CHAPTER - 01

INTRODUCTION

1.1. The Structure and Functions of Skin 1
1.2. Drug Delivery in Dermatological Diseases 2
1.3. Use of Herb Since Antiquity To Date 4
1.4. Need for The study 5
1.5. Objective of the work 6
1.6. Gel as a Topical Delivery Systems 8
1.7. Ideal Physicochemical Parameter limits for Passive Transdermal Delivery 21
1.8. Basic Components of Topical Drug Delivery Systems 21
1.9. Penetration Enhancers 22
1.1. The Structure and Functions Of Skin

The skin has several layers. The overlying outer layer is called as epidermis. The different layers of epidermis are Stratum corneum, Stratum lucidium, Stratum granulosum, Stratum spinosum and Stratum germinativum. The layer below the epidermis is called as dermis. Beneath the dermis are subcutaneous fatty tissues.

![Figure 1: Structure of Skin](image-url)
The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Having lost their nuclei and cytoplasmic organelles, the corneocytes of the stratum corneum are nonviable. The cells are flattened and the fibrous keratins are aligned into disulfide cross-linked macrofibres in association with filaggrin, the major protein component of the keratohyalin granule. Each cell develops a cornified envelope resulting from cross-linking of involucrin and keratohyalin, forming an insoluble exoskeleton that acts as a rigid scaffold for the internal keratin filaments. The intercellular spaces are filled with hydrophobic lamellar lipids derived from membrane-coating granules. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. In skin disorders, the thickened epidermis may further diminish the penetration of pharmacological agents into the dermis.

1.2 Drug Delivery in Dermatological Diseases.
Molecules can penetrate the skin by three routes: through intact stratum corneum(a,c), through sweat ducts(b), or through the sebaceous follicle(d). The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Passage through this outermost layer is the rate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin. i.e, Release of drug from the vehicle.

Topical therapy often is employed for superficial infections caused by wounds and injuries. **Neomycin** is active against staphylococci and most gram-negative bacilli. It may cause allergic contact dermatitis, especially on disrupted skin. **Bacitracin** inhibits staphylococci, streptococci, and gram-positive bacilli. **Polymyxin B** is active against aerobic gram-negative bacilli. Bacitracin and polymyxin B are combined in a number of over-the-counter preparations. Mupirocin is highly active against staphylococci and all streptococci except those of group D. It is less active against gram-negative organisms, but it has *in vitro* activity against *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Pasteurella multocida*, *Moraxella catarrhalis*, and *Bor-detella pertussis*.

Deeper bacterial infections of the skin include folliculitis, erysipelas, cellulitis, and necrotizing fasciitis. Since *streptococcal* and *staphylococcal* species also are the most common causes of deep cutaneous infections, penicillins and cephalosporins are the systemic antibiotics used most frequently in their treatment.
Novel antibacterial agents such as linezolid, quinupristin-dalfopristin, and daptomycin have been approved for the treatment of complicated skin and skin-structure infections.

1.3.Use of Herb Since Antiquity To Date

The vast majority of people on this planet still rely on traditional Materia medica (medicinal plants and other materials) for their everyday health care needs. It is also a fact that one quarter of all medical prescriptions are formulations based on substances derived from plants or plant-derived synthetic analogs, and according to the WHO, 80% of the world’s population, primarily those of developing countries rely on plant-derived medicines for their health care. It is likely that the profound knowledge of herbal remedies in traditional cultures were developed through trial and error over many centuries. Ayurveda is, perhaps, the most ancient of all medicinal traditions and is probably older than the traditional Chinese medicine. It is considered to be the origin of systemized medicine. It is actually a set of practical and holistic set of guidelines to maintain balance and harmony in the system. Dioscorides (who influenced Hippocrates) is thought to have taken many of his ideas from India. Ancient Hindu writings on medicine contain no references to foreign medicines whereas Greek and Middle Eastern texts do refer to ideas and drugs of Indian origin. Ayurveda is derived from the Indian words Ayur (Life) and Veda (Knowledge or Science) and hence it means the Science of Life. In India, knowledge and wisdom have been passed on from one generation to the next through songs and poems, which scholars and physicians had to learn by heart and recite. The Veda is an ancient text in four parts (Rig Veda, Sama Veda, Yajur Veda and Artharva Veda), the earliest of which dates back to the year 2000 BC.
Modern allopathic medicine has its roots in ancient medicine and it is likely that many important new remedies will be discovered and commercialized in the future; as it has been till now, by following the leads provided by traditional knowledge and experiences. People who use traditional remedies may not understand the scientific rationale behind the use of their medicines, but they know from personal experience that some medicinal plants can be highly effective if used in appropriate therapeutic doses. Since we have, today, a better understanding of how the body functions, we are thus in a better position to understand the healing powers of plants and their potential as multifunctional chemical entities for treating different disease conditions. Medicinal plants typically contain mixtures of different chemical compounds that may act individually, additively or in synergy to improve health. Modern allopathic system of medicine usually aims to develop a patentable single compound or a magic bullet to treat specific conditions.

1.4. Need for the Study

Topical agents are widely used to treat skin conditions. The skin is readily accessible and topical agents can be applied at high concentration, achieving effective levels locally with little systemic toxicity. The high local levels of antibiotic that can be achieved with topical formulations can to help to kill bacteria in bacterial biofilms. The era of antimicrobial therapy is now in its eighth decade. The major scientific discoveries made during this period have saved countless lives and markedly reduced the morbidity due to infectious diseases. It is reported that, on an average, two or three antibiotics derived from microorganisms are launched each year. After a downturn in that pace in the recent years, the pace is again quickening as scientists realize that the effective life span of any antibiotic is limited. These
achievements are now threatened by the global emergence of resistant strains. Although microbial resistant rates are not equally distributed around the world, microbial resistance to antibiotics has become a worldwide medical, economical, and public health problem. The overuse, misuse, and widespread prophylactic application of antimicrobial drugs are some factors leading to the emergence of drug resistant microorganisms. Unlike antibiotics, antiseptics are potentially toxic, not only to microbial cells but also to host cells. Therefore, topical antiseptics should be used only where clinically indicated and for limited periods that too only under specialist guidance. As the development of bacterial resistance to antibiotics and controversy regarding the use of topical antiseptics persist, man turned to his prehistory and found literally thousands of phytochemicals from plants which inhibit different types of microorganisms and which are safe and broadly effective agents which do not induce microbial resistance. The antimicrobial compounds from plants may inhibit bacterial growth by different mechanisms than those presently used antimicrobials and may have a significant clinical value in the treatment of resistant microbial strains. New approach has been developed to isolate active components from botanicals and formulate them into suitable forms. This development of new drugs will adequately address the problem.

1.5. Objective of the work

In the present work primary objective was to formulate and evaluate a topical gel with a new herbal single compound having marked antimicrobial activity.

To achieve this primary objective a series of sub-objectives were charted out which are as follows.
The most commonly used plants against skin infecting pathogens were selected from Ayurvedic texts and publications relating to herbal medicine.

The quality of selected herbal crude drugs are to be evaluated and their antimicrobial activities are to be compared.

The potent antimicrobial compound from the selected plant are to be isolated.

The topical gels of isolated compound with suitable permeation enhancers are to be formulated and evaluated

The plan of work for formulation development is as follows

1. 12 different batches of Chrysophanol gels will be prepared by using carbopol as gelling agent. The effect of three levels of carbopol and three different permeation enhancers on Chrysophanol permeability will be determined.

2. Evaluation studies for the selection of best permeation enhancer for Chrysophanol will be carried out by studying the extent of enhancement of permeation by chemical penetration enhancers namely dimethyl formamide, dimethyl sulfoxide and propylene glycol.

3. For the formulation of topical gels, Carbopol-940 will be studied at three different concentrations of 1, 1.25, 1.5% w/w. In order to access the prime factor that determines the rate of enhancement, the study was designed in a systematic pattern similar to 3X3 Latin Square design so that data analysis using two way-Analysis of Variance can be performed.

4. Analysis of in vitro Kinetic data, which will be obtained by evaluating the formulations for their in vitro release behavior using treated cellophane membrane as semi permeable barrier to simulate the skin environment, will be done to stimulate the Kinetic Parameters such as Flux, Diffusivity, Exponential values of Peppas equation, Enhancement ratio etc.
5. Evaluation of physical characteristics of the topical gels will be done in order to ensure the acceptability of the formulations. Test for content uniformity, homogeneity and extrudability will be carried out.

6. *Ex vivo* permeation studies will be carried out to justify the selection of cellophane membrane and treatment methods used to simulate the *in vivo* skin conditions.

7. *In vivo* evaluation of the best *in vitro* formulation will be done to assess the non-irritancy of the formulations and their ant-microbial and wound healing efficiency when compared with a marketed formulation.

1.6. Gel as a Topical Delivery System.\textsuperscript{13-16}

The United States Pharmacopeia (USP) defines gels as semisolids, being either suspension of small inorganic particles or large organic molecules interpenetrated with liquid. 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 exist in solution as randomly coiled flexible chains. These molecules, either natural or synthetic polymers, tend to entangle with each other because of their random motion. Systems such as this are actually single phase in the macro-sense the organic molecule being dissolved in the continuous phase. However, the unique behavior of long molecules in solution, leading to fairly high viscosity and gel formation, makes it possible to consider such a system as two phase one on the micro level –the colloidal polymer molecule and the solvent. Gels find use as delivery systems for oral administration as gels proper or as capsule shells made from gelatine, for topical drugs applied directly to the skin, mucous membranes, or eye, and for long acting forms of drugs injected intramuscularly or implanted into the
body. The topical use of gels is well established in the cosmetic and personal care product markets. Interest in topical pharmaceutical uses has been revived by efforts to reduce systemic exposure to drugs through the use of local therapy. Several nonsteroidal anti-inflammatory drugs like felbinac, piroxicam, and ketoprofen have been incorporated into gels for topical therapy. These products, containing carbomer or poloxamer as the gel former, have been shown to provide adequate tissue levels at the site of application, avoiding common G.I. side effects after oral administration. Gels may also offer the potential for preparing a topical product when other dosage forms fail. Hydrocortisone-17-valerate is not stable in traditional emulsion or cream systems but was successfully incorporated into hydroxypropyl cellulose gels along with sulconazole nitrate for the treatment of fungal infections.

**Gels are classified mainly by two methods based on:**

a) ) **Based on nature of colloid phase**

   i) Inorganic gels

   ii) Organic gels

b) **Based on nature of solvent**

   i) Aqueous gels

   ii) Non aqueous gels

**Gel Forming Compounds**

A number of polymers are used to provide the structural network that is the essence of a gel system. These include natural gums, cellulose derivatives, and carbomers. Although most of these function in aqueous media, several polymers that can get nonpolar liquids are also available.
Natural polymers

Natural gums have been used in commerce since the beginning of recorded history. Typically, they are branched chain polysaccharides. Most are anionic (negatively charged in aqueous solution or dispersion), although a few, such as guar gum, are neutral Molecules. Differences in the proportion of the sugar building blocks that make up these molecules and their arrangement and molecular weight result in significant variations in gum properties. Because of their chemical makeup, natural gums support microbial growth and are subject to microbial degradation. Aqueous systems containing gums should contain a suitable preservative. As mentioned earlier, cationic antimicrobials are not generally compatible with the anionic gums and should usually be avoided. Although many of the most familiar gums are plant exudates or extracts, gums from other sources are also used. Many derivatives of natural materials, such as cellulose, starch, and alginate have been prepared. Several are very important commercially and are considered below.

1. Alginates

These are polysaccharides, containing varying proportions of \( p \)-mannuronic and \( L \)-guluronic acids derived from brown seaweed in the form of monovalent and divalent salts. Although other alginate salts are available commercially, sodium alginate is by far the most widely used. The National Formulary (NF) defines sodium alginate as “the purified carbohydrate product extracted from brown seaweed...” and goes on to say: “It consists chiefly of the sodium salt of alginic acid, a polyuronic acid composed of \( \beta-p \)-mannuronic acid residues linked so that the carboxyl group of each unit is free, while the aldehyde group is shielded by a glycosidic linkage”. Gelation occurs by reduction of pH or reaction with divalent cations. Reduction of
pH converts the carboxylate ions to free carboxyl groups. This reduces hydration of polymer segments as well as the repulsion between them. Generally, some calcium must be present; the small amounts contributed by the alginate may be sufficient. The pH at which gelation occurs is inversely related to the amount of calcium in solution. Alginates with low residual calcium begin to gel below a pH of 4. Gel strength is a function of alginate concentration; 0.5% is a practical minimum. Gel will also form at neutral pH in the presence of polyvalent ions. Calcium ions react preferentially with the polyguluronate segments to form cross-links that tie polymeric strands together into a three-dimensional network. Gel strength and such characteristics as brittleness and the tendency to undergo syneresis (Squeezing out of liquid from a gel) are a function of the chemical makeup of the alginate, which in turn, depends on its source.

2. Carrageenan

Carrageenan, the hydrocolloid extracted from red seaweed, is a variable mixture of sodium, potassium, ammonium, calcium, and magnesium sulfate esters of polymerized galactose, and 3,6-anhydrogalactose. All the carrageenans are anionic. Gels of kappa-carrageenan, which tend to be brittle, are strongest in the presence of potassium ion; gels of iota-carrageenan, which tend to be brittle, are strongest in the presence of potassium ion; iota-carrageenan gels are elastic and remain clear in the presence of calcium. Various commercial grades are available for particular applications, mainly in the food industry.
3. Tragacanth

Tragacanth is defined in the NF as the “dried gummy exudation from *Astragalus gummifer* L, or other Asiatic species of *Astragalus* (Fam. Leguminosae).” Tragacanth is a complex material composed of an acidic polysaccharide (Tragacanthic Acid) containing calcium, magnesium, and potassium, and a smaller amount of a neutral polysaccharide. Tragacanthin. The gum swells in water; concentration of 2% or above of a “high quality” gum produces a gel. Hydration takes place over a period of time, so that development of maximum gel strength requires several hours. The rheological properties of Tragacanth dispersions depend on the grade used as well as its treatment.

4. Pectin

Pectin, the polysaccharides extracted from the inner rind of citrus fruit or apple pomance, may be used in pharmaceutical jellies as well as in foods. The gel is formed at an acid pH in aqueous solutions containing calcium and possibly another agent that acts to dehydrate the gum. Gel formation is more extensive in pectins with a low methoxyl content. Such properties as gel strength depend on a host of factors, which include concentration of additives and pH, in addition to the characteristics of the raw material.

5. Xanthan Gum

Although xanthan gum is used most frequently as a stabilizer in suspensions and emulsions at concentrations below 0.5%, higher concentrations in aqueous media (1% and above) yield viscid solutions that are jellylike in nature. Xanthan gum is produced by bacterial fermentation and its availability and quality are not subject
to many of the uncertainties that affect other natural products, particularly those that are extracted from plants whose habitat falls within politically unsettled parts of the world. Thermally reversible gels result from combinations of xanthan with guar or locust bean gum.

Gellan Gum

Gellan gum is another polysaccharide produced by fermentation that has FDA clearance for use in foods. Partially acetylated gum forms gels that are thermally reversible with hysteresis. The gels based on material with a lower content are firmer, similar in consistency to gelatin or agar gels. Gel strength is a function of gum concentration and ionic content. The gum is highly efficient; as little as 0.5% is required for gel formation. Gels will not form in the absence of free cations. While both monovalent and divalent ions can induce gelation, the divalent ions are required in much lower concentrations, roughly 1/25 the concentration of monovalent ions.

Guar Gum

Guar Gum is a nonionic polysaccharide derived from seeds. Aqueous guar solutions can be cross-linked by several polyvalent cations to form gels. The mechanism is believed to involve chelate formation between groups in different polymer chains.

Chitosan

Chitosan is a natural biopolymer derived from the outer shell of crustaceans. Chitin is extracted and partially deacetylated to produce chitosan. Unlike most gums, chitosan carries a positive charge (at pH below 6.5) and is thus attracted to a variety of biological tissues and surfaces that are negatively charged. Various derivatives
are being explored for specific applications. Concentrated aqueous solutions have a gel-like consistency. Firmer gels result from interaction with polysaccharides, such as alginate.

B. Acrylic polymers

Carbomer P934 is the official name given to one member of a group of acrylic polymers cross-linked with a polyalkenyl ether. Manufactured under the trade name Caropol P934, it is used as a thickening agent in a variety of pharmaceutical and cosmetic products. The suffix “p” identifies a highly purified polymer, suitable for use in orally administered dosage forms, although carbomer P934 is also used widely in topical preparations. Carbomer forms gel at concentrations as low as 0.5%. In aqueous media, the polymer, which is marketed in the free acid form, is first uniformly dispersed. After entrapped air has been allowed to escape, the gel is produced by neutralization with a suitable base. The introduction of negative charges along the polymer chain causes it to uncoil and expand. In aqueous systems, a simple inorganic base such as sodium, ammonium or potassium hydroxide or a basic salt such as sodium carbonate may be employed. The pH should be adjusted to a neutral value; gel character will be adversely affected by either insufficient neutralization or excessively high pH. Certain amines, such as triethanolamine, are sometimes used in cosmetic products. By employing organic amines as neutralizing agents, it is possible to gel many semipolar liquids or mixtures of these liquids with water. Compatibility of the polymer with nonaqueous liquids depends on the formation of ion pairs with the amine. Polyols are capable of hydrogen bonding with the polymer, forming reversible links that augment viscosity. The viscosity of carbomer dispersion is lowered in the presence of ions; the addition of 1% sodium chloride causes more
than a 50% drop in Brookfield viscosity (20 rpm) of neutralised carbomer P941, 1%, at neutral pH. A hydrophobic derivative of polyacrylic acid has been developed as a polymeric emulsifier. This substance is highly efficient and is required in concentration below 1%. It can function alone or in combination with low levels of surfactant. Because of the polymer’s sensitivity to salts, emulsions based on this polymer break when applied to the skin, depositing an oil film onto the skin surface. The film does not re-emulsify when placed in contact with water and clings to the skin. Acrylic resins widely used in tablet coating also have the capability of producing gels with polar organic liquids, such as glycerin, propylene glycol, and low molecular weight polyethylene glycols. Gel systems containing various drugs have been suggested as a novel drug delivery systems for rectal administration. A copolymer of methacrylic acid and its methyl ester seemed to function effectively to deliver sustained blood levels of model drugs when unsaturated fatty acids were included in the formulation.

C. Cellulose Derivatives

Many useful derivatives are fashioned from cellulose, a natural structural polymer found in plants. Treatment in the presence of various active substances results in breakdown of the cellulose backbone as well as substitution of a portion of its hydroxyl moieties. The major factors affecting rheological properties of the resulting material are the nature of the substituent(s), degree of substitution, and average molecular weight of the resultant polymer. The cellulose derivatives are subject to enzymatic degradation and should be protected against contact with sources of cellulase. Sterilization of aqueous systems or addition of suitable
preservatives is used to prevent viscosity reduction resulting from depolymerization caused by enzyme production by microorganisms.

1. Carboxymethyl cellulose (CMC)

Carboxymethyl cellulose, also known as sodium carboxymethyl cellulose, CMC, and cellulose gum, is an anionic polymer available in a variety of grades that differ in molecular weight and the degree of substitution. Gelation requires addition of an electrolyte with a polyvalent cation to a solution of the polymer; aluminum salts are preferred. Gel characteristics, such as firmness and elasticity depend on polymer concentration and molecular weight. Sequestrants are useful in controlling the availability of free cations and preventing polymer precipitation, which can result if the reaction takes place too rapidly.

2. Methylcellulose and Ethylcellulose (MC&EC)

These are examples of a polymer whose solubility in water decreases as the temperature is raised. If an aqueous solution is heated, viscosity increases markedly at a certain point as the result of formation of gel structure. This property, known as thermal gelation, is a function of polymer chemistry and the presence of additives.

3. Other Cellulose Derivatives

Hydroxypropyl cellulose is soluble in water as well as many polar organic solvents, Consequently, it is useful as a gelling agent for such liquids and for many mixtures of water and various organic liquids, such as alcohol, that adversely affect the rheological properties of gums and certain other hydrophilic agents. High molecular grades of hydroxypropyl cellulose and hydroxyethyl cellulose can be used
in the formation of viscid, jelly like aqueous solutions. The solutions, though highly viscous, behave as fluids and do not exhibit a yield value.

D. Polyethylene

Various forms of polyethylene and its copolymers are used to gel hydrophobic liquids. The result is a soft, easily spreadable semisolid that forms a water resistant film on the skin surface. Polyethylene itself is a suitable gellant for simple aliphatic hydrocarbon liquids but may lack compatibility with many other oils found in personal care products. For these, copolymers with vinyl acetate and acrylic acid may be used, perhaps with the aid of a cosolvent. To form the gels, it is necessary to disperse the polymer in the oil at elevated temperature (above 80oC) and then shock cool to precipitate fine crystals that makeup the matrix.

E. Colloidally Dispersed Solids

Certain finely divided solids can function efficiently as thickening agents in various liquid media. Gel formation depends on establishment of a network in which colloidal particles of the solid are connected in an asymmetric fashion. This requires mutual attraction of the particles (flocculation) and partial wetting by the liquid.

1. Microcrystalline Silica

Microcrystalline silica can function as a gellant in a wide range of liquids. Network formation results from attraction of the particles by polar forces, principally hydrogen bonding. Silica with high surface area (small particle size) is most efficient in producing the “chicken-wire” structure to encapsulate liquid. Low concentrations are required in nonpolar liquids; in highly polar liquids competition of the medium
for hydrogen bonding sites weakens particle-particle interactions and thus much higher silica concentrations are required to produce a gel.

2. Clays

Montmorillonite clays are capable of swelling in water as the result of hydration of exchangeable cations and electrostatic repulsion between the negatively charged faces. At high concentrations in water, thixotropic gels form because the particles combine in a flocculated structure in which the face of one particle is attracted to the edge of another (house of cards). The gels are highly thixotropic, tending to liquefy on agitation. Because of the importance of electrostatic forces in flocculation, it is not surprising that rheological properties of clay dispersions are sensitive to salts. Reaction with certain organic molecules converts the clay particle surface to one that is more hydrophobic, making such derivatives compatible with organic liquids. The addition of the correct amount of a polar additive, such as an alcohol, assists in delaminating the clay platelets, thus augmenting the thickening effect. If the polar liquid content is low, there will be insufficient clay platelet separation; too high a concentration interferes with interparticle attraction.

3. Microcrystalline Cellulose (MCC)

Microcrystalline cellulose is another solid used as a stabilizer and thickener in aqueous systems. Several commercial products contain a hydrophilic polymer, such as sodium carboxy methylcellulose, to aid in dispersion of the colloidal particles and protect them from electrolytes. The characteristics of gels based on any of these solid particles depends on the method of preparation. High shear is usually required to break down the powdered raw material into primary particles and individual platelets in the case of the clays so as to produce the most extensively bonded network.
F. Surfactants

Clear gels can be produced by combinations of mineral oil, water and high concentrations (typically 20% to 40%) of certain nonionic surfactants. These combinations result in the formation of microemulsions, the semisolid rheology encountered is due to the existence of liquid crystalline phases. Gel characteristics can be varied by adjusting the proportion and concentration of the ingredients. Many commercial applications of this type of gel have been in hair-grooming products. Poloxamer 407 is a polyoxyethylene / polyoxy propylene block copolymer that functions as a surfactant. A 25% solution is liquid at refrigerator temperature, but is a gel at room temperature. Drug solutions can easily be prepared at temperatures below the gelation point. Drug release from gels of poloxamer 407 was inversely related to gellant concentration and lipophilicity within a group of related solutes.

G. Other Gellants

Various waxy materials are employed as gallants in nonpolar media, Examples are beeswax, carnauba wax, and cetyl esters wax. Aluminium stearate, a hydrophobic soap, has been employed as a bodying agent in oils for many years. These gelling agents are generally incorporated by fusion. High molecular weight poly(ethylene oxide) , cross-linked by high energy irradiation,can form hydrogels at concentrations of about 5%. Applications include use as culture media and treatment of burned skin.
Advantages of Gel as Topical Drug Delivery Systems.

In order to achieve optimal cutaneous and percutaneous delivery of drugs, topical administration has recently gained importance because this route of administration has the following advantages:

- Gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and interaction of the drugs with food and drinks are avoided.
- Substitute for oral administration of medication when that route is unsuitable.
- First pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption is avoided thereby avoiding the inactivation of drugs by digestive and liver enzymes.
- Non-invasive and hence results in better patient compliance.
- Less greasy and can be easily removed from the skin.
- Less expensive and hence cost effective.
- Dose can be altered without any cumbersome process.
- Localized effect with minimum side effects.

Disadvantages of Gel as Topical Drug Delivery Systems.

- Skin irritation of contact dermatitis may occur due to the drug and / or excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergic reactions.
- Can be used only for drugs which require very small plasma concentration for their action.
✓ Enzymes in epidermis may denature the drugs
✓ Drugs of larger particle size are not easily absorbed through the skin

1.7. Ideal Physicochemical Parameter limits for Passive Transdermal Delivery

Aqueous solubility >1mg/ml
Lipophilicity \(10 < \frac{K_o}{w} < 1000\)
Molecular weight < 500 Daltons
Melting point < 200
pH of saturated aqueous solution 5-9
Dose deliverable <10 mg/ day

1.8. Basic Components of Topical Drug Delivery Systems

Polymer matrix or matrices.
The drug
Permeation enhancers
Other excipients

The Polymer controls the release of the drug from the device. Possible useful polymers for topical gel systems were discussed earlier as gel forming substances. The drug should be chosen with great care for successfully developing a topical drug delivery system and it should have the desired physicochemical properties as discussed earlier.
1.9 Penetration Enhancer

Percutaneous absorption can be enhanced in two ways either by chemical penetration enhancer or by physical method.

Chemical Penetration Enhancer

General Principles

Although many chemicals have been evaluated as penetration enhancers in human or animal skins, none has been proven to be an ideal one. Some of the desirable properties for penetration enhancers acting within skin are:

- They should be non-toxic, non-irritating and nonallergenic.
- They should ideally work rapidly, and 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.
- They should work unidirectionally, i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
- When removed from the skin, barrier properties of the skin should be restored back, both rapidly and fully.
- They should be appropriate for formulation into diverse topical preparations. i.e they should be compatible with both the excipients and the drugs.
- They should be cosmetically acceptable with an appropriate skin ‘feel’.

Not surprisingly, no such material has yet been discovered that possesses all the above ideal properties although some chemicals demonstrate several of the above attributes. Penetration enhancers may be incorporated into formulations in order to
improve drug flux through skin. Diffusion through skin, controlled by the outer most layer, the stratum corneum, can be regarded as diffusion through a passive membrane. The steady state flux ($J$) of a drug through skin can be approximated by Fick’s second law of diffusion;

$$\frac{\delta C}{\delta t} = D \frac{\delta^2 C}{\delta x^2} \tag{1}$$

where $C$ is the concentration of the diffusing substance,

$x$ the space co-ordinate measured normal to the section,

$D$ the diffusion coefficient,

$t$ is the time.

With skin permeation studies, investigators often use an in vitro protocol with a membrane clamped between two compartments, one of which contains a drug formulation (the donor) and the other compartment holding a receptor solution which provides sink conditions (essentially zero concentration). With sufficient time, steady state diffusion across the membrane prevails. Under these conditions Eq. (1) may be simplified to;

$$\frac{dm}{dt} = \frac{(DC_0)}{h} \tag{2}$$

where $m$ is the cumulative mass of permeant that passes per unit area through the membrane in time $t$, $C_0$ is the concentration of diffusant in the first layer of the membrane at the skin surface contacting the source of the penetrant, and $h$ is the membrane thickness. In most experimental protocols it is difficult to measure $C_0$ but $C'_0$, the concentration of diffusant in the donor phase, which bathes the membrane, is usually known. $C_0$ and $C'_0$ are related by;
\[ C_0 = P \ C'_0 \]

where \( P \) is the partition coefficient of the diffusant between the membrane and bathing solution.

Substituting Eq. (3) into Eq. (2) gives:

\[ \frac{dm}{dt} = \frac{(D C'_0 P)}{h} \]

From Eq. (4), the classic equation used to analyse skin permeation data, it can be seen that the flux (\( \frac{dm}{dt} \)) is governed by the diffusion coefficient of the drug in the stratum corneum, the dissolved effective concentration of the drug in the vehicle, the partition coefficient between the formulation and the stratum corneum and the thickness of the membrane. 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 increase the effective concentration of the drug in the vehicle (for example acting as an cosolvent), could improve partitioning between the formulation and the stratum corneum (perhaps by altering the solvent nature of the skin membrane to improve partitioning into the tissue) or, less likely, by decreasing the skin thickness (perhaps by providing a permeation ‘shortcut’ as opposed to a tortuous pathway for a permeant).

**Chemical penetration enhancer** can be conveniently be classified under the following main heading:

**Solvents:** These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Examples include water, alcohols like methanol and ethanol; alkyl methyl sulfoxide, dimethyl sulfoxide, alkyl homologs of methyl
sulfoxide, dimethyl acetamide and dimethylformamide; pyrrolidones- 2 -pyrrolidone, N-methyl, 2- pyrrolidone; laurocapram (Azone), miscellaneous solvents like propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

**Surfactant:** These compounds enhance polar pathway transport, especially of hydrophilic drugs. The ability of the surfactant to alter penetration is a function of polar head group and the hydrocarbon chain length. The following surfactants are commonly used:

**Anionic surfactants:** These can penetrate and interact strongly with skin. Examples are Dioctyl sodium sulphosuccinate, Sodium lauryl sulphate, etc.

**Cationic surfactants:** Cationic surfactants are reportedly more irritating than anionic surfactants. They are not widely studied as skin permeation enhancers.

**Nonionic surfactants:** Nonionic surfactants have the least potential for irritation. Examples are Pluronic F127, Pluronic F68 etc.

**Miscellaneous chemicals:** These include urea, N,N-dimethyl-m-toluamide, calcium thioglycolate etc.