CHAPTER–1
INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentration\textsuperscript{1,2}. The route of administration has a significant impact on the therapeutic outcome of a drug\textsuperscript{3}. Most of these drug delivery systems are composed of polymer, which contain the drug in the form of a dispersion of the solid drug particles either in a solid or in liquid medium\textsuperscript{4}.

Topical Dosage Form

Topical dosage forms are those which are applied directly to external body surface either by in unciting it (spreading and rubbing in a semi-solid with the fingers), by spraying or dusting it on, or by instilling it (applying a liquid as drops)\textsuperscript{5,6}. Topical dosage form are applied to the skin either for their physical effects, that is for the ability to act as skin protectants, lubricants, emollients, drying agents, etc. or for specific effect of medicinal agents present. Preparations sold over the country frequently contain mixtures of medical substances used in the treatment of such conditions as minor skin infection, itching, bruise, acne, psoriasis and eczema\textsuperscript{7}. Topical dosage forms have been used since very ancient times. The application of medicinal substance to skin or to various body orifices is a concept as old as humanity. Various ointments, creams, gels, lotions, pastes, powders and plasters have been used for many years\textsuperscript{8}.
Advantages of Topical Systems

- Avoidance of first pass metabolism of drugs.
- Peak plasma levels of drug are reduced, leading to decreased side effects.
- Reduction of fluctuation in plasma levels of drugs.
- Utilization of drug candidates with short half-life and low therapeutic index.
- Reduction of dosing frequency and patient compliance.
- Avoid the risk and inconvenience of intravenous therapy.
- They eliminate the variables, which influences gastrointestinal absorption such as food intake, stomach emptying and intestinal motility and transit time.
- Topical drug delivery systems are relatively inexpensive compared to conventional dosage forms.

Limitations

- The route is not suitable for drugs that irritate or sensitize the skin.
- The route is restricted by the surface area of delivery system.
- Limited drug permeability through skin.
- Percutaneous absorption is a slow process, thus a drug must be pharmacologically active.

The Skin

The skin is one of the most extensive and readily accessible organs of the human body. The skin of an average adult body covers a surface area of approximately 2 m² (or 3000 inch²) and receives about one-third
of the blood circulating through the body. It is elastic, rugged and under normal physiological conditions, self-regenerating, with a thickness of only a few mm (2.97±0.28 mm).

**Anatomy of the Skin**

Microscopically the skin is a multilayered organ composed of, anatomically, many histological layers, and is generally described in terms of their tissue layers, the epidermis, the dermis and the hypodermis or subcutaneous fat layers. One can find several skin glands and appendages namely: Hair follicles and their associated sebaceous glands (pilo sebaceous glands), Eccrine sweat glands, Apocrine sweat glands, Nails of the fingers and toes. Each of the skin glands has its unique population density and distribution at desperate body locations. There are the characteristics differences in the appearances of structure from place to place on the body as well. The outermost layer of the skin appearing in the exploded epidermal.

**Stratum corneum** is the principal barrier element of the skin. It is a multicellular, comprised of flattened, stacked, hexagonal cell – building block formed from once living cells. These cellular building blocks are layered 15-25 cells deep over most of the body. The stratum corneum differ in thickness depends on the body surfaces like (palms and soles). However, the average thickness on most part of the body is about 10μ. It is a dense tissue of about 1.4 g/cm³ in the dry state. The stratum corneum is under continuous formation. Microscopic flakes (squamae) dislodged from the surface through wear and tear are replaced with new cells from
beneath, with complete turnover of the horny layer occurring roughly every 2 weeks in normal individuals. During their transit through the epidermal mass, the cells flatten actually and internally the protein and lipid components that eventually characterized the fully differentiated horny layer. A basic protein that slain deeply to give the granular layer is characteristic appearance is filagrin. Filagrin induces individual helical starch of prokeratin protein to twist together into multi stranded fiber that themselves have helical geometry. These fibers in turn are spontaneously bundled and concentrated so that the intracellular space of the fully differentiated horny layer is literally packed full with this semi-crystalline L-keratin and amorphous keratin counterpart. The keratin containing cells known as corneocytes are arranged in an interlocking structure somewhat to bricks and mortar. Thus, stratum corneum forms a major permeability barrier for external environment. The stratum corneum cells are formed and replenished by slow upward migration of cells produced by the basal cell layers of stratum germinativum.

**Viable Epidermis**

The multilayer epidermis varies in thickness ranging from about 0.8 mm on the palm and soles to 0.006 mm on the eyelids. The animate cells of the epidermis make a sharp, upper interface with the lifeless stratum corneum. They also have a well demarcated, deep interface with the dermis. Viable epidermises are a wedge of tightly massed like cells. Consequently, the whole of this line, cellular mass is regarded as a singular diffusional field (resistance) in percutaneous absorption models. These layers reflect the progressive differentiation of the cells that
eventuates in their death and placement as “bricks” within the horny structure. The stratum corneum may be only 10 μm thick when dry, but sweat several folds in water. There are two main types of horny layers, the pad of palm and the sole, which are adapted for weight bearing and friction and the remaining flexible rather impermeable membrane layer. The basal cell layer also includes melanocyte, which produce and distribute melanin granule to the keratinocytes. Langerhan’s cells are prominent in epidermis.

**Dermis**

The dermis is 1 mm – 5 mm thick, appears as a non-descript region lying between the epidermis and a region of sub-cutaneous fat. It consists of a matrix of connective tissue, woven from fibrous protein that is embedded in an amorphous ground substance of muco-polysaccharide. Nerves, blood vessels and lymphatics traverse the matrix and skin appendages pierce it. The dermis needs an efficient blood supply to convey nutrients, remove waste products, regulate pressure and temperature, mobilize defence forces and contribute to skin colour. Branches from arterial plexus deliver blood to sweat glands, hair follicles, sub-cutaneous fat and dermis itself. The supply reaches to within 0.2 mm of the skin surface, so that it quickly absorbs and systematically dilutes most compounds passing the epidermis. The generous blood volume in the skin usually acts as a sink for diffusing molecules reaching the capillaries. Keeping the penetrants concentration in dermis, very low, maximizing epidermal concentration gradients, and thus promoting percutaneous absorption.
Structure of Skin

Layers of stratum corneum
Functions of the Skin\textsuperscript{12}

- Protection from harmful external stimuli.
- Microbial barrier, Chemical barrier, Radiation barrier, Thermal barrier, Electrical barrier, Blood pressure regulation, Synthesis of metabolism.

Reception of external stimuli:

- Pain, Thermal, Absorption, Excretion, Sodium chloride in sweat.

Purpose of Topical Preparation\textsuperscript{13}

In order to formulate an effective and efficient topical preparation, consideration must be given to the intended purpose. This is directly concerned with the site of action and the desired effect of the preparation.

Surface Effects: Cleansing (removal of dirt and germs), cosmetics (enhancement of appearance), protective (prevention of moisture loss, sunscreen), antimicrobial (reduction of infection).

Stratum corneum effects: There are two actions targeted to this tissue, namely emolliency, the softening of the horny tissue, which comes through remoisturizing it, and keratolysis (a sloughing of the skin, useful in the treatment of psoriasis), protective (e.g., sunscreen that penetrate this layer).

Viable epidermal and dermal effects: Several classes of drugs may penetrate to these layers (anti-inflammatory, anesthetic, antipuritic, anti-histamine). Although it is difficult for drug to penetrate the stratum
corneum, once they are in the dermis, they can diffuse into the general circulation.

**Systemic effects:** A few drugs, such as scopolamine, nitroglycerine, clonidine and estradiol have been formulated in a manner to achieve systemic effects.

**Appandage effect:** Some classes of drugs are intended to exert their action in this portion of the skin (Depilatory, exfoliant, antimicrobial and antiperspirant).

**Fungi**

Fungi are eukaryotic protista that differ from bacteria and other prokaryotes. They possess rigid cell walls containing chitin, mannan and other polysaccharides. The cytoplasmic membrane contains sterols. They possess true nuclei with nuclear membrane and paired chromosomes. They divide asexually, sexually or by both processes. They may be unicellular or multicellular. Fungi had been recognized as causative agents of human disease earlier than bacteria. Fungi causing farms (*Trichophyton schonleinni*) and thrush (*Candida albicans*) had been described as early as in 1839.

Fungal infections are extremely common and some of them are serious and even fatal. With the control of most bacterial infections in the developed countries, fungus infections have assumed greater importance.
Classification

Depending on cell morphology, fungi can be divided into four classes:
Yeast, Yeast like fungi, Moulds, Dimorphic fungi.

**Yeast**: The yeasts are unicellular fungi which occur mainly as single spherical or ellipsoidal cells and reproduce by budding on artificial media, they form compact colonies with a creamy, mucoid or pasty consistence (e.g., like those of Staphylococcus). Cryptococcus neoformens is the only important pathogen.

**Yeast like fungi**: The yeast like fungi grow partly as yeast and partly as long filamentous cells joined end to end, forming a “pseudo-mycelium” e.g., Candida Albicans.

**Moulds**: The moulds (filamentous, mycelial fungi) grow as long filaments or hyphae which branch and interlace to form a meshwork or mycelium, and reproduce by the formation of various kinds of spores. When grown to a large size on artificial medium, the mycelium is seen as a filamentous mould colony, this may become powdery on its surface due to the abundant formation of spores (e.g., ring worm fungi).

**Dimorphic fungi**: Dimorphic fungi can occur as filaments or as yeasts, depending on the conditions of growth. In host tissues or cultures at 37°C they occur as yeasts, while in the soil and in cultures at 22°C, they appear as moulds. Most fungi causing systemic infections are dimorphic fungi.
Fungal infections\textsuperscript{17,18.}

Fungal infections are termed mycoses and in general can be divided into superficial infections (affecting skin, nails, hairs or mucous membranes) and systemic infections (affecting deeper tissues and organs). In the last 20-30 years, there has been a steady increase in systemic fungal infections, not only by known pathogenic fungi but also by fungi previously thought to be innocuous. These last are termed opportunistic infections.

Superficial Fungal Infections\textsuperscript{19,20,21.}

Superficial fungal infections can be classified into the dermatomycoses and candidiasis.

Dermatomycoses

Dermatomycoses are infections of the skin, hair and nails, caused by dermatophytes. The commonest are due to Tinea organisms, which cause various types of ringworm. Tinea capitis affects the scalp, tinea cruris, the groin, Tinea pedis, the feet (causing athlete’s foot) and Tinea Corporis, the body. In superficial candidiasis, yeast – like organism infects the mucous membrane of the mouth (thrush) or vagina, or skin. Some of the surface fungal infections and cutaneous fungal infections which fall into superficial mycoses groups are:

Pityriasis versicolor: Pityriasis versicolor (Tinea versicolor) is a chronic usually asymptomatic, involvement of the stratum corneum, characterized by discrete or confluent macular areas of discoloration or depigmentation of the skin. The area involved is mainly the chest,
abdomen, upper limbs and back. The causative agent is lipophilic, yeast like fungus, Pityrosporum arbiculare (*Malassezia furfur*).

**Tinea Nigra**: Tinea nigra is a localized infection of the stratum corneum, particularly of the palms, producing black or brownish macular lesions. It is found mainly in the tropics and is caused by cladosporium Wernickii (now designated as Hortaea Wernickii). Skin scrapings show brownish, branched, septate hyphae and budding cells.

**Piedra**: Piedra is a fungus infection of the hair, characterized by the appearance of firm, irregular nodules along the hair shaft. The nodules are composed of fungus elements cemented together or the hair. Two varieties of Piedra are recognized black piedra caused by Piedraia hortae and white piedra caused by Trichosporon beigelli.

**Chromoblastomycosis**: The most common form of chromomycosis is known as chromoblastomycosis or verrucous dermatitis the lesions consist of warty cutaneous nodules which resemble the florest of cauliflower. The disease is usually confined to the subcutaneous tissue of the feet and lower legs.

**Sporotrichosis**: Sporotrichosis is caused by the fungus sporothrix (sporotrichum) schenckii and is characterized by the development on the skin, in subcutaneous tissues and in lymph nodes, of nodules which soften and break down to form indolent ulcers.

**Rhinosporidiosis**: Rhinosporidiosis is a chronic granulomatous disease characterized by the development of friable polyps, usually confined to the nose, mouth or eye but rarely seen on the genitalia or other mucous
membrane. Histologically the lesion is composed of large numbers of fungal spherules embedded in a stroma of connective tissue and capillaries. The causative fungus is Rhinosporidium seeber.

**Blastomycosis**: This is a chronic infection caused by the dimorphic fungus blastomyces dermatitis, characterized by the formation of suppurative and granulomatous lesions in any part of the body. The cutaneous disease is usually on the skin of the face or other exposed parts of the body.

**Candidasis**: Candidosis (Candidiasis, moniliasis) is an infection of the skin, mucosa and rarely of the internal organs, caused by yeast like fungus Candida albicans, normally present in the mouth, intestine and vagina. Candida albicans is an ovoid or spherical budding cell, which produces pseudo-mycelia both in culture and in tissues. Candida species are normal inhabitants of the skin and mucosa.

Over the last two decades, there has been a dramatic increase in the rate of superficial and invasive fungal infections. Approximately three-quarters of all women experience at least one episode of vulva-vaginal candidiasis during their lifetime and nearly half of them suffer from multiple episode. The manifestations of vulva vaginal candidiasis are often painful and uncomfortable and can include intense itching, irritation, vaginal discharge and dysuria. The prevention of fungal infections has been improved by the antifungal agents such as terbinafine HCl.
Hcl, a allylamine group antifungal drug is used in the treatment of superficial and systemic fungal infection.

Hydrotropy and solubilization

Hydrotropy is the term originally given by Neuberg (1916) is a solubilization process whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Winsor considered hydrotropy as a solubility phenomenon. He noted that hydrotropic salts are essentially the same as low molecular weight amphiphiles with marked hydrophilic solvent affinity. Additives may either increase or decrease the solubility of solute in a given solvent. Those salts that increase solubility are said to "Salt in" the solute and those salts that decrease solubility "Salt out" the solute.

Several salts with large anions or cations that are themselves very soluble in water results in "Salting in" of non-electrolytes called "Hydrotropic salts" a phenomenon known as "Hydrotropism". Hydrotropy is simply another type of solubilization with the solute dissolved in oriented clusters of the hydrotropic agents. Solubilization has been defined by McBain as the spontaneous passage of poorly water-soluble into an aqueous solution of soap or a detergent, in which a thermodynamically stable solution is formed. Lyophilic surfactants with hydrophilic-lipophilic balance (HLB) values higher than 15 are the best solublizing agents.

Fungal Diseases

The images depicting fungal infections in various parts of body

- **Tinea corporis** (Wrist)
- **Tinea pedis** (athlete's foot)
- **Onychomycosis** (Foot Nails)
- **Cutaneous candidiasis** (Scalp)
- **Tinea nedis** (Foot)
- **Tinea Versicolor** (Back Neck)
Hydrotropy also known as chaotropes and have traditionally occupied a niche somewhere between salts, counter ions, surfactants, and co-solvents. There is a growing recognition that hydrotrope behavior is a sequence along the continuum of surfactant behavior and that a great deal of hydrotrope behavior can be understood by treating them as surfactants with very high critical micelle concentrations.

Hydrotropes are available in powder and liquid form as sodium and calcium salts. Hydrotropes normally comprises hydrophilic and hydrophobic moieties, with the hydrophobic moiety typically too small to induce micellar formation. Hydrotropes induce a characteristic steep increase in aqueous solubility of sparingly soluble hydrophobic compounds around a certain hydrotrope concentration after which solubility remains unchanged. The sudden increase in solubilization by hydrotropes after a certain threshold concentration called the minimum hydrotrope concentration (MHC). The function of hydrotrope in the system is to stabilize other surfactants in order to allow them to remain soluble in case of nonionic’s, which have limited acid and alkaline stability. Formulators need a hydrotrope to optimize the upper temperature stability limit, the cloud point, and lower temperature stability limit, the Kraft point, of nonionic and anionic surfactants incorporated within alkaline-based cleaners. There is a growing recognition that hydrotrope behavior is a sequence along the continuum of surfactant behavior with very high critical micelle concentration (CMC).
Classification of Hydrotropes

The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behavior (some examples of hydrotropic agents are benzoic acid, Nicotinamide, Sodium salicylate, Sodium benzoate, Urea). Alkyl benzene sulphonates based on toluene, xylene and cumene, polyhydroxy benzene, sodium salts of lower alkanols and derivatives of aromatic acids are generally considered to be effective hydrotropes. Other examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α- and β-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, sodium dodecyl sulphate (SDS) and dodecylated oxidibenzene. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotropic action may be due to the availability of interactive Π-orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g., salts of aromatic amines, such as procaine hydrochloride.23

Mechanism of Hydrotropes

The mechanism by which this effect occurs is not clear. Some workers have speculated that hydrotropy is simply another type of solubilization with the solute dissolved in oriented clusters of the hydrotropic agents. However hydrotropic solutions do not show colloidal properties. Others feel that this phenomenon is more closely related to complexation with a weak interaction existing between the hydrotropic
agent and the solute. Still others, reason that the phenomenon must be due to change in solvent character because of the large amount of additive needed to bring about the increase in solubility.”24 The hydrotropic effect is related to alterations in the water structure induced by the hydrotrope molecules and to the presence of hydrotrope aggregates that furnish an appropriate niche for the surfactant amphiphile. The influence of large concentration of ascorbic acid in the solubility of norfloxacin due to the complex formation. The shape of such a complex may be the sandwich type with molecule of ascorbic acid being sandwiched between the molecules of norfloxacin. This is the classic example of the hydrotropic solubilization, applied to pharmaceutical system.

**Applications of Hydrotropes**

Hydrotropes widely used in vesicle preparation, selective separation processes (precipitation of proteins, separation of isomers), in development of pharmaceutical formulations, as dispersants, extraction, stabilizer of o/w micro emulsion, and viscosity modifiers, as well as in pesticides, cements emulsic polymerization, pigments and dye stuff, cleaning agent in liquid household detergents, shampoos. Degreasing compounds and printing pastes25. They are also used to extract pentosans and lignins in the paper industry, as an additive for glues and tanning used in the leather industry. Hydrotropes has been employed for organic synthesis in aqueous solutions in the microwave enhanced Hantzsch dihydropyridine ester synthesis, increase in cloud points of detergent
solutions, enhance rates of reactions in multiphase transformation, and the Claisen-Schmidt reaction. We can conclude that hydrotropes used for enhancement of solubility thus improvement of bioavailability of poorly absorbed drugs.

**Topical Semi-solid Preparations**

**Definition**

Topical semi-solid preparations are intended to be applied to the skin or to certain mucous surfaces for local action or percutaneous penetration of medicaments or for their emollient or protective action. Topical semi-solid preparations consists of a simple or compound basis in which, usually, one or more active substances are dissolved or dispersed. According to its composition, the basis may influence the action of the preparation and the release of the active substance. The bases may consist of natural or synthetic substances and may be single-phase or multiphase systems. According to the nature of the basis, the preparation may have hydrophilic or hydrophobic properties. Several categories of topical semi-solid preparation can be distinguished – ointments, creams, gels and pastes.

**Ointments**

Ointments are greasy, semi-solid preparation for application to the skin. They are often anhydrous and contain the medicament. Substances, which are dispersed, should be in the form of a fine powder. Unmedicated ointments are used for the physical effects they provide as protectants, emollients or lubricants. The bases that are used mainly in
the preparation of ointments may be classified into hydrocarbon bases, absorption bases, emulsifying bases and water soluble bases.

**Creams**

The term “cream” in pharmacy and medicine is applied to viscous emulsions of semi-solid consistency intended for application to the skin or mucous membrane. They may be of the water-in-oil (oily creams) or oil in water (aqueous cream) type. The vanishing creams are oil-in-water emulsions containing large percentages of water and stearic acid or other oleaginous components. After application of the cream, the water evaporates, leaving behind a thin residual film of the stearic acid or other oleaginous component.

**Pastes**

Pastes are semisolid preparation intended for application to the skin. Pastes are stiffer preparation than ointments and contain a high proportion of powder dispersed in fatty bases. They are originally formulated on the principle that the high content of powder would absorb exudate but it is unlikely that a powder which has been preferentially wetted with oil will be capable of absorbing an aqueous fluid. Because of their very stiff consistency, pastes are useful for applying active medicaments (e.g. dithranol and coal tar) to circumscribed areas of the skin since they tend to localize the effect of the active ingredients.
Gels

The word ‘gel’ is derived from ‘gelatin’ and both ‘gel’ and ‘jelly’ can be traced back to the Latin gelu for ‘frost’ and gelare, meaning ‘freeze’ or ‘congeal’. This origin indicates the essential idea of a liquid setting to a solid-like material that does not flow, but is elastic and retains some liquid characteristics.

Definition

The term ‘gels’ is broad, encompassing semisolids of a wide range of characteristics from fairly rigid gelatin slabs, to suspensions of colloidal clays, to certain greases. Gels can be looked on as being composed of two interpenetrating phases. The United States Pharmacopoeia defines gels as semisolids, being either suspensions of small inorganic particles or large organic molecules interpenetrated with liquid.

Classification of gels

Gels are classified in the BP according to the characteristics of hydrophobic or hydrophilic characteristics of the gelled liquid.

Hydrophobic gels

The bases of hydrophobic gels (oleogels) usually consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica or aluminium or zinc soaps.
**Hydrophilic gels**

The bases of hydrophilic gels (hydrogels) usually consists of water, glycerol or propylene glycol gelled with suitable gelling agents such as tragacanth, starch, cellulose derivatives, carboxy vinyl polymers and magnesium aluminum silicates.

**Characteristics of gels**

Ideally, gelling agents for pharmaceutical and cosmetic use should be inert, safe and non-reactive with other formulation components. The inclusion of a gelling agent in a liquid formulation should provide a reasonable solid like matrix during storage that can be broken easily when subjected to the shear forces generated in shaking a bottle or squeezing a tube, or during topical application. The gel should exhibit little viscosity, changes under the temperature variation of normal use and storage. A topical gel should not be tacky. Too high a concentration of gel former or the use of an excessive molecular weight may produce a gel difficult to dispense or apply. The gel characteristics should match the intended use. The aim is to produce a stable, elegant, economical gel product adequately suited for its intended use.

**Use of gels**

The uses of gels and gelling agents are quite widespread. Gels find use as delivery systems for oral administration as gels proper or as capsule shells made from gelatin. Gelling agents are useful as binders in tablet granulation, protective colloids in suspensions, thickeners in oral
liquids and suppository bases. Cosmetically, gels have been employed in a wide variety of products including shampoos, fragrance products, denitrifices and skin and hair care preparation. Medicated gels may be prepared for administration by various routes including the skin, the eye, the nose, the vagina and the rectum.

**Structure**

Inorganic particles are capable of gelling a vehicle because of the formation of a “house of cards” structure. Clays such as bentonite or kaolin possess a lamellar structure that can be extensively hydrated. The flat surfaces of bentonite particles are negatively charged, while the edges are positively charged. The attraction of face to edge of these colloidal lamellae creates a three-dimensional network of particles throughout the liquid, immobilizing the solvent. Salts may attract parts of the water of hydration of the polymer, allowing the formation of more intermolecular secondary bonds, leading to gelation and precipitation. This is known as salting out. The effect of temperature depends on the chemistry of the polymer and its mechanism of interaction with the medium. Many gel formers are more soluble in hot than cold water. If the temperature is reduced once the gel is in solution, the degree of hydration is reduced and gelation occurs.

Molecular weight is an important consideration in gel formation. Very long polymers can entangle to a greater extent, leading to higher viscosity at a given concentration. Thus, lower concentration of a higher
molecular weight polymer may be required to gel the solvent. This can be a drawback perceived as difficult spreading of a topical gel due to the high cohesive interaction between the gel strands. Although polymer gels vary considerably in chemical structure, they all behave as elastic solids at low applied stresses, even though they primarily consist of liquid. The difference in chemical composition, however, results in several types of gel microstructure.

**Covalently Bonded Structures**

Covalently cross-linked gel networks are irreversible systems. They are typically prepared from synthetic hydrophilic polymers. In the first method of preparation, infinite gel networks arise from the non-linear copolymerization of two or more monomer species, with one being at least tri-functional. Both the dissection and position by which each polymer chain grows during the reaction are random, resulting in the final microstructure of these gels being completely disordered. The other method for preparing chemically cross-linked gel structures involves covalent cross-linking of individual linear or branched polymer chains, using a low concentration of cross-linking agent.

Examples of chemical and physical cross-links, which may exist in a gel network of covalently linked linear chains, are illustrated in figure.
Chemical and physical cross-links associated with covalently bonded polymer gels (a) bi and tri functional chemical cross-links; (b) simple and trapped physical entanglements; (c) in effective chemically bonded loop and dangling arch

Physical Bonded Structure

Physically bonded gel networks are reversible systems, factors such as temperature and ion additives can induce a transition between the sol and gel phases. These gels are formed primarily by natural organic polymers (proteins and polysaccharides) and semi-synthetic cellulose derivatives. Polymer chains exist most often in the sol as random coils, which undergo conformational transition to yield a gel, such transitions may involve large ordered sections of one or more chains, which fold into a single, double, or triple helix. The three-dimensional network is then formed by cooperative association of several sections into higher ordered regions called junction zones. Many junction zones are dispersed throughout the amorphous domains of the network, thus giving mechanical strength to the gel. The microstructures of physically bonded gels are much more complex than those of the disordered chemically cross-linked gels. The spatial arrangements assumed by polymer chains in forming junction zones may differ, as well as the secondary
intermolecular forces that hold these zones together. The physical properties of gels, including rigidity, melting temperature, and yield point, are related to the type of junction zone formed. Several types have been identified or hypothesized.

The particular organization of polymer chains in a junction zone depends on the chemical structure of the repeating unit. For example, sulfated polysaccharides (e.g., agar and κ-carrageenan) that contain an assortment of sulfated galactose residues form double helices, two or more of which aggregate into multi-helical junction zones. The presence of a few contaminant residue units greatly reduces gelling ability. The residues produce links that effectively block helix formation in large sections of chains, indicating that steric fit is critical to gel formation. The microstructure of these gels is represented in figure.

Microstructures associated with physically bonded polymer gels (a) multi-helical junction zones of agar gels (b) egg-box model junction zones of calcium alginate gels

Gels composed of semi-synthetic cellulose derivatives, including sodium carboxymethyl cellulose, contain microcrystalline junction zones. Residual crystallinity in the form of chain bundles can survive the
derivatization processing of cellulose. The bundles are connected through common chains to yield a gel, and the ultimate gel strength depends on the efficiency by which the bundles were previously dispersed throughout the sol.

**Well-ordered Gel Structure**

Silica, alumina and clay aqueous dispersions form rigid gels or lyogels. When clays belonging to the smectite class, such as bentonite, aluminum, magnesium silicate, hectorite and laponite come into contact with water, they undergo interlayer swelling spontaneously, followed by osmotic swelling to produce a gel. The plate-like clay particles associate into an ordered, extended network for which two models have been described. The “house of cards” model is based on attraction between weak positively charged particle edges and negatively charged particle faces, edge to edge association of particles into flat ribbons has also been proposed.

**Rheological Properties**

The rheological properties (study of deformation and flow of matter) are required in various pharmaceutical areas.

**Some of the reasons for determining rheological properties are:**

It helps in understanding the physicochemical nature of the vehicle and the quality control of ingredients, test formulation and final products, together with manufacturing process such as mixing, milling, pumping, stirring, filling and sterilization.
It reflects the effects such as temperature and storage time. It helps to assess topical formulations with respect to patient usage e.g., ease of removal of preparation from the jar or tube without spillage or spreadability and adherence to the skin. Finally it helps to monitor the effects of the vehicle consistency on the release of a drug from the preparation and its subsequent percutaneous penetration.

**Spreadability:**

One of the criteria for gels to meet the ideal qualities is that it should possess good spreadability. Spreadability is a term express to denote the extent of area to which the gel readily spreads on application to skin or the affected parts. The therapeutic efficiency of a formulation also depends upon its spreading value. Hence, determination of spreadability is very important in evaluating gel characteristics. Spreadability is expressed in terms of time in seconds taken by two slides to slip-off the gel, placed in between the slides under the direction of certain load. Lesser the time taken for separation of the two slides, better the spreadability.

**Extrudability**

It is a useful empirical test to measure the force required to extrude the material from a deformable bottle or tube. Since the packing of gels have gained a considerable importance in delivery of desired quantity of gel from jar or extrusion of gel from collapsible tube, therefore, measurement of extrudability becomes an important criteria for gels.