Chapter 5

An Overview of Transdermal Drug Delivery system
\section*{5.1 Introduction}

From several decades almost 16th century BC the concept of cosmetics is emerging with a purpose to act in a man kind ailment as well as a beautifying agent \cite{1}. The earlier recommended use of castor oil husk in headache till 17\textsuperscript{th} Era was modernize with a motive to enhance the percutaneous absorption \cite{2}. Dating back to late seventeen century transdermal drug delivery system (TDDS) comes into the picture for the replacement of oral drug delivery system (ODDS) \cite{3}. In contrary to that transdermal route lacks its potential where stratum corneum renders or decreases the absorption rate, as like in GI tract where ingested drug has to face the similar problem in absorption. As mentioned above stratum corneum regulates the drug absorption rate with in the skin and on another side it becomes the major obstacle for topically administered drug. From the anatomical view the stratum corneum constitutes non-viable flattened keratinized epidermal cell. Hygroscopic, water impermiablity, intercellular space packed with hydrophobic molecules and its keratinized nature makes the tissue more flexible and tougher. Sudden anatomical variation of stratum corneuem ranging from ten microns (in the skin) to 600 microns (on palms and soles) thickness gives the proper idea in selecting permeation enhancers in TDDS \cite{4}. Furthermore TDDS is a more acceptable tool to attain desired concentration in systemic circulation. From the earleir times the traditional peoples explored the
medicinal herbs in the form of topical agents such as ointments, gels, creams and medicinal lotions. By the sustained release and better therapeutic action nicotine patch brings an revolutionary change in TDDS. Currently this concept is well applied for the emphysema related disorders occurring due to the purging of lungs in the cigarette smoker’s. Another well acceptable example in TDDS is scopolamine patch which releases the alkaloid till three days and helpful in preventing motion sickness. Thus provide a comfort to the patient by avoiding the repeteadely oral intake of tablet. Fentanyl (for long-lasting analgesic effect) and estrogen–progestin contraceptive patch (to prevent pregnancy) are few more examples which reduce patient monitoring and produce desirable pharmacological effect {5}. These outstanding evidences facilitate the future development of drug in TDDS and circumvent the problems related with oral delivery.

5.2 Rationale for transdermal drug delivery

While designing an excellent module in transdermal administration several factors need consideration such as molecular absorption is always preferred over rapid bolus-type drug inputs {6}.

5.2.1 Advantages of transdermal drug delivery

Naturally the skin owned its mechanism to regulate the drug transmission in to the systemic circulation over a long period of time.
Thus the skin has its own physiological advantage which requires a further focus to overlook the designing of formulation in TDDS \cite{7}.

1) TDDS acts like an alternatives for the narrow therapeutic index drugs which provides constant concentrations in the plasma and hence minimise the risk of toxic effects which are usually associated with conventional oral dosing.

2) From the clinical perspectives, therapeutic effectiveness of the drug can be improved by TDDS through local application \cite{8}.

3) Additionally TDDS circumvent the problems related with the oral drug delivery which improves the poor bioavailability and results in the improved patient compliance \cite{9, 10}.

4) Drug characterization further requires focus on parameters such as molecular mass, potency, lipophilicity, solubility, melting point etc. to understand absorption through skin.

5.2.2 Innovations in transdermal drug delivery

Several related work has been done in this field with a purpose to motivate the futuristic development in TDDS \cite{13}. Some of the novel technologies recently introduced in TDDS are based on chemical penetration enhancement, iontophoresis, sonophoresis, transferosomes, thermal energy, magnetic energy, microneedle applications, electroporation and high velocity jet injectors \cite{14-19} which germinates certain advancements and modernization concepts.
in TDDS. These technologies offer great advantages over traditional methods. However owing to the skin tolerability and regulatory approval, the TDDS still demands a powerful research tool to focus on the product development.

5.3.1 Human skin

5.3.1.1 Structure and functions of skin

The skin is a large multilayered physiological organ that in the average adults weighs about eight pounds, excluding fat. It covers a surface exceeding 20,000 cm² and it is readily accessible organs for in-vitro evaluation. Moreover one-third part of blood circulates through the basement of the skin. Dermatologically skin is classified in to three tissue layers namely the epidermis, dermis and subcutaneous fat layer (hypodermis). Figure 5.1 represents the section of skin showing associated of hypodermis with hair follicles, sweat ducts, apocrine glands and nails \(\{20, 21\}\). The skin plays a paramount role in temperature, pressure and pain regulation.
Figure 5.1 Organization of human skin

5.3.1.2 The epidermis (viable and non-viable)

The upper epidermal layer comprises of four anatomical layers namely stratum basale, stratum spinosum, stratum granulosum and stratum germinativum. Stratum corneum is the rate limiting barrier that restricts the movement of chemicals. Structurally, the stratum corneum is a heterogeneous tissue exhibiting difference in thickness over the body. It is as thick as several hundred micrometers on the palms of hands and
soles of feet. It is about 10 um thick when dry, increasing up to 50 um on hydration. The texture of the non-viable cells embedded in the epidermis consists of 15 - 25 flattened, stacked, hexagonal and cornified cells immersed in lipid layer \(^{22}\).

5.3.1.3 The dermis

The soft tissues membranes anchored by specific immune cells and vascular network furnish elasticity to the epidermis as well as supplies all of its nutritional requirements. In contrary, surface membrane of dermis essentially consists of about 80% fibrous protein (collagen, elastin and reticulin) in a matrix of mucopolysaccharide which provides elasticity to the whole layers. As like said, from periphery the dermis composed of numerous blood vessels, lymphatic and nerves as well as epidermal appendages such as the hair follicles, sebaceous glands and sweat glands present beneath to it. Hair follicles are distributed over the entire skin surface with the exception of soles, palms and red portion of lips \(^{23}\).

Subcutaneous connective tissue

Usually this adipose layer does not play a major role in the percutaneous absorption. Anatomically, hypodermis consist of loose textured mass, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. However,
several reports explain the drug permeation rate in the circulatory system through the depot formation in the fatty tissue \cite{23}.

### 5.3 Mechanism of Percutaneous Absorption

Superficial experimentation is quite a easier or simple job although mechanistic studies requires special attention on the other side to regulates drug rate in systemic circulation. Several scientific-workers have deeply exploited the utilization and applicability of the mechanism and routes of penetration from which drugs and toxic compounds may penetrate in the skin, to diversify its exploration in pharmaceutical and cosmetic industry \cite{24, 25}.

i. Partitioning of drug into the stratum corneum, barrier membrane

ii. Diffusion and dissolution of drug through the SC,

iii. Partitioning from the SC into the aqueous viable epidermis,

vi. Uptake of drug into systemic circulation through the local capillary network \cite{26-28}.

An in depth anatomical and physiological knowledge of skin is essential in rational designing and development of a formulation for cosmeticeutical or pharmaceutical purposes \cite{29}.

#### 5.3.1.4 Routes of Transdermal drug permeation
For an efficient DDS a desirable therapeutic concentration should be attained in the blood circulation in sufficient quantities which is dependent on the physicochemical properties of the chemical. Additionally, partition coefficient plays a wide role in relative drug absorption through the biological membrane. Penetrants pass through different mechanism in TDDS (Figure 5.2) [30-32].

(i) Transport through appendages such as hair follicles  
(ii) Transcellular transport through the corneocytes  
(iii) Intercellular transport via the extracellular matrix.

*Figure 5.2 Route of drug penetration through stratum corneum*  
*I=intercellular T=transcellular A=appendageal*

Usually, the drug penetrates through the intercellular spaces in the skin.

5.3.1.6 Enhancing transdermal drug delivery
Here in TDDS enhancement usually correlation was made between rate of drug transmitted and its retention power in the blood. However, this evaluation requires high concentration of drug on the periphery \(\{33\}\). Conclusively, these findings made a relationship between time period and the dose values of the drug transmitted \(\{34\}\). For the further penetration improvement there is a sudden requirement of penetration enhancers to achieve the desired concentration of drug in blood by different mechanisms.

5.3.1.7 Physical approach

One of the most acknowledgeble areas is the hidden flux related mechanical characterization of biological membrane in molecular mechanichs. This focuse can be more enhanced by the recent topical agents that utilise mechanical energy to increase the drug flux across the skin by either altering the skin barrier or increasing the energy of the drug molecules. Biotechnological investigation gives an idea about the morphological view and its associated structures. Now this may help in understanding the physiological membrane depending characterization of novel peptides proteins and oligonucleotides based molecule. This characterization transforms certain structure related changes in the molecule which not only improve the potential, polarity and specificity nevertheless opens a gate for the new therapy.

5.3.1.8 Chemical approach
I. Ceratan chemical copounds form the entire class of penetration enhancers also known as accelerants or sorption promoters. Reversible regulation of barrier and constant release of drug in the blood promotes the drug flux by interacting with skin constituents \cite{35, 36}.

Usually these characteristics were not found in the single system and thus it requires prior toxicity management to help in predicting toxicity risk calculations.

5.3.1.9 Criteria for selection of drug for transdermal drug delivery system

A pharmaceutical industry plays a major role in identification of molecules with the purpose to certify their approved classification. In the drug development optimal biological activity of the molecule can be assessed by biological assay. Moreover selection of pharmacophore is rather easy for product development but in practice sophisticated properties of molecules renders its development. Nevertheless a rational and therapeutic approach is required to formulate the molecules in proper way. Drug molecules were handled in such a way so that they can easily interacts with receptors without changing their shape. Additionally dermatological therapy is another tool to select leading compounds of pharmaceutical significance \cite{37}.

5.4 Biological properties of the drug
5.4.1 Potency

Topically skin control the amount and rate of transmission and maintains the drug inputs in blood for specific period of time. The most rapidly transmitted drugs exert certain fluctuations in blood-plasma conc leading to altered therapeutic activity. This can be resolved by working on few parameters such as thickness of membrane, particle size and lipophilicity.

5.4.2 Half-life

While approaching towards sustained and controlled drug delivery the long life of drug should be preferred.

5.4.3 Toxicity

Few studies require more attention from the view of toxicity and hypersensitivity to produce a lead compound which is devoid of former mentioned effects.

5.5 Physical properties

5.5.1 Partition co-efficient of drug

Usually Lipophillic linkages increase the drug permeation when they linked with parent molecule. The intacellular spces present in the biological membrane regulates the permeation rate of the drug
transmitted through the physiological barriers. Additionally, they will not interfere in the natural immunological reactions usually occurred in the body system. Skin membrane form lipidal barrier that separates the body interior to the exterior environment. Therefore, diffusion of lipophillic compounds is more easily than hydrophilic compounds. Earlier reports show that the drugs having log p value between 1 to 3 has maximum permeation rate in the stratum corneum \( \{38\} \).

5.5.2 Diffusivity of drug molecule

Diffusivity of a drug depends on its chemical structure, which is mainly due to interactions between the polar head groups of the intercellular lipids with polar functional groups present in the chemical moiety (drug structure). According to general principle, not more than two hydrogen bonding group should be present in the drug. Small molecules with good water as well as lipid solubility are better candidates for percutaneous absorption. These drugs also possess melting point, (typically less than 200°C) as the energy required for the molecules to leave crystal lattice are are less \( \{5\} \). In order to predict the permeability of hydrophobic drugs, many mathematical models have been discussed. An equation of correlation was established between physicochemical properties (molecular mass, partition co-efficient) and skin permeability of a drug in aqueous solution with of solute \( \{39\} \).

5.5.3 Polar nature of drug candidates
Based on hydrophilicity, polar and non-polar substances diffuse through skin by different mechanisms. Usually more polar drugs follow intercellular pathways, whereas the non-polar drugs may permeate through the lipid matrix present in the skin. Since many newly synthesized permeants are weak acids or weak bases, their permeation depend on the degree of ionization, pH partition coefficient and their influence on the solubility in the applied phase and thereby its partition into the skin. One of the problems involved in understanding permeation data of ionised compounds is that the species that permeate through skin, are not single ionized species but a composite of free acid (or base) of the ionised material and ion pairs that can exist along with the counter ions present either in the formulation or in the skin, which adds to the complexity and requires extra care in interpretation of data obtained through permeation studies [40].

5.6 PRINCIPLES INVOLVED IN DIFFUSION OF DRUG

Kinetics of percutaneous absorption has been described with the help of various methods. Mostly these models utilize either diffusion-based or compartmental equations. The later model involves a number of parameters which are found to be complex and therefore make practically impossible [41]. However, a sharp knowledge of above mathematical principles of membrane transport is essential to expand
our understanding of permeability of these membrane barriers and for effective alteration of their permeation properties to our advantage. Theoretical description of heat transfer, conductance and the basic of the diffusion equations germinates new principle of transmembrane diffusion of drugs i.e Fick’s first law according to earlier reports \cite{42}.

### 5.6.1 Fickian model

#### 5.6.1.1 Fick’s first law of diffusion

This is based on the fundamental principle of irreversible thermodynamics, which states that the flow, at any point in the system, at any instant, is proportional to the appropriate potential gradient.

In the transport of drugs through skin, the flow (or flux, \(J_i\) in mol cm\(^{-2}\) s\(^{-1}\)) is directly proportional to the concentration (\(C_i\) in mol cm\(^{-3}\)) of the molecules in motion and the velocity of molecular movement (\(v\) in cm s\(^{-1}\)) as shown in equation 1.

\[
J_i = C_i \times v
\]  
\[(1)\]

#### 5.6.1.2 Fick’s second law of diffusion

This law relates the rate of change in concentration with time at a given point in a system to the rate of change in concentration gradient at that point. The Fick’s law of diffusion, states that the flux \(J\), at steady state.

\[
dQ/dt = J = DC_0/h
\]  
\[(2)\]
It is often impractical to use the forms of equation shown (2) because it is extremely difficult to measure a term $C_0$ (the concentration of permeant in the outer layer of the membrane) which is involved in this equation. Concentration in the vehicle $C_V$ can be replaced through the introduction of value of partition co-efficient $K$, which upon rearrangement yield an equation

$$DQ/dt = J = DKC_V/h \quad \{3\}$$

The diffusant concentration in the membrane lamina can be obtained from the product of the partition co-efficient and the donor vehicle concentration. Therefore Diffusibility, Concentration in the vehicle and thickness of barrier layer ie diffusional pathlength are the main variables which influence the rate of diffusion. Although, there is a practical difficulty in measuring the diffusional pathlength, particularly in biological membranes and the information regarding the individual effects of changes in $K$ and $D$ is often not required, and composite parameter is usually used to replace these values in equation. The permeability co-efficient $P$, is thus defined as $P = KDh$,

and

$$J = PC_V \quad \{4\}$$

This equation comes upon simplification of above equation.

Probably in the routine estimation of membrane permeability, basic equation \{4\} can be used more frequently. However, this equation is based on the principles that the the diffusion has reached stagnant
concentration when donor concentration is constant (as \( C_v \) is much greater than \( C \)) \cite{43}.

5.7 METHODS FOR STUDYING PERCUTANEOUS ABSORPTION

The demand for data describing the rate, degree and route of penetration of compounds across human skin is increasing day by day. For maximum therapeutic efficacy, optimised delivery of dermatological drugs into various skin strata is always required. Second, beyond the traditional methods of drug delivery, the transdermal and topical routes have become popular alternatives. The toxicological and risk assessment implications of the everyday use of a wide range of potentially harmful materials in the agrochemical, chemical, cosmetic, household and pharmaceutical sectors has also stimulated the demand for such data. In new drug product, the safety and efficacy are demonstrated as a key aspect of controlled clinical trials. Nevertheless, routine quality control tools can not utilize such the time and expense associated trials which are used to study changes in formulation or method of manufacture \cite{44, 45}.

5.7.1 Design of Diffusion cell

In order to study diffusion of active ingredients from semisolids, numerous designs of apparatus have appeared in the literature, which vary mainly in their geometry \cite{46, 47}. Generally, diffusion cell consist
of a receptor cell or compartment which contain the chosen receptor medium and a side tube from which samples are withdrawn at regular time intervals and a donor cell or compartment, containing the formulation. A membrane may or may not be included in the system for separation of the two phases and means of stirring and/or controlling the temperature of the receptor medium may be provided \cite{48}. Inert, non-reactive materials (such as glass, stainless steel, Teflon) should be used for fabrication of \textit{in vitro} diffusion cells. Prerequisition for the success of the experimentation is inertness (lack of absorption) to all components of the cell, including flow-through lines and the collection chambers themselves. During the permeation experimentation, care must be taken to ensure that no loss of drug through its volatility has taken place. A quantitative adjustment in calculations must be made, if such problems like volatility arise with the drug. The receptor medium should provide an effective sink for the permeating drug for steady state diffusion. Ideally, the volume of receptor medium should be kept as less as possible to facilitate analysis because, in general it is easier to assay the amount of drug with more accuracy and precision if the drug in the collection medium is more concentrated. The cell design should allow a well stirred receptor fluid to ensure uniform concentration and temperature in order to minimize sampling errors. \textit{In vitro} systems vary in complexity from being a simple two-compartment static diffusion cell to complex
multijacketed flow-through cells, often attached with autoanalyzers \cite{49}. Different geometrical modifications of the various systems are described in earlier studies \cite{50-55}. Two types of diffusion cells design have been shown to possess the highest prospective for use as standardised, compendial methods. These are Franz and modified Franz (Vertical diffusion cells for measurement of percutaneous absorption) which require the use of a membrane when measuring drug release. On other hand immersion cells may be used with or without a membrane with the standard USP dissolution apparatus \textit{(i.e., the European Pharmacopoeia diffusion cell)} \cite{56-60}.

\textbf{5.7.2 Franz and modified Franz diffusion cell}

A number of workers had used vertical Franz-type cells for the studies involving \textit{in vitro} release from semisolid dosage forms \cite{61}. Franz described finite dose techniques and the design of a static one-chambered diffusion cell \cite{62-63}. In further studies, after identification of shortcomings in the original Franz diffusion cells, a new and modified design was proposed with improved solution hydrodynamics, mixing efficiency and effective temperature control \cite{64}. These modified diffusion cell was executed in this study. The modified Franz diffusion cell consists of a jacketed glass chamber, 12.5 ml in volume (modified cells exist with slightly different receptor volumes) which act as receptor in which a glass sampling port is provided. The membrane is
placed horizontally over the receptor chamber, and a cell cap is attached over that, and the components are held together with the help of a metal clamp. The formulation under test can then be applied to the surface of the membrane at the top of the cell cap, which act as donor compartment and is open to the atmosphere unless sealed by the user. Pefile et al. (65) in a study in his laboratory reported that the inability to control the evaporation of the volatile components from the formulation result into erratic drug release from the unoccluded bases with significant variability in drug release rates. Therefore, he advised to seal the top of the cell cap during the diffusion studies. At the bottom of the receptor chamber, a micro-magnetic stirrer is usually placed to avoid sampling errors.
A water jacket that surrounds the receptor compartment is used to control the temperature in the bulk of the receptor medium by circulating water (controlled temperature). A multiple-cell drive unit contain entire cell which is positioned in the magnetic stirrer to agitate the receptor medium at a controlled rate, usually 100 rpm [66].

5.8 Dermatological Formulations

Topical formulations are widely prescribed in various diseases and ailments and are frequently compounded. Many pharmacists, who otherwise seldom do compounding works, are often asked to prepare ointments and creams. Generally, this may consist of something as
basic as the addition of an active ingredient to a topical vehicle like white petrolatum. However, many dermatological products are much more complex, requiring at the same time the experience and skill and diverse requests of the physician along with the disorders experienced by the patient and the compounding ability and facilities available with the pharmacist \(^\text{[67]}\). Before century, there have been noteworthy progress in the understanding of the physicochemical properties of both ingredients and their formulation. These have led to the ability to develop physically, chemically and biologically more stable products with improved efficacy. There has also been a significant advancement in our understanding of the properties of the skin and the factors that control permeation of drugs through skin. Now, it has been well established that the percutaneous absorption of drugs through intact skin is controlled fundamentally by the Stratum Corneum. The chemical composition, physiology and morphology of this layer usually determine the rate and extent of absorption. There are numerous reports available now which suggest methods and approaches to modify this barrier by chemical or physical means and thereby alter the rate of diffusion of many permeating substances. However, this knowledge has largely been generated by investigations on normal skin, rather than pathological skin and is a basic deficiency in the application of our understanding of the barrier properties of the skin to dermatological and transdermal therapy. The relevance of such
information obtained from investigations on normal skin to diseased skin, for which permeation characteristics are probably significantly altered, has yet to be established. Recently, therapeutic moieties in suitable formulations are applied to the skin for dermatological (within the skin), local (regional) and for transdermal (systemic) delivery. However, for success of therapy, it is usually a prerequisite that the drug crosses the outermost layer of the skin irrespective of the target site or organ. The selection of formulation type for such dermatological products is usually influenced by the pathophysiology of skin and the opinion of the Pathologist or Microbiologist. Usually, a practicing dermatologist prefers to apply a wet formulation (ranging from simple tap-water to complex emulsion formulations with or without drug) to a wet lesion and a dry formulation (e.g., petrolatum) to a dry lesion. Solutions and powders have low retention time and lack adhering power on the skin and can provide only momentary relief. In modern-day pharmaceutical practice, semisolid formulations are the preferred vehicles for dermatological therapy because they remain \textit{in situ} and deliver the drug over extended time periods. The term vehicle implies a demarcation between active and inactive ingredient, whereby the active ingredient is embedded into a medium, the vehicle. The desired effect is achieved with the aid of the vehicle that delivers the active principle to the application site or target organ \cite{68}. Developed
formulation will be an ointment, emulsion, gel or cream which are found in most cases {69}.

5.9 Classification of Topical formulation

5.9.2 Gels

Gels are used for a variety of applications in the administration of medications and can be used orally, topically, intranasally, vaginally and rectally. Gels vary in their appearance being transparent whereas and others are translucent, since the ingredients involved may be in the form of ionic or molecular dispersion or they may be formulated as coarse dispersion. Suspensions of small inorganic particles or large organic molecules in semisolid gel are interpenetrated by suitable vehicle {70}. The common characteristic of all gels is that they contain continuous structures that possess viscoelastic properties. Where the
gel is classified as a two-phase system in which mass consists of a network of small, discrete particles is one system and other is vehicle in which the particles are dispersed in a suitable ratio. In these two-phase systems, magma is referred for the dispersed phase containing large particle size. Single phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent interfaces exist between the dispersed macromolecules and the vehicle. Single-phase gels may be formulated using synthetic macromolecules (polymers) or by using natural gums (mucilage). Generally, water is used as continuous phase in gels, but alcohol or oleaginous can also be used. A number of properties like imbibition, swelling, syneresis and thixotropy and viscoelasticity exhibit in a gel \cite{71}. There are a variety of semi-synthetic cellulose derivative which is used in gel formulations as thickeners or vehicle itself. These include methylcellulose, carboxymethylcellulose, and hydroxyethyl cellulose and hydroxypropyl cellulose and hydroxypropyl methylcellulose etc. Naturally occurring plant origin branched-chain polysaccharide gums are tragacanth, pectin, carrageenan and agar, which possess widely varying physicochemical properties, depending on their source and their processing. However, the most extensively employed gelling agents in the pharmaceutical and cosmetic industries are the carboxyvinyl polymers known as carbomers. Carbomers or carbopol are widely used gelling agents and they are preferred due their
availability in purest form with varying viscosity and hydrophilicity
grades, compatibility with wide variety of therapeutic moieties and
ability to withstand diverse processing conditions and most important
of all the stability of formulation.

*Table 5.1 Classification of gel*

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Example</th>
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<tbody>
<tr>
<td>Class I</td>
<td>(Nature of colloid phase)</td>
<td>Inorganic Usually two phase systems</td>
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<tr>
<td></td>
<td></td>
<td>Organic Usually single phase systems</td>
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<tr>
<td>Class II</td>
<td>(Nature of solvent)</td>
<td>Hydrogels Contains water, natural and synthetic gums</td>
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<td></td>
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<td>Organogels Inorganic gels Hydrocarbon type</td>
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**5.10 Factor affecting percutaneous absorption of Topical gel**

There are numerous factors which affect permeability of drugs through skin, which are as follows:
1. Structure of skin
2. Hydration
3. Temperature
4. Anatomic location
5. Age
6. Disease and pathophysiology of skin
7. Ethnicity
8. Region of body

5.11 Formulation of Gel

5.11.1 EXCIPIENTS

5.11.1. Gelling agents

Carbopol polymers and co-polymers are the in-house gelling agents used in the extemporaneous manufacture of gels. USP-NF assign a new a new generic (i.e., non-proprietary) name for various Carbopol® polymers is carbomer. Acrylic acid cross-linked with either allylsucrose or allylethers of pentaerythritol are found in high molecular weight polymers synthetic Carbopol polymers whereas Carbopol co-polymers are synthetic high molecular weight polymers of acrylic acid with small amounts of long chain alkyl acrylate co-monomers crosslinked with allylpentaerythritol. Same acrylic acid structural backbone is found in all these polymers [72]. Furthermore on the basis of calculation of dry mass, these polymers contain between 56.0 - 68.0% of carboxylic acid...
(COOH) groups, they are white, mildly acidic, fluffy, flocculated powders with particle size varying from 2 to 7 microns in diameter. A network structure of primary particle of linear polymer chains is interconnected by cross-links. These linear polymeric networks are soluble in a polar solvent, such as water. Carbopol polymers, along with polymeric emulsifiers Pemulen are usually cross-linked and swell in water up to 1000 times their original volume (and ten times their original diameter) to form a gel when exposed to a pH environment maintained at pH 4.0 to 6.0.

5.11.2 Triethanolamine

Primarily in various topical pharmaceutical formulations, Triethanolamine (triethylolamine, trihydroxytriethylamine or tris (hydroxyethyl) amine) is widely used in the formation of emulsions. This viscous liquid is clear, colourless to pale yellow-coloured with a slight ammoniacal odour. In our study triethanolamine was used as a weak neutralizing agent to commence the gelling process by converting the free acidic hydrogens into amine salts. It should be stored in an airtight container, protected from light, in a cool, dry, place otherwise it may turn brown on exposure to air and light (75).

5.11.3 Propylene glycol
In a pharmaceutical formulations (variety of parenteral and non-parenteral formulations), Propylene glycol, chemically known as 1, 2-propanediol, is widely used as a solvent extractant and preservative. Like glycerin, it is a clear, colourless, viscous, practically odourless liquid with a sweet acrid taste. Propylene glycol has wide variety of application as an antimicrobial agent, preservative, disinfectant, humectant, plasticizer and a water-miscible co-solvent. Ethanol 95% v/v or water increase chemical stability of Propylene glycol when mixed. Due to its hygroscopic nature, it should be stored in an airtight container, protected from light, in a cool and dry place (76). Propylene glycol was mainly employed as a water-miscible co-solvent and a chemical penetration enhancer to aid in the dissolution of drug during the manufacture in various research works.

5.11.4 Ethanol

Ethanol commonly known as alcohol or ethyl alcohol are used as a solvent which is a colourless, clear, volatile, flammable liquid and employed in the manufacture of variety of formulations including topical formulation. However, inspite of its use in enhancing solubility of non-polar drugs, but with hydrophilic polymers their use as co-solvents is often limited, where surface active agents are employed (76).

5.11.5 Pippermint oil
Peppermint oil is obtained from the *mentha piperita* L. (peppermint), which has been used as home remedy for many years for the treatment of indigestion. Peppermint oil also possesses analgesic (pain-killing) properties and is used in various topical formulations [77]. By differential scanning calorimetry (DSC) studies of testosterone, it has been found that the skin absorption of a drug increase via forming a eutectic mixture and lower its melting point drastically from 153.7°C to 39.9°C which further increase its solubility and rate of absorption [78].
5.12 References


