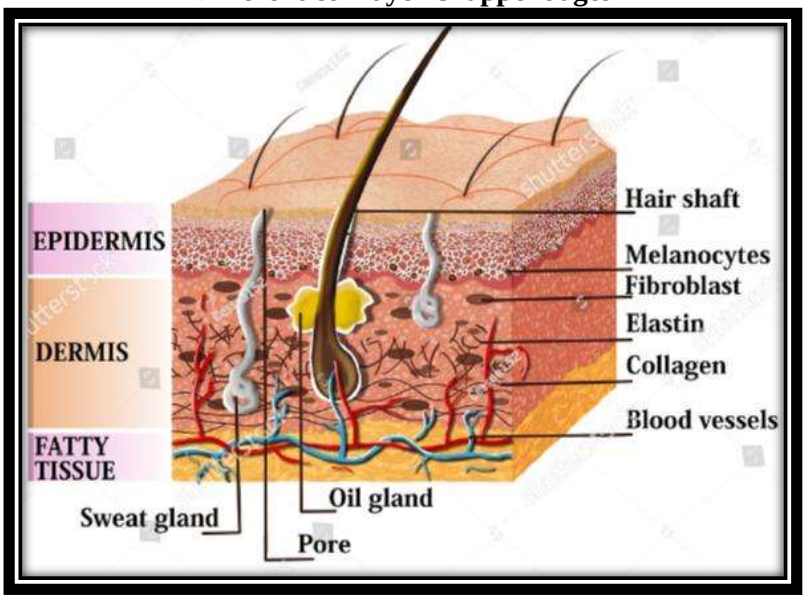
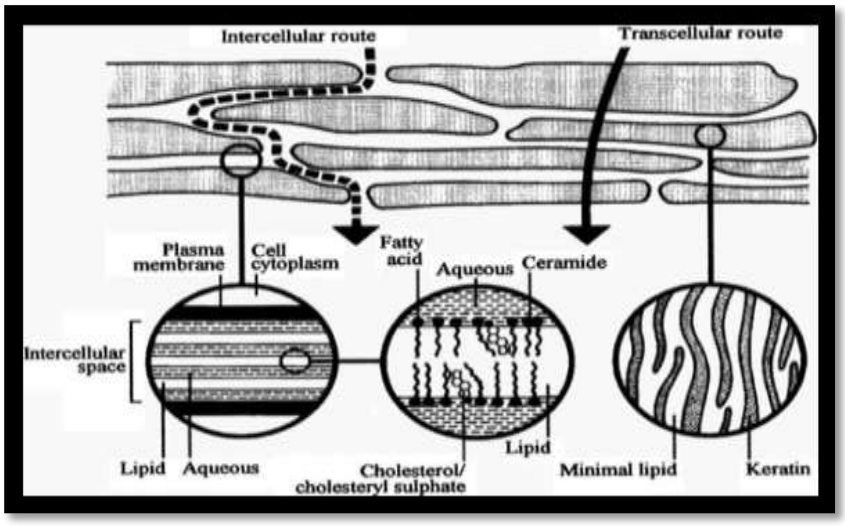


Fig. 4: Structure of stratum corneum and penetration pathways



Permeation enhancers [15]

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.

Table No. 3: Manufacturing of permeation enhancers

Sr. No.	Company	Enhancers
1	Oramed Pharmaceuticals	Protease inhibitors and omega 3 fatty acids
2	Nordic Bioscience	8- (N-2-hydroxybenzoyl)-amino – caprylicacid
3	Isis Pharmaceuticals	Fatty acids chains , salts, and derivatives
4	Unigene	Combination of protease inhibitors , permeation enhancers , pH modifier enteric coating
5	Soligenix	Lipid polymer Micelles
6	Archimedes Phgarma	Chitosan
7	Aegis Therapeutics	Alkyl glycosides
8	Generex	Lipids mixed micelle spray
9	Chiasma	Suspension of sodium caprylate in hydrophobic medium with matrix forming polymer.

Ideal Characteristics of Permeation Enhancers [15]

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.

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.

Classification of topical drug delivery system

1. **Solid preparation:** Topical Powders, Plasters Ointments, Poultices.
2. **Semi solid preparation:** Creams, Poultices, Gels, Pastes, Ointment.
3. **Liquid preparation:** Liniment, Lotions, Solution, Tinctures, Emulsions, Suspensions, Paints.
4. **Miscellaneous preparation:** Transdermal drug delivery systems, Tapes and Gauzes, Rubbing alcohols, Liquid cleanser, and Topical aerosol.

Factor affecting topical absorption of drug

Physiological and physicochemical considerations are taken into account for drug absorption in topical areas.

Physiological factors

1. Thickness of skin

2. Lipid content

3. Density of hair follicles

4. Density of sweat glands

5. PH of skin

6. Blood flow

7. Skin hydration

8. Inflammation of skin

Physicochemical factors [16]

1. Partition coefficient

2. Molecular weight (<400 Dalton)

3. Degree of ionization

4. Effect of vehicles

Factor to consider while choosing a topical preparation

1. Potential for enragement or sensitization in general, ointments and creams with water and oils are less irritating, whereas gels irritate. If you have an allergy to preservatives or emulsifiers, ointments are not for you.

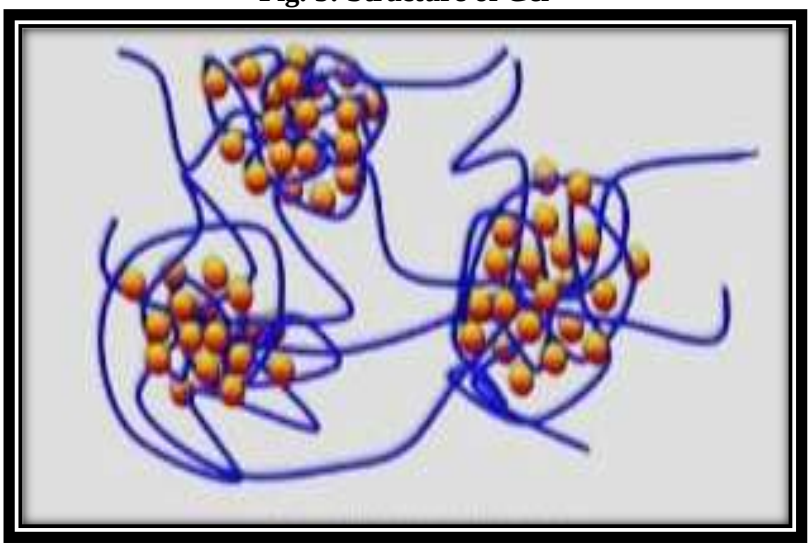
2. The type of preparation should correspond to the type of lesions.

3. Match the kind of preparation to the location. (For example, for hairy places, a gel or lotion)[17]

Structure of gel

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The type of the particles and the type of force that is responsible for the linkages, which tells about the structure of the network and the properties of gel. The single particles of hydrophilic colloid may consist of either spherical or an isometric aggregate of small molecules, or single macromolecules. The possible arrangements of such particles in a gel network. In linear macromolecules the network is composed of entangled molecules, the point of contact between which may be either relatively small or consist of several molecules aligned in a crystalline order. The force of attraction responsible for the linkage between gelling agent particles may range from strong primary valences, as in silicic acid gels, to delicate hydrogen bonds and Van Der Waals forces. The infirm nature of these latter forces is indicated by the fact that a slight increase in temperature often causes liquefaction of gel.[18]

Fig. 5: Structure of Gel



Properties of topical gel

1. Ideally, the gelling agent for pharmaceutical or cosmetic use should be inactive, secure, and should not react with other formulation components.

2. The gelling agent included in the preparation should produce a reasonable solid like nature during storage that can be easily broken when subjected to shear forces generated by squeezing the tube or during topical application.

3. The topical gel should not be tacky.

4. Drug highly acidic or alkaline.

Characteristic of gel

The gels should withhold the following characteristics

(a) The gelling agents used in formulations that should be inert, safe and should not interact with active ingredient and other excipients.

(b) The gels reserve appropriate anti-microbial activity towards microbial infections.

(c) Gelling agents are one of the ingredients for formulation of gels, when introduce shear forces to squeeze or for topical application it will generate solid like nature during shored condition that can be easily breakable.

(d) The topical gels should not be viscid.

(e) The gels administered for ophthalmic that should be sterile.

1) Ageing

Ageing colloidal systems traditionally produce slow vigorous aggregation. This phenomenon is known as ageing. In the formulation of gels, ageing emerges the continuous generation of denser network of gelling agents.

2) Syneresis

Numerous/Innumerable gels are with stand and emit, when they are frequently contract spontaneously with some fluid medium. This is referred as syneresis. The degree of syneresis increases as the concentration of gelling agent is decreases. The phenomenon of syneresis indicates that the original gel was thermodynamically unstable.

3) Swellings

Gelling agents when they subjected to liquid media by utilizing the adequate extent solvates, they swell or rice the volume. This activity is called as swellings and this approach is happened by getting solvents into matrix. Gelling agents are introduce shear forces to squeeze or for topical application it will generate solid like nature during shored condition that can be easily breakable. The gel-gel interactions are converted into gel – solvents interactions. The rate of swelling is directly proportional to number of linkages between individual molecules and strength of these linkages of gelling agents.

4) Rheology

The gelling agents as solution disperses s of flocculated solid as pseudo plastic that is possess Non-Newtonian behavior, characterized with decrease in viscosity and increase in share rate.

5) Structure

The rigid structures of gels emerge from the inertness of network generated by interlinking gelling agent particles. [19]

Classification of gel

(A) Based on source of gelling agents

a) Natural- These are gelling agents which are obtained from natural sources and employed for the preparation of gels. Ex: Starch, Pectin, Gelatin and Tragacanth etc.

b) Synthetic -These are obtained from synthetic sources. Ex: Methyl cellulose, (HPMC) and Carbomer.

(B) Based on nature of gelling agents

a) Organic- The gels with gelling agents which are organic in nature for ex-polyvinyl alcohols.

b) Inorganic- It includes gelling agents which are inorganic in nature such as Bentonite, Veegum (magnesium aluminium silicate).

(C) Based on solvents used

a) Organo gels - These gels are prepared by incorporating organic solvents as their continuous phase. Ex- Metallic stearate dispersion in oils and Olga aerosol gel.

b) Hydrogels -These are the gels which utilizes water as continuous liquid phase in preparation. Ex-Poloxamer gel, gelatin, Mennonite magma, cellulose derivatives.

c) Xero gels - These gels contain solvent in low concentration and are prepared by freeze drying or solvent evaporation. They can be subjected to reconstitution by swelling on addition of fresh fluid. Ex- Dry cellulose, Tragacanth ribbons and acacia.

(D) Based on number of phases

(a) Single phase

The twisted synthetic polymers with large organic molecules of the gel formers and which are generally bounded by Vander Waals forces or entangle with one another their random motion.

(b) Double phase

These upon standing are thixotropic forming semisolids and which upon agitation turns to liquid. Hence, named as double phased or two-phase system. It exhibits three dimensional structures all through the gel and is comprised of smaller particles in the gel structure and is not stable always.

Depending upon application gels are categorized as described below

(1) Lubricating gels

(2) Medicated gels

(3) Miscellaneous gels

(1) Lubricating gels

These are the gel preparations intended for lubrication of diagnostic equipment namely Cystoscopes, Rectal thermometers, surgical gloves, catheters and fingerstalls etc. It is mandatory to maintain sterility of these gels as they are also used for insertion into sterile region of body like urinary bladder etc. They are usually water soluble, thin and transparent.

(2) Medicated gels

These are primarily used on skin and mucus membrane due to its local anesthetic, antiseptic and spermicidal. For example, phenyl mercuric nitrate gel is employed as spermicidal contraceptive.

(3) Miscellaneous gels

These gels mainly serve the following purposes,

a. Patch testing: To detect sensitivity these gels as vehicles for allergens are usually applied on the skin.

b. Electro-cardiography: These gels are generally made up of sodium chloride, pumice powder and Glycerine and are primarily meant for application on the electrode in a way to diminish the electric resistance between electrode and patient's skin.

Gel forming substances [20]

Polymers are used to give the structural network, which is essential for the preparation of gels-gel forming polymers are classified as follows

1) Natural polymer

a) Proteins: Examples: Gelatin, collagen

b) Polysaccharides: Examples: Alginic acid, agar, tragacanth, pectin, xanthin, guar gum

2) Semi synthetic polymers

Cellulose derivatives: Examples: Hydroxy ethyl cellulose, methyl cellulose, carboxy methyl cellulose

3) Synthetic polymers

a) Carbomer: Examples: carbopol-941, carbopol-940

b) Poloxamer: Examples: poly vinyl alcohol, poly Acrylamide

4) Inorganic substances: Examples: Bentonite, aluminium hydroxide

5) Surfactants: Examples: Brij-96, cetostearyl alcohol [20]

Method of preparation of gel

Gels are normally in the industrial scale prepared under room temperature. However, few of polymers need special treatment before processing. Gels can be developed by following methods.

1) Thermal changes
2) Flocculation
3) Chemical reaction

1. Thermal change

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is decreasing, the degree of hydration is reduced and gelatin occurs (cooling of a concentrated hot solution will produce a gel).

Examples: Gelatin, agar sodium oleate, guar Gum and cellulose derivatives etc. In contrast to this, some materials like cellulose, ether have water solubility to hydrogen bonding with the water raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which cause gelation.

2. Flocculation

Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce gel state but insufficient to bring about complete precipitation. It is needed to ensure rapid mixing to avoid local high concentration of precipitant.

Examples: Solution of ethyl cellulose, polystyrene with benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The gels formed by flocculation method are thixotropic in behavior.

3. Chemical reaction

In this method, gel is produced by chemical interaction between the solute and solvent.

Examples: Aluminium hydroxide gel can be developed by interaction in aqueous solution of an aluminium salt and sodium carbonate, an increased concentration of reactants will produce a gel structure.

Evaluation parameter of formulated gel [21]

1) Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100ml distilled water and reserved for 2 hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

2) Drug content:

1gm of the prepared gel was mixed with 100ml of deserved solvent. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was measured.

3) Spreadability

It indicates the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficiency of a formulation also depends upon its spreading value. Spreadability is considered in terms of time in seconds taken by 2 slides to slip off from gel which is placed in between the slides under the direction of certain load. If the time taken for the separation of two slides is lesser, then spreadability will be better. It is calculated by using the formula.

S=M.L/T

M= weight tied to upper slide

L= length of glass slide

T= time taken to separate the slides

4) Viscosity study

The measurement of viscosity of the prepared gel was done with a brook field viscometer. The gels were rotated at 0.3, 0.6 and 1.5 rotations per minute. At separate speed, the coinciding dial reading was noted. The viscosity of the gel was calculated by multiplication of the dial reading with factor given in the brook field viscometer catalogues.

5) Extrudability study

The formulations were filled in the collapsible tubes after the gels were set in the container. The extrudability of the formulation was determined in terms of weight in grams required to expel a 0.5 cm ribbon of gel in 10 seconds.

6) Skin irritation study

Guinea pigs (400-500 gm. of weight) of either sex were used for testing of skin irritation. The animals were used for testing of skin irritation. The animals were retained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was rimed from back of guinea pigs and area of 4cm was mark done both the sides, one side served as control while other side was test. Gel was applied (500 mg/guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any, was graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema without or with edema, respectively.

7) Homogeneity

After the gels have been set in the container, all prepared gels were tested for homogeneity by visual inspection. They were examined for their appearance and presence of any aggregates.

8) Grittiness

All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence, obviously the gel preparations fulfill the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

9) Consistency

The quantification of consistency of the prepared gels was done by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the center of the glass cup filled with the gel. The stabbing by the cone was measured from the surface of the gel to the tip of the cone inside the gel. The extent travelled by cone was noted after 10sec.

10) In vitro diffusion studies

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane and the diffusion studies were carried out at 37±1° using 250ml of phosphate buffer (pH 7.4) as dissolution medium. 5ml of each sample was withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8hrs and each sample was replaced with equal volume of fresh dissolution medium. Then the samples were interpreted for the drug content by using phosphate buffer as blank.

11) Stability

The stability studies were carried out for all the gel formulation by freeze- thaw cycling. In this syneresis was observed by subjecting the product to a temperature of 4°C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates, separating is noted.

Emulgel

Emulgel is a combination of gel and emulsion where emulsion used can be both type w/o and o/w as a vehicle for purpose to deliver selected drug to the skin. Water phase containing the gelling agent converts a classic emulsion in emulgel. Dermatological use of emulgel has many favorable properties like easy spreadable, greaseless, being thixotropic, water-soluble, easy removal, longer shelf life, non-staining, and bio-friendly.

Nanoemulgel

Formation containing Nanoemulsion in gel base are called Nanoemulgel, is the addition of Nanoemulsion system intergraded into gel matrix which influences a better skin permeation. This mixture of Nanoemulgel acts as drug reservoirs, influencing the release of drug from inner phase to outer phase and further. Nanoemulgel on intact with skin release the oil droplets from the gel and this oil droplets penetrate into the sc of the skin and deliver the drug to intended site. Nanoemulsion-gel have a good adhesion property and high solubilizing of drug in oil phase leads to larger concentration gradient towards the skin that further increase skin penetration of drug. Also, patient compliance is improved due to increased spared ability compare to creams and ointments and decreased stickiness. [22]

Method of formulation

Formulation of Nanoemulsion-gel can be summarized in to following steps,

a) Screening of components

b) Preparation of Nanoemulsion

c) Preparation of Nanoemulgel

A) Screening of components

Drug Solubility was determined in different oils by excess addition of drug into different components followed by continuously stirred 72 hours to achieve equilibrium. After that determined by appropriate analytical methods. Then, excipients in each category with the highest solubility of drug are selected for further studies. [23]

Psedoternary Phase Diagram

Surfactant and co-surfactant (Nmix) were mixed in different ratios (2:1, 3:1 and 5:1). Each ratio chosen in increasing amount of surfactant respect to co surfactant for a study on the phase diagrams. Here aqueous phase (Distilled water) used as dilution media. Oil and Nmix was mixed at different ratios from 9:1 to 1:9 in different vials for each Nmix. Main objective for this is to cover for the study to decide boundaries of phases formed in the diagrams. It was developed using titration method with help of water as aqueous media. Slow titration of oil and Nmix is performed and visual observations are made for transparency of Nanoemulsion. The state of Nanoemulsion is marked on one axis of aqueous phase, the second one of oil and the third one of Nmix (surfactant and co-surfactant). [24]

B) Preparation of Nanoemulsion

The drug is then solubilized in oil and oil is addend in to mix, this mixture is diluted with water to form of Nanoemulsion of given drug.

C) Preparation of Nanoemulgel

Gel base is prepared using 1g of the Carbopol in a required quantity of water. After complete swelling and dispersion of Carbopol solution during 24 hours period, prepared Nanoemulsion is slowly added under continues stirring. By mixing socked Carbopol with prepared nanoemulsion and then sufficient aqueous phase is added. Addition of Triethanolamine gives homogeneous gel dispersion. Finally required remaining part is adjusted with distilled water.

Assessment of permeation enhancers

The changes like chemical and structural in epidermal layer are determined by using Differential Scanning Colorimetry (DSC). In order to assess mechanism of permeation, thermal transitions in desiccated sc membranes of rats is investigated by means of DSC. Both treated and untreated skin samples were previously hydrated on 27% Sodium-Br solution for at least 48h to ensure lowering hydration to 20%. The skin samples are stored over silica gel, for 3 day in desiccators before analysis. The skin sheets is cut into pieces and 4 mg weighted pieces is sealed in 10µL aluminium pans and kept in the differential scanning colorimetry unit along with empty pan as a reference. Flow of Nitrogen is adjusted to 20ml/min which is used as purge gas. Samples are heated continuously at 10°C/min rate for the range of 30-40°C and fluctuation in DSC Graph is noted and studied. [25]

Drugs can penetrate into the skin structure:

(a) Through thick stratum corneum (SC)

(b) Sebaceous follicle

(c) Sweat ducts of skin

Stratum corneum covers more than 99% of skin available from drugs to be absorbed. Passing through this is the rate limiting step for drug percutaneous absorption. Establishment of a concentration gradient thought to be major steps involved in percutaneous absorption, which provides force necessary for drug adsorption across the skin.

Pathway of Transdermal Permeation:

There are three ways in which permeation occurs. These are mentioned in the table below-

Approaches for penetration enhancers

There are mainly three approaches for the penetration enhancement. [26]

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 partition in the stratum corneum with help of co-enhancer.[27]

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. 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:

1. Alcohol

Alcohols can increase 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. [28, 29]

(a) 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 to increase intracellular drug diffusion. The drug flux is directly proportional to length of carbon chain (up to 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 cosolvent 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.

(b) 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.

2. Amides and Amines

Urea promotes drug penetration transdermally by promoting hydration of the SC (Stratum Corneum) and 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.

3. 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 hydrogels release profile through cellulose nitrate membrane was improved by complexing clonazepam with methyl-β-cyclodextrin. To increase their critical micellar concentration, Cyclodextrins get 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-Oethyl-β-cyclodextrin (CME-β-CD) complex were obtained. These were compared with hair free skinned 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.

4. Fatty acids

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.

5. Pyrrolidones

(a) N-methylpyrrilidone

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

(b) 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 a co-solvent of v/v of 1% NMP made in ethanol to tricaprylin (TCP) had no effect on permeation. Various enhancers which were made using 2-pyrrolidone. They at The 1 stand 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 in permeation of indomethacin through the SC. [30]

(c) Azone

Azone forms one of the major classes of surface permeation enhancers. The flux of methotrexate and piroxicam increased when PG was complexes 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. [31] 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.

6. Sulfoxides

Dimethyl sulfoxide

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 Dimethylacetamide (DMAC) and Dimethylformamide (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.

7. Surface active agents

(a) Cationic surfactant

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.

(b) 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.

(c) 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.

8. Terpenes

Terpenes and terpenoids are essential ingredients of essential oils. It is formed of repeating isoprene (C5H8) 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 approaches

I. Synthesis of bioconvertible prodrugs

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. 6-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 approaches

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 (Direct Current) 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. [32] 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 effect

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.

When these bubbles are disturbed and damaged then a shock wave releases which cause changes in the structure of the surrounding cells and tissues. [33] 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.

b) Convective transport

When porous medium exposed to ultrasound, interference occurs between the incidents and reflected US (ultrasounds) waves. Cavitation bubbles also undergo oscillations due to which different velocities are produced in the fluid. [34]

c) Thermal effect

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 effect

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.

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 Controlled Heat-aided Drug Delivery system (CHADD), which gives heat for a certain time at a certain intensity and oxidation reaction occurs within the heating unit.

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 micro-scissuining 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. [35]

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, paraffin's and other emulsions could be applied. Among these plastic films and oily substances are the most effective. [36]

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

(1) Microneedle arrays

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.

(2) 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 smallpores 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

(1) 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 degradingreleasing the drug which is maintained in the therapeutic level to carry out desired actions.

(2) 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.

(1) Cyclo-penta-deca-lactone

It is also referred to as penta-deca-lactone. It is a type of permeation enhancer marketed by Bentley Pharmaceuticals; Inc. CPEX pharmaceuticals are also promoting it under the name of CPE-215. Penta-deca-lactone is currently used in Testim (testosterone gel applied trans-dermally). It is made up of a gel formulation primarily containing ethanol with 8% penta- deca-lactone. 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.

(2) 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 cromolyn lipophilicity 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 B_{12} and calcitonin arecurrently 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.

(3) 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 having200 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 isknown to giving useful reductions in bone resorption biomarkers and cartilage degradation.

(4) 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 zoledronicacid (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 heparinachieved 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 inclinical phase 1 and phase 2 studies.

(5) Sodium Caprate

Isis pharmaceuticals used Sodium caprate as a bulking agent to increase the soaking of an antisense oligonucleotide ofmolecular 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 ISIS104838 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.

(6) Transient Permeability EnhancementSystems

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.

(7) 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.

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, "capsuling". It uses "Generally Recognized as Safe (GRAS)" fillers for the purpose of increasing absorption.

Advantages

Permeation enhancers provide us the following advantages:

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

Limitation

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 reaction.[37]

4. 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.

Lornoxicam (LRN)

Microparticles offer various significant advantages as drug delivery systems, including,

(i) An effective protection of the encapsulated active agent against (e.g. enzymatic) degradation.

(ii) The possibility to accurately control the release rate of the incorporated drug over periods of hours to months.

(iii) An easy administration, desired, pre-programmed drug release profiles can be provided which match the therapeutic need of the patients.

Lornoxicam (LRN) is a non-steroidal anti-inflammatory drug (NSAID). Its anti-inflammatory and analgesic activity is related to its inhibitory action on prostaglandin and thromboxane synthesis through the inhibition of both Cox-1 and Cox-2 .In order to overcome the formulation problems of LRN in addition to the barrier properties of the intact skin which limit the permeability of wide variety of pharmaceutical active agents, the development of a suitable vehicle system for optimum topical delivery of LRN is required. [38]

Valdecoxib

Topical gels of Valdecoxib topical gel prepared using different gelling agents (Viz, Carbopol, HPMC, sodium alginate, Sodium CMC). Formulations were evaluated for pH, rheological behavior, drug content and in vitro drug diffusion drug content was high (>98 %) in gels. Valdecoxib chemically, 4 (5-methyl-3-phenyl-isoxazole) benzene sulphonamide and is a dietary substituted isoxazole. It exhibits anti-inflammatory, analgesic and antipyretic properties. The mechanism of action is believed to be due to inhibiting prostaglandin synthesis primarily through inhibition of Cox-2. Valdecoxib when present in the form of topical gel can reduce local inflammations. In study, the efficiency, safety and tolerability of Valdecoxib gel (1%) in adult patients was evaluated. [39]

Advantages of topical delivery

a) The deactivation by digestive and liver enzyme.
b) They are non-invasive and have patient compliance.
c) They are less greasy and can be easily removed from the skin.

d) Cost effective.
e) Less dose as compare to oral dosage forms.
f) Local action with minimum side effects.
g) Avoidance of risks and inconveniences of intravenous drug delivery.
h) Easily abort the medications, when desired
i) Avoids fluctuation in drug plasma levels, inter and interpatient variations
j) Delivers drug more selectively to a specific site
k) Improving physiological and pharmacological response.

Therapeutic application of topical gel

1) To convey topical drug directly to the skin, mucous membrane or the eye.
2) As long-acting forms of drug injected intramuscularly.
3) As binders in granulation, protective colloids in suspensions, thickeners in oral liquid
4) Topical oral gels for dental use to control dental bleeding.
5) Enhancement of wound healing by topical Gels with epidermal growth factor.
6) In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations.
7) Gel products containing anti-inflammatory steroids are used to treat inflammations of scalp because this is an area of the body where creams and ointments are too greasy for patient acceptance.
8) Gels have better potential as a vehicle to administer drug topically in comparison to ointment, because they are non-sticky, requires low energy.

Conclusion

The current review reveals that topical medication administration is a relatively new approach. Researchers can easily access different medications into the skin using topical formulations. Topical drug delivery system is primarily utilized in skin injuries and arthritis. The main focus is to prepare absorption enhancement system which produce zero or no skin irritation. Their clinical application is limited by the fact that mostly this increased enhancement leads to toxicity. The topical formulation with addition of permeation enhancers 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. There is lots of scope in modern discovery and modelling techniques which aims to produce structures with minimal toxicity and optimal characteristics.

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