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Review Article

Transdermal Gels: A Soft Revolution in Drug Delivery Technologies

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ABSTRACT

The benefits of topical drug administration include extended half-lives and direct delivery of the medication to the site of action. The skin serves as the primary channel for topical drug delivery systems and is one of the most accessible and widely distributed organs on the human body. Numerous commonly used topical medications, such as. The fact that ointments, creams, and lotions are typically quite sticky and make patients uncomfortable when applied is just one of their many drawbacks. The paper also includes a brief discussion of hydrogels, which are three-dimensional structures that can hold large amounts of water and allow biological fluids to swell. In-situ gels are an innovative method in pharmaceutical gel technology. An example of in-situ gels is hydrogels, which are solution-like but form a gel when they come into contact with bodily fluids or when their pH changes. Several polymers, including carbopol-934, HPMC, guar gum, xanthan gum, carrageenan, xyloglucan, pectin, chitosan, and others, are utilised in in-situ gelling systems. The classification, formulation mechanism, and application of gels and hydrogels (in-situ gels) as innovative pharmaceutical approach systems are the primary topics of this paper.

INTRODUCTION

Gels are semisolid formulations that are applied to the skin or to mucosal membranes that are accessible, such as the mouth cavity. The gel is a three-dimensional matrix composed of two interpenetrating systems, in which colloidal particles, sometimes referred to as the gelator or gelant, are evenly dispersed throughout a solvent or dispersion medium. The gels are made by mixing an organic, inorganic, or aqueous solvent or solvent system with a gelling agent, which can be a natural, synthetic, or semi-synthetic polymer or tiny molecules with a low molecular weight. In gels, the polymer serves as the structural core of the gel matrix. Gel's structural strength, enhanced adherence to the surface where it is applied, and reduced penetration of bigger molecules are all

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made possible by the polymeric meshwork, which also enables retention. A gel may appear as a two-phase system with distinct floccules of particles or as a single-phase system with no discernible boundaries. Swelling happens during gel formation as a result of solvent penetration, which causes the polymer network to entwine the drug particles within it and stretch and maintain its structure. In order for a gel to form, viscosity is essential. In its solution state, a gel needs a particular polymer concentration to become more viscous. The continuous liquid phase inside is immobilised by an infinite rigid network structure formed by an appropriate but proportionately enormous amount of liquid. A gel is a state of matter that is in between a solid and a liquid; this quality is known as viscoelasticity. Both organic macromolecules, mostly polymers, and inorganic particles can make up the structural components that make up the gel network. Physical or chemical interactions can result in the formation of cross linkages. As a result, gels are categorised as either chemical or physical gel systems. Gels consist of a two-phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase, and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains. The term "gel" originates from the word "gelatin," and the words "gel" and "jelly" may both be traced to the Latin word "gelu," which means "frost," and "gel," which means "freeze" or "congeal." This source illustrates the fundamental concept of a liquid solidifying into a solid-like substance that is elastic and retains some liquid properties but does not flow. The term "gel" was first used as a categorisation in the late 1800s when scientists tried to group semisolid materials based on their phenomenological traits rather than their molecular makeup. The USP defines gels (sometimes called jellies) as semisolid systems containing either suspensions made up of small inorganic particles or large organic molecules, interpenetrated by the gel, which is categorised as a two-phase system when its mass comprises a network of tiny, distinct particles. In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes called magma. Single-phase gels consist of organic macromolecules uniformly circulated through a liquid in such a way that no apparent boundaries occur between the dispersed macromolecules and the liquid. Physical or chemical interactions can result in the formation of cross linkages. Topical drug distribution is the application of a material on the skin to treat or cure skin problems. These topical drug delivery techniques are frequently used when other routes of administration are ineffective, such as in cases of localised fungal infections of the skin. Its deeper skin penetration improves absorption. In no way is topical application better than conventional dosage forms. They are generally believed to be less hazardous and more effective than conventional formulations due to the bilayer structure and content. As a result, limited movement decreased the effectiveness of medications. The creation of carriers marked a step forward and may be encased, or immobilised, with medications, enabling the medication to securely and harm-free reach the intended location. These carriers made it possible for drugs to be released in previously unreachable locations. Over time, these carriers' composition evolved from ceramics to natural and synthetic materials. Three-dimensional matrices were used as carrier materials after consideration of factors like flexibility, integrity, and biocompatibility. Avoiding the dangers and hassles of intravenous treatment as well as the various absorption circumstances, such as pH fluctuations, the presence of the benefits of topical treatments also include stomach emptying time and enzymes. Although foams, sprays, medicated powders, solutions, and even medicated adhesive

systems are used, semi-solid formulations in all their varieties predominate in topical administration methods. The topical drug delivery method is typically employed in situations where other medication administration methods are ineffective or primarily for the treatment of pain, incontinence, and contraception. Drugs have been administered to the human body in a variety of ways during the past few decades, including oral, sublingual, rectal, parental, topical, and inhalation. Gels consist of a bilayer structure where a large number of natural particles are broken down in the disordered stage, randomly curled into flexible chains, and inorganic particles are not broken down but rather dispersed throughout the disordered stage.

Advantages Of Gel

- Unlike other semisolid dosage forms, gels are simple to make.
- A gel is a sophisticated, oil-free solution. By entangling the polymer multiple times, it can be utilised as a controlled release formulation.
- Gels are biodegradable and biocompatible, and they exhibit good adhesion properties to the application site.
- Compared to other topical dose forms, gels have a longer retention period.
- They are very tolerant of some stressful situations.
- They provide superior spreadability and cooling due to solvent evaporation.
- They are washable and nontoxic, and they provide a protective layer on the application site.
- Their long-term stability problems are rather minor.
- Both polar and non-polar medications can be administered using them.

Disadvantages Of Gel

- Gels have a longer-lasting and relatively slower effect.
- The gelators or additives have the potential to irritate.
- The likelihood of microbial or fungal attack in gels may be increased by the water concentration.
- Gels may undergo syneresis, which is the evacuation of solvent from the gel matrix, while being stored.
- The gel may dry as a result of solvent evaporation from the formulation.
- Certain gels include covalent connections that can make them indestructible, keeping the medication inside the gel matrix.
- In certain gels, flocculation might result in an unstable gel.
- The impact of temperature, humidity, and other external conditions can change the rheology of various gels.
- Salting out may occur as a result of the gelling agents precipitating.
- Because gel formulation contains polymers, certain medications may deteriorate.
- They could result in adverse application reactions.

- When applied, they may result in skin allergies.

Uses Of Gel

- Gels are utilised to provide dose forms with prolonged release.
- They serve as carriers for many medicinal drugs as well as lubricants.
- It is possible to formulate both polar and non-polar medications in a single gel.
- They can be used for topical, intraocular, intranasal, vaginal, rectal, and occasionally parenteral and intramuscular medication administration.
- They are extensively utilised in the food and cosmetics industries.
- as a means of delivering medications that are taken orally.
- For topical medications that are applied straight to the skin, mucous membranes, or eyes.
- As long-acting medications that are implanted in the body or given intramuscularly.
- As thickeners in oral liquid, suppository bases, protective colloids in suspensions, and binders in tablet granulation.
- Shampoos, fragrances, dentifrices, and skin and hair care products are examples of cosmetics.
- Foundations for patch testing.
- Electrocardiography with NaCl gel.
- Gel containing sodium fluoride and phosphoric acid for preventative dental care.

Structure Of Gel

The network of particles created by the gelling agent's interlinking gives a gel its stiffness. The characteristics of the particles and the force that creates the connections define the network's structure and the gel's characteristics. The individual hydrophilic colloid particles can be solitary macromolecules or spherical or isometric clumps of tiny molecules. Potential configurations of these particles within a gel network are displayed in. Entangled molecules make up the network of linear macromolecules, and the point of contact between which, as illustrated in (d), can be either comparatively tiny or comprise several molecules arranged in a crystalline arrangement. The force of attraction that connects the particles of the gelling agent can vary from strong primary valencies, like in reduced van der Waals forces and hydrogen bonding in silica gels. The fact that the liquefaction of gel is frequently caused by a minor increase in temperature indicates the weaker character of these latter forces. Gelling agent particles can be linked by a variety of forces of attraction, from weaker hydrogen bonds and Vander Waals forces to stronger primary valencies, like in silica acid gels. The fact that the liquefaction of gel is frequently caused by a minor increase in temperature indicates the weaker character of these latter forces.

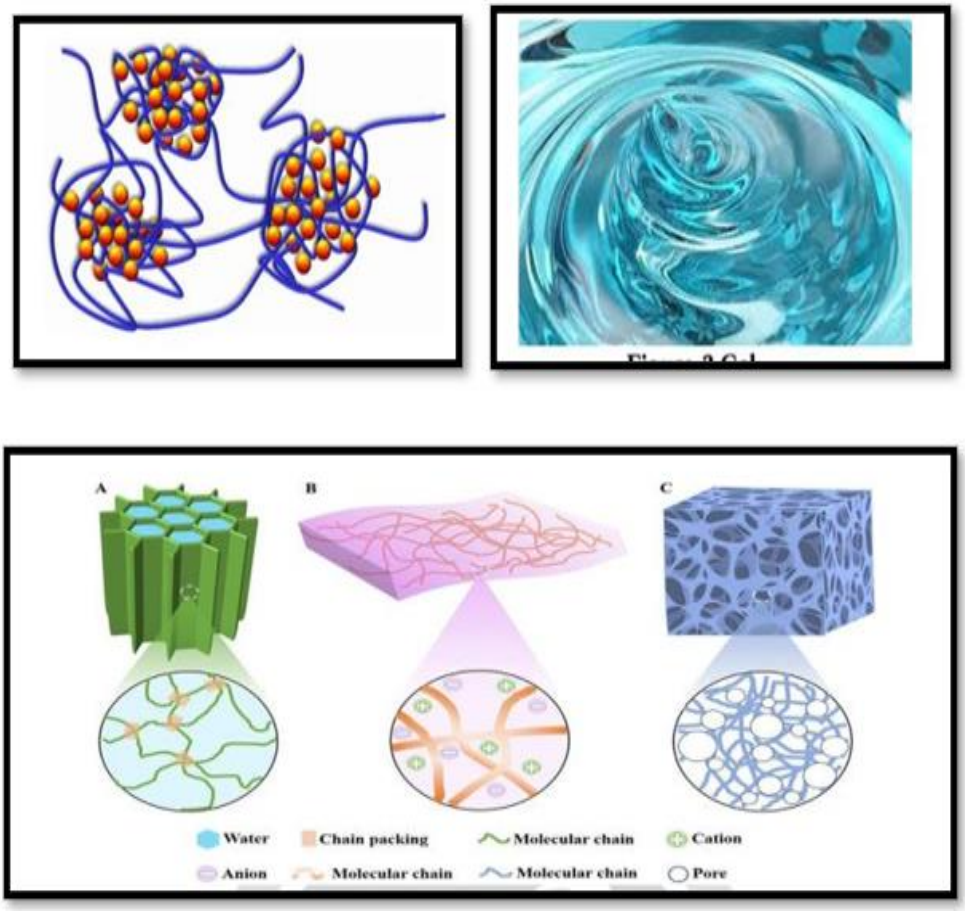

Fig :1 - Structure of Gel

Ideal Properties of Gel

- The gel should be clear and homogenous.
- The gel should be inert.
- The gel should be non-sticky.
- The gel should not interact with any other formulation component.
- The gel should be stable.
- It should be irritating to the skin or any part where the gel is applied.
- The viscosity should be optimum.
- It should have anti- microbial activity.
- The ophthalmic gel must be sterile.
- The apparent viscosity or gel strength increases with an increase in the effective crosslink density of the gel. However, a temperature rise may increase or decrease the apparent viscosity, depending on the molecular interactions between the polymer and solvent.
- They exhibit the mechanical characteristics of the solid state.
- Each component is continuous throughout the system.
- There is a high degree of attraction amongst the dispersed phase and water medium, so the gels remain equally uniform upon standing and do not freely settle.

Classification

Based on the nature of the solvent, its affinity, and the physical state, gels are classified into two basic groups, i.e., organogels and hydrogels.

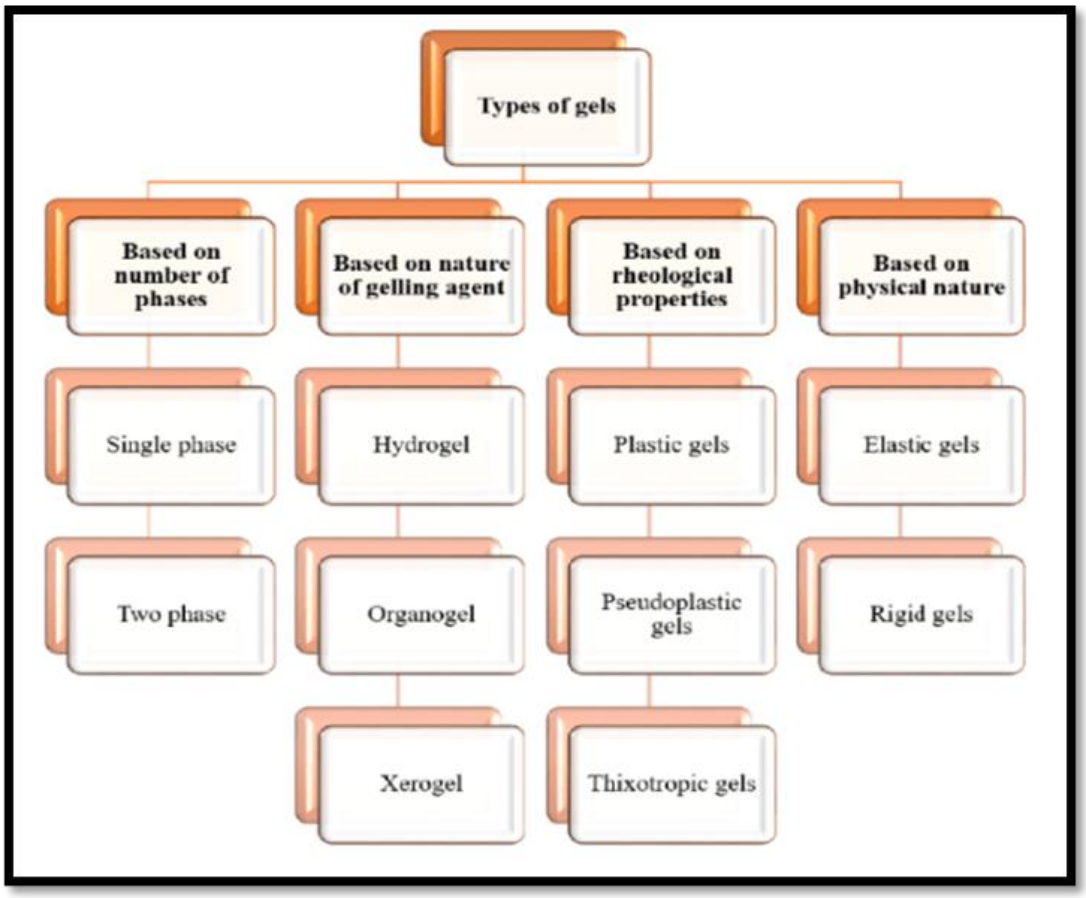

Fig:2- Classification of Gels

Based On Number of Phases:

Colloid Phase: Divided into two systems:

Inorganic (Two-Phase) System: Floccules of tiny particles, rather than bigger molecules, make up this system. If the dispersed phase partition size is noticeably big, the gel structure becomes unstable and takes on a three-dimensional aspect. When disturbed, these gels must change from a semisolid to a liquid, a property known as thixotropic behaviour. Gels composed of bentonite magma and aluminium hydroxide are two examples. A system that is composed of floccules of small particles rather than larger molecules and a gel structure is not always stable if the dispersed phase partition size is rather large and forms a three-dimensional structure throughout the gel. They have to be thixotropic, becoming semisolid when left alone and liquid when stirred.

Organic (Single-Phase) System: Twisted threads in this system host large organic molecules that remain continuously dissolved. The majority of organic gels belong to single-phase solutions, incorporating organic liquids such as plastic base and gelling agents like carbomer and tragacanth. These comprise big organic molecules residing on the twisted strands dissolved in a continuous phase. This larger organic molecule, either natural

or manufactured polymers, are called as gel formers, they prefer to entangle with each other their random motion or bound together by Vander walls forces.

Based On the Nature Of Gelling Agent:

Hydrogel (Water-based):

A hydrogel is a three-dimensional material made of hydrophilic polymers that have a high ability to interact with and hold onto large volumes of biological fluids and water. Numerous functional groups found in polymer chains, such as amino (-NH2), carboxylic acid (-COOH), hydroxyl (-OH), amide (-CONH), and sulfo groups (-SO3H), are responsible for this ability [16]. The polymer undergoes hydration to varying degrees, influenced by the nature of the aqueous medium and the polymer's composition. A hydrogel is a network of hydrophilic polymer chains that is rarely encountered as a colloidal gel with water acting as a dispersion medium. They are networks of natural or artificial polymers that are very absorbent. Because of their high water content, they also have some flexibility, similar to that of natural tissue. Depending on the type of side groups, hydrogels can be categorised as either ionic or neutral. They can be categorised as affine or phantom networks based on their structural and mechanical properties. Furthermore, depending on the preparation technique, they may be homopolymer or copolymer networks. Lastly, they can be categorised as amorphous, semicrystalline, hydrogen-bonded, supermolecular, and hydrocolloidal aggregates according to the physical structure of the networks.

Types of Hydrogels:

- ♣ pH-Sensitive Hydrogel
- ♣ Nano Hydrogels
- ♣ Temperature-Sensitive Hydrogel
- ♣ Glucose-Sensitive Hydrogel

Fig:3 - Hydrogel

Advantages Of Hydrogel:

- It's easy to prepare.
- Lower in price.
- biodegradable.
- malleable, contains a wide range of chemicals, and serves as the main building block for numerous different gel forms, including bigels, emulgels, and liposomal gels.

Disadvantages Of Hydrogel:

- Hydrogels' mechanical strength could be a problem.
- The hydrophilic nature of transdermal medication distribution can present issues.
- Hydrogels based on polysaccharides may become contaminated by microorganisms.
- Hydrogels are difficult to integrate lipophilic chemicals into.

Uses For Hydrogels:

- Medication delivery methods with sustained release.
- Drug delivery and diagnosis in the rectal region.
- Cell culture has been conducted in wells coated with hydrogel.
- As tissue engineering scaffolds.
- As a detector of environmental sensitivity.
- Silicone hydrogels, Polyacrylamides, and Polymacron contact lenses.
- Medical electrode for ECG.
- Healing dressing.
- For instance, carpooler, gelatin, cellulose derivatives, bentonite magma, and poloxamer gel.

Organogels (non-aqueous solvent)-

Pharmacopoeias describe some non-aqueous liquids for the topical administration of lipophilic medications and the inclusion of these liquids in gel forms known as Organogel. Through absorption through the skin, these gels are known to produce systemic effects in addition to local ones. When combined with the appropriate analgesics, organogels' remarkable penetration capability makes them useful in the treatment of chronic conditions like osteoarthritis. These are made up of big molecules that are dissolved in a continuous phase on the twisted strands. These bigger organic molecules, which can be either natural or synthetic polymers, are known as gel formers because they tend to bind together or entangle with one another randomly by the armies of Vander Walls. An Organogel is a kind of gel that contains a liquid organic phase inside a three-dimensional, cross-linked network. Lecithin solution in organic solvents organogellates, or gelates, when a polar solvent is added.

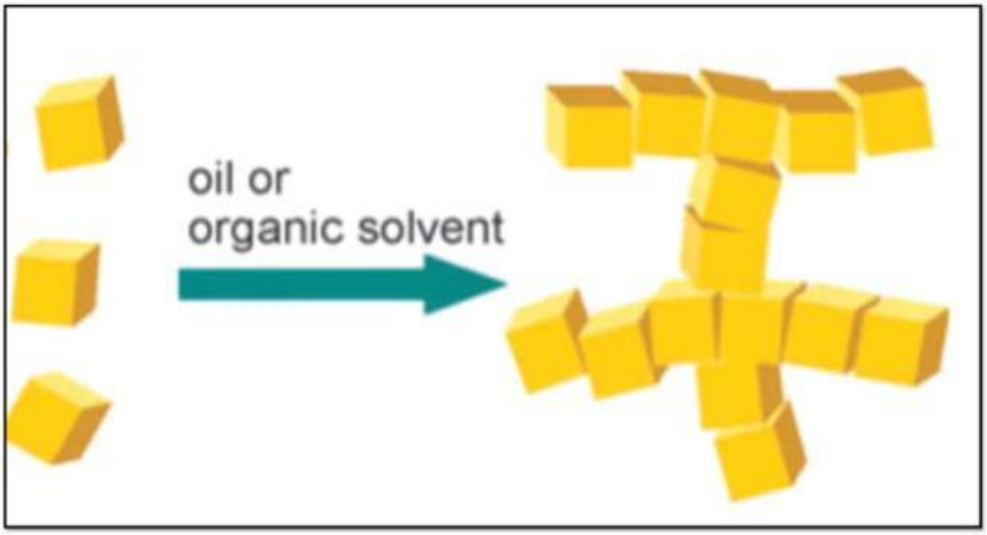

Fig :4 - Organogel

Advantages Of Organogel:

- It's easy to prepare.
- Lower in price.
- The Organogelator is responsible for the improved mechanical strength.
- An increased ability to pass through the skin Unwashable.
- Thermoreversible.
- Resistant to contamination by pathogens.

Disadvantages Of Organogel:

- More advantageous for lipophilic medications.
- Heat may cause instability unless it is properly controlled.
- An unpleasant aspect of cosmetics can be their greasy texture.
- Difficult to wash.

Xerogels

Xerogel is the term for the gel matrix that is left behind when the solvent is extracted from a gel either by evaporation or freeze-drying. They are more solid because of their low solvent concentration. They are easily reconstituted and are able to swell up (aerogels). Tragacanth ribbons, polystyrene, dry cellulose, etc., are a few examples. Gels can also be divided into two-phase and single-phase systems. When a gel is dried with uncontrolled shrinkage, a solid is created. It usually maintains a very small pore size (1–10 nm), a large surface area (150–900 m2/g), and high porosity (15–50%). The network does not shrink when the solvent is withdrawn under supercritical circumstances, and an extremely porous, low-density substance called an aerogel is created. Applying heat to a xerogel at a higher temperature effectively turns the porous gel into a thick glass by causing viscous sintering.

E.g. Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose and polystyrene.

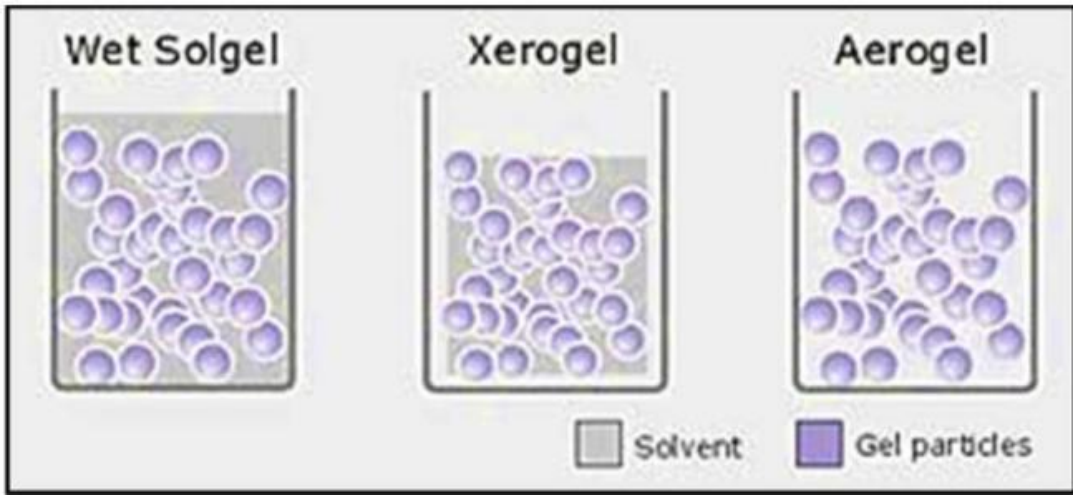

Fig :5 - Xerogel

Advantages Of Xerogel:

- Unlike xerogels, aerogels can be customised for extended drug delivery.
- Extremely stable.
- Thermal stability and low heat conductivity.
- Lots of surface space for transporting drugs.
- For regulated drug delivery, xerogels and aerogels can both be employed.

Disadvantages Of Xerogel:

- Costly technique.
- Issues with the biodegradation of xerogels and pure silica aerogels.

Based On Rheological Properties

Gels typically demonstrate non-Newtonian flow properties and can be classified into:

Plastic Gels: For example, flocculated solutions of aluminium hydroxide and Bingham bodies both display plastic flow. The yield value, above which the elastic gel bends and starts to flow, is shown by the rheogram plot.

Pseudo Plastic gels- These gels have no yield value, and their viscosity falls as the rate of shear increases. The disorganised molecules start to align their long axis in the direction of flow with the release of the solvent matrix as the shearing force increases. For instance, a liquid tragacanth and Na+ CMC dispersion. A shearing action on the linear polymers long-chain molecules produces the rheogram. As the shearing stress rises and the solvent is released from the gel matrix, the dispersed molecules start to align their long axis in the direction of flow.

Thixotropic gels:

These gels have extremely weak particle-to-particle connections that are easily disrupted by shaking. The final solution will go back to because of the particles collision and subsequent reversible isothermal gel-sol-gel transformation, which returns the material to gel. This creates a scaffold-like structure in a colloidal system with non-spherical particles.

EX: Kaolin, bentonite and agar.

Based On Physical Nature:

Elastic Gels:

Agar, pectin, guar gum, and alginates are examples of gels with elastic qualities. At junction sites, relatively weak interactions like dipole attraction

and hydrogen bonding hold fibrous molecules together. An extra bond in the form of a salt bridge is present if the molecule has a free -COOH group. The formation of (-COO-X-COO) occurs between two neighbouring strand networks. Carbopol and alginate are two examples.

Rigid gels:

This can be created from macromolecules with a primary valence connection connecting their framework. For instance, silica acid in silica gel Si-O-Si-O bonds hold molecules together to form a polymer structure with a network of pores.

Characteristics Of Gels

Swelling

Gels can swell, absorbing liquid as their volume increases. One could consider this to be the first stage of dissolution. Gel-solvent interactions take the place of gel-gel interactions when the solvent penetrates the gel matrix. A certain amount of cross-linking in the gel matrix that inhibits complete breakdown typically causes limited swelling. This type of gel swells significantly when the solvent combination has a characteristic of solubility similar to the gellant's. When the gelling agent comes into contact with the liquid, it starts to absorb water, which causes swelling and an increase in volume. A large amount of fluid is devoured by the gelling expert, and the volume increases to the point where a fluid is left in touch with them, solvating it. We refer to this as expanding. The gelling specialist consumes a lot of fluid, and the volume rises when a fluid comes into contact with it and solvates it. This is what we call expanding. This mechanism is caused by soluble ingestion into the framework. When a gelling agent is kept in contact with a liquid that solvates it, a sizable amount of the liquid is absorbed, increasing the volume. We refer to this phenomenon as swelling. This process occurs when the solvent enters the gel network. The force of attraction between these links and the quantity of linkages between the gelling agent molecules determine how much swelling occurs.

Syneresis

When standing, many gel systems contract. The interstitial fluid is released and gathers near the gel's surface. This phenomenon, known as syneresis, has been observed in both inorganic and organogel hydrogels and is not exclusive to organic hydrogels. Generally, syneresis intensifies with decreasing polymer concentration. The relaxation of elastic strains created during the gel's setting has been linked to the contraction process. The release of these tensions results in less interstitial space for the solvent, which forces fluid expression. Since pH and electrolyte concentration affect syneresis from gels made of the ionic gel formers gelation or psyllium seed gum, osmotic effects have been suggested. The relaxation of elastic stress created during gel setting has been linked to the contraction process. As these the liquid is forced out when tensions are released, and the amount of interstitial space available for the solvent is decreased. Many gels spontaneously contract while standing and release a fluid medium. We call this process syneresis. As the concentration of the gelling agent drops, the degree of syneresis increases.

Ageing

Slow accumulation normally appears in colloidal framework. This cycle is known as maturing. In gels, maturing causes the gradual development of a denser organization of the gelling specialist. Typically, slow spontaneous aggregation is seen in colloidal systems. Ageing is the term used to describe this process. Age causes a thick network of the gelling ingredient to gradually accumulate

in gels. According to Theimer, since the fluid medium is lost from the freshly formed gel, this process is comparable to the original gelling process and continues after the initial gelation. Colloidal frameworks often exhibit slow buildup. We call this cycle maturing. As gels mature, a denser organisation of the gelling specialised eventually develops.

Structure

The network created by the interlinking of the gelling agents' particles gives a gel its stiffness. The structure of the network and the gel's characteristics are determined by the kind of particle and the force that forms the connections. The network created by the interlinking of gelling agent particles gives a gel its stiffness. The characteristics of the particles and the force type that is in charge of the connections establish the network's structure and the gel's characteristics. The individual hydrophilic colloid particles can be solitary macromolecules or spherical or isometric clumps of tiny molecules. A crucial part of formulation is choosing the right gelling agent since it affects the gel's hardness and aids in binding viscosity between the medium and the particles.

Rheology

Gelling agent solutions and flocculated solid dispersions are pseudoplastic, meaning they display non-Newtonian flow behaviour, which is defined by a drop in viscosity as the shear rate increases. Because of the breakdown of the interparticulate connection, applied shear stress disrupts the fragile structure of inorganic particles scattered in water, causing them to exhibit a higher tendency to flow. In a similar vein, regarding macromolecules, the molecules are straightened out, and the resistance to flow is reduced when the applied shear stress aligns them in the direction of the tension. Gels break the tenuous structure of inorganic particles scattered in water, and ageing causes the slow development of a gelling agent network that is denser. Allows, for instance, the Non-Newtonian stream conduct, which is characterised by a decrease in thickness as the shear rate increases. Two examples of fake flexibility are gelling specialised arrangements and flocculated strong dispersion. Displaying a decrease in variance in non-Newtonian float conduct is characterised by thickness and an increase in shear stress. The dubious design of inorganic waste diluted in water is finally overturned as a tighter organisation of the gelling specialised forms as n gels increase.

Additives Used in Gel Formulation

Preservatives - Preservatives, such as propyl and methyl paraben, are used to prolong the gel's shelf life and keep it from spoiling.

Drug solubilizer - When a medicine has poor solubility, a drug solubilizer is utilised. Drug solubilizers aid in the dissolution of certain medications that are poorly soluble in the medium. For instance, PVP (polyvinyl pyrrolidine) and triethyl-o-amine.

Stabilizers - Certain gels with heavy metals and other substances are kept stable by chelating agents like EDTA.

Penetration Enhancer - An ideal penetration enhancer should have the following properties:

• It should be pharmacologically and chemically inert and chemically stable.

• It should be non-toxic, non-irritant, noncomedogenic and non-allergenic

• It should have a rapid onset of action, predictable duration of activity, as well as a

reproducible and reversible effect.

• It should be odorless, tasteless, colorless, and inexpensive

• It should be pharmaceutically and cosmetically acceptable. It should be non-toxic, non-

irritating, and non-allergenic.

• It should have a solubility parameter similar to that of skin. It should have no

pharmacological activity within the body, i.e., it should not bind to receptor sites.

• It should be appropriate for formulation into diverse topical preparations and, thus, should be

compatible with both excipients and drugs.

• It should be cosmetically acceptable with an appropriate skin "feel."

Drug substance - The main medicinal ingredients in gels include antimicrobial, antifungal, analgesic, anti-inflammatory, etc. The most crucial element of drug integration is that the substance should permeate the skin with ease.

Physicochemical Properties:

- The medication should have a molecular weight of less than 1000 Daltons.
- Drugs show a preference for both hydrophilic and lipophilic phases.
- The drug's low melting point is its best feature.

Biological Properties:

- A regular dosage of several milligrams of the medication should have a strong effect.
- The medication should not cause allergic reactions or skin irritation, and its half-life (t1/2) should be brief.
- Topical administration is a good option for medications that are prone to gastrointestinal tract degradation or that are rendered inactive by first-pass actions in the liver.
- It is important to avoid developing tolerance below the release threshold near topical application.
- It is possible to create drugs for topical administration that require lengthy use or have undesirable effects in tissues other than the intended target.

Polymer - In contrast to the drug release process, the gels' structure network is created by the addition of inorganic particles, organic molecules, and polymers. Primarily depends on the drug's physicochemical characteristics and the polymer employed. The polymers may have a natural origin or be synthetic, semisynthetic, or both.

1) **Natural polymers** –

- Polysaccharides- Tragacanth, Agar, Dextran, Pectin, Guar gum, Locust gum, Hyaluronic acid, Starch, Xanthine, Alginic acid, Carrageenan
- Proteins- Gelatin, Collagen, Casein, Albumin.

2) **Semi synthetic polymers –**

- Cellulose derivatives- Methyl cellulose, Hydroxymethyl cellulose, Hydroxypropyl methyl cellulose, Hydroxyethyl cellulose, Carboxymethyl cellulose, Ethyl cellulose, and Hydroxypropyl cellulose.
- Magnesium aluminium silicate

3) **Synthetic Polymers -** Poloxamer - Acrylic acid (AA), Methacrylic acid (MAA), Chitosan, Poly vinyl alcohol, Polyethylene, Polyacrylamide Polyethyleneglycol acrylate/methacrylate (PEGA/PEGMA), Polyethylene oxide, Carbomers (Carbopol-934 Carbopol-940).

4) **Inorganic Substances** – Bentonite, Aluminium hydroxide.

5) **Surfactants** - Brij-96, Cetostearyl alcohol.

Surfactants - They make the formulation more stable by lowering interfacial tension, such as sodium lauryl sulphate, sodium glycolate, etc.

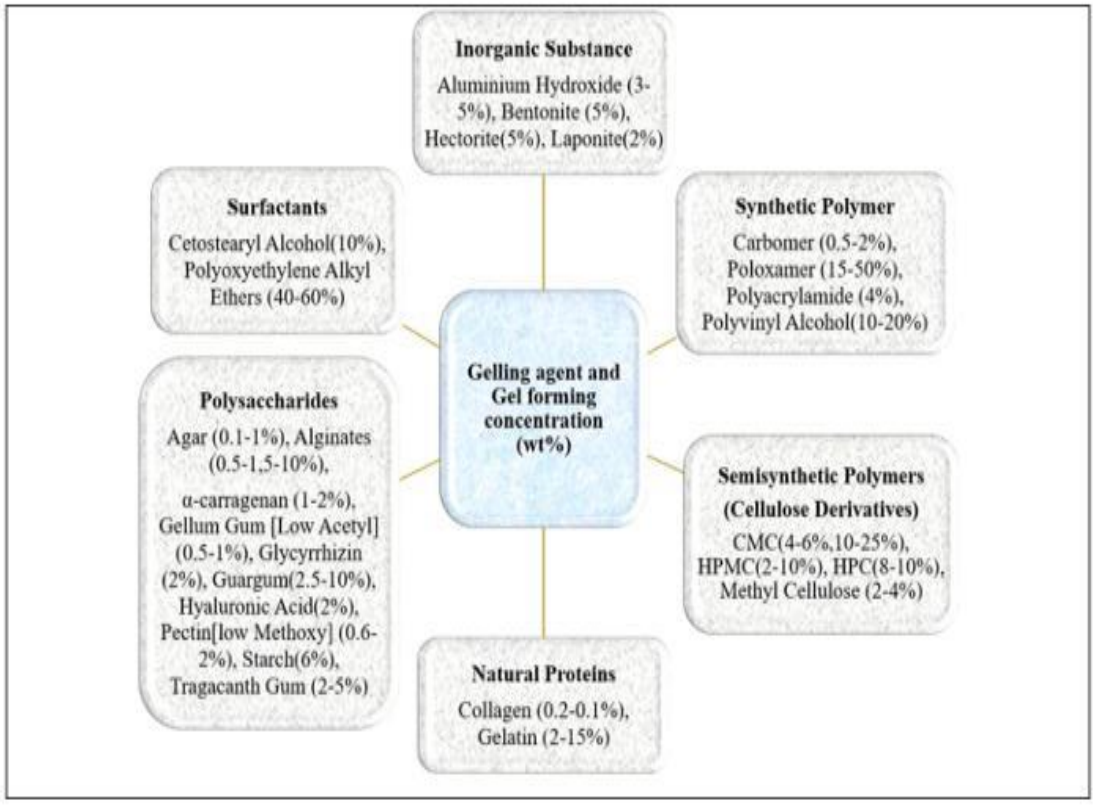

Fig :6 - Gelling Concentration for Substances Used In Pharmaceutical Products

Preparation / Formulation of Gels

Gels are often made on an industrial basis at room temperature. But some polymers require particular processes after treatment. The following techniques can be used to make gels.

1. Thermal changes.
2. Flocculation.
3. Chemical reaction.
4. The fusion method.
5. Cold method.
6. Dispersion method.

1. Thermal changes - Gelatin is created when solvated polymers (lipophilic colloids) are heated. Numerous hydrogen formers are more soluble in hot water than in cold water. Gelatin forms as the temperature drops and the level of hydration decreases. A gel will form when a concentrated hot fluid cools. For instance, cellulose derivatives, guar gum, gelatin, agar sodium oleate, etc. On the other hand, certain substances, such as cellulose ether, are soluble in water and form hydrogen bonds with it. As the temperature rises, the reduced solubility and weakened hydrogen bonds in these

solutions will cause gelation. This makes it impossible to use this method as a standard for making gels. Gelation will result from the disruption of hydrogen bonds and decreased solubility caused by raising the temperature of these solutions. As a result, this technique cannot be used generally to make gels.

2. Flocculation - Here, gelation is created by adding just enough salt to cause a precipitation that creates an age state but not enough to bring regarding total precipitation. Rapid mixing is required to prevent a significant precipitant concentration in one area. For instance, ethyl cellulose and polystyrene in benzene can be quickly mixed with appropriate volumes of a non-solvent, like petroleum ether, to gel the solution. Adding salts to Coagulation occurs in hydrophobic solutions, while gelation is infrequently seen. The flocculation process produces gels with a thixotropic behaviour. Only high electrolyte concentrations can alter hydrophilic colloids like gelatin, proteins, and acacia; when the effect is to "salt out," the colloidal and gelation don't happen.

3. Chemical reaction - The solute and solvent interact chemically in this process to form a gel. For instance, an aluminium salt and sodium carbonate can combine in an aqueous solution to create an aluminium hydroxide gel; a higher reactant concentration will result in a gel structure. A few other instances of chemical reactions that cross-link the polymeric chain are PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), and methane diphenyl isocyanine (MDI).

4. The fusion method - This approach involves blending the medicine, gelling agents, carriers, and additives at high temperatures until a semi-solid texture is achieved.

5. Cold method - Every material used in this process, aside from any medication or active pharmaceutical ingredient, is a component, which are heated and mixed at the same time. After lowering the mixture's temperature and adding the medication, more components are added, and the mixing process is repeated until the gel has formed**.**

6. Dispersion method - In this technique, the medication is dissolved in the medium and mixed in while the gelling agent is agitated with water until it begins to swell. If required, add a buffer solution to the gel to change the pH.

Mechanism Of Gel Formation:

Gels are formed via three types of cross-linking:

a) Chemical cross-linking.
b) Physical cross-linking.
c) Ionic cross-linking.

a) Chemical cross-linking - In their assembly, polymers containing bound groups also exhibit chemical cross-linking. Such polymers result in an irreversible interaction between the free group and the added chemical when cross-linking compounds bring them together. In this kind of reaction, viscosity rises after reaching a particular concentration, leading to gel formation. For instance, polyacrylic acid contains many carboxylic acids.

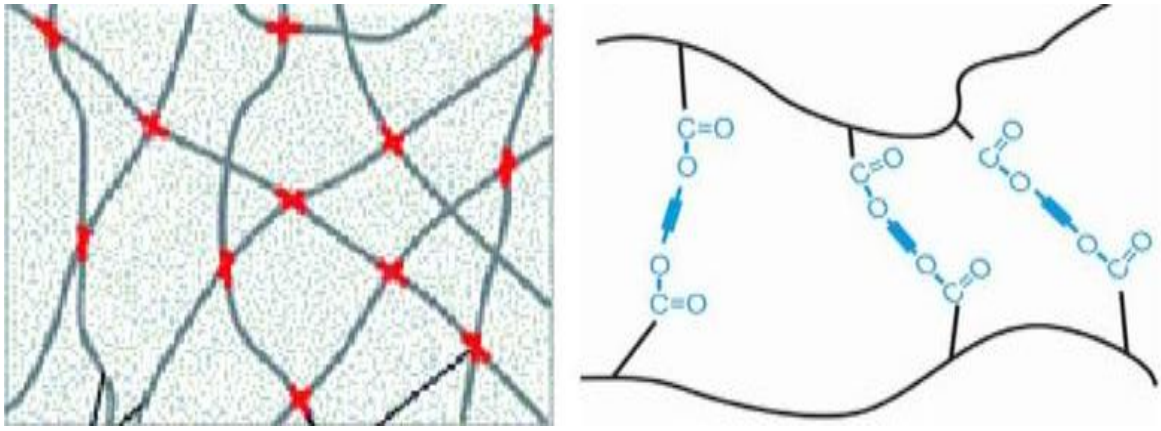

Fig :7 - Chemically Cross-Linked Gel

These gels have an irreversible nature and are covalently linked. Additionally, polymers can be used to create chemical cross-linking, having groups in their structure that are not bound. When a cross-linking compound is added to these polymers, the free group and the new component undergo an irreversible chemical reaction. This irreversible process raises the viscosity, and once the concentration reaches a particular point, a gel is created. For example, polyacrylic acid, which contains numerous carboxylic acids, and glycols, which include hydroxyl groups, combine to make chemical cross-linking gels.

b) Physical cross-linking - In certain situations, the transition from solution to gel can occur by the creation of hydrogen bonds, the solubilisation of crystalline components, Hydrophobic interactions, temperature changes, or concentration variations. These gels include cellulose gels, poly (N-isopropylacrylamide) gels, dextran gels, and others.

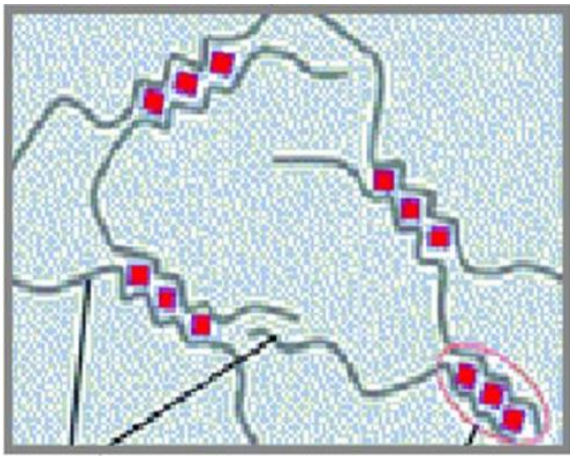

Fig :8 - Physically Cross-Linked Gel

c) Ionic cross-linking - Creating charges on polymers or other molecules (solvents) that may attract one another to form a gel is another method of cross-linking (Fig. 6). The charges on these molecules cause ionic bonds to form. For instance, when calcium ions are present, polysaccharide alginate forms a gel matrix that can encapsulate specific substances (enzymes, etc.). Changing the medium's (solvent's) pH can also result in ionic gelation. Gelation is the outcome of altering the pH of such mixes; for example, pectin gels when exposed to an acidic pH in an appropriate medium.E.g. – pectin forms gel when subjected to acidic pH in a suitable medium.

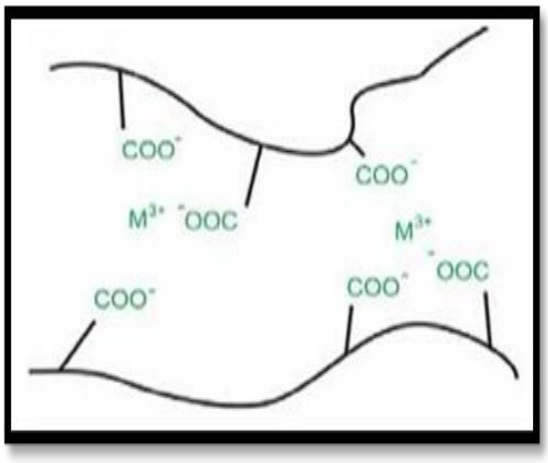

Fig :9 - Ionic Cross-Linking in Gel

Evaluation Parameters of Gel

a) **Measurement of pH-** A digital pH meter can be used to measure pH. For instance, 1g of gel was combined with 100ml of distilled water and left for two hours. pH is measured three times, and the average is computed.

b) **Drug content-** One gram of gel has been dissolved in one hundred millilitres of the suitable solvent stock solution. Using the appropriate dilution, aliquots of varying concentrations are made, and absorbance is measured. The drug content is determined using linear regression analysis of the calibration curve.

c) **Viscosity study-** For its investigation, the gels are rotated at 0.3, 0.6, and 1.5 Rpm using a Brookfield viscometer. At each speed, the resulting dial readings are recorded. By dial reading the X factor specified in the Brook Field viscometer catalogues, viscosity was determined.

d) **Spreadability-** It displays the coverage of the area where gel readily spreads when applied to the skin or affected area. Spreading value is what determines the effectiveness of the cure. The amount of time in seconds it takes for two slides to separate from the gel that is placed between them and travel in the direction of a specific lead is a measure of spreadability; the shorter the time, the greater the spreadability. It can be designed with the formula

Spreadability [s] = M x L/T

Where, M= Weight tied to upper slide

L Length of glass slides

T= Time taken to detach the slides.

e) **Extrudability study**- Formulations are packed in collapsable tubes before being placed inside the container. The mass in grams is used to determine this. A 0.5-centimetre ribbon must be extruded at gel in 10 seconds.

f) **Skin irritation study**- In this study, 400–500 g guinea pigs of each sex were employed. Which have unfettered access to water and are fed standard animal feed. Hair was shaved from the back, and five millilitres of each sample were extracted at one, two, three, five, six, seven, and eight-hour intervals. Next, a fresh dissolving medium of the same size was added to each sample. The drug content of the sample was then investigated using pH buffer guinea pigs and a 4-cm blank zone on either side, one of which was used as the test and the other as the control. The gel was used twice a day for a single wear and site, and any sensitive reactions were recorded.

g) ***In-vitro* dissolution studies**- The Franz diffusion cell is used to study how a cellophane membrane causes the gel to dissolve and discharge. The cellophane membrane contained 0.5 of the gel sample. Diffusion experiments were conducted at 37±1oC with a dissolution medium of 250ml of PH buffer (PH 7.4).

h) ***In-vivo* dissolution studies**- Six male Wistar albino rats are used, split into three groups.

Carefully rub 100 milligrams of the prepared gel on each paw twice at one and two hours. Determine the inhibition % using a mercury paleothermometer.

i) **Stability**- Freeze-thaw cycling is used. Syneresis has been observed when the products are maintained at 4°C for one month, 25°C for one month, and 40°C for one month. The liquid exudates are separated from the gels, which are maintained at room temperature.

j) **Homogeneity**- Visual inspection was used to check the homogeneity of each formed gel after it had been placed in the container. They were examined to determine whether any aggregates were present and how they looked.

k) **Grittiness**- Every formulation was examined under a microscope to check for the presence of any significant particle matter, which was observed via a light microscope. Therefore, it is clear that the gel preparation satisfies the necessary freedom from specific matter and grittiness for any topical preparation.

Applications Of Gel

- used in both hard and soft gel tablets.
- Making the suppositories. For instance, glycerin in BP suppositories.
- Continuous release formulations are made with gels.
- used to administer drugs via a variety of routes, including parenteral, intramuscular, vaginal, rectal, tropical, intranasal, and intraocular.
- The food and cosmetics industries make extensive use of them. Dental care uses sodium fluoride gel and phosphoric acid.

Factors Affecting Gel Formulation:

A number of factors are known to affect gel preparations. Some major factors have been listed as follows:

i. Concentration of the gelling agent.
ii. The molecular weight of the gelling agent.
iii. Solubility and affinity of gelling agent to the solvent being used.
iv. Nature of the solvent.
v. pH of the solution.
vi. Ionic strength of the solution.
vii. vii. Temperature at which the gel is being formulated.
viii. Humidity and other environmental conditions.

Anatomy Of Skin

The largest organ in the body is the skin, which forms the outermost layers and protects the body from the outside world. Because it is a complex organ that interacts in both physiological and pathological ways, its function is vital to survival. Three components to skin:

1) Epidermis
2) Dermis
3) Hypodermis

Epidermis: it has five regions:

i. Stratum germinativum - It contains polygonal cells externally and column or cuboidal epithelial cells in more profound parts. It contains mitotically active keratocytes, and also, glands and keratin structures are derived from this layer

ii. Stratum corneum- The skin is mechanically protected by this outermost layer, sometimes known as the third layer. It serves as a barrier to prevent water loss. Coenocytes make up its

composition. Under pressure, these cells lose their nuclei and die. Keratin A is a protein found in cells that stops water from evaporating.

iii. Stratum spinosum- This is also called the prickle cell layer for the reason that it contains spinous cells, which have a spine-like appearance. They are also composed of keratin filaments.

iv. Stratum Granulosum - This is composed of two to five rows of compressed rhomboid cells arranged in a thin layer called Granular cells. The cytoplasm contains keratohyalin granules. It is mostly found in the palms and soles and stops water loss.

v. Stratum lucidum - These are epithelial cells that have been flattened. The cells have a glossy appearance. The palms and soles are where this is most common. The layer is known as the stratum lucidum because it resembles a shiny zone.

Dermis:

Dermis is the interior coating of the skin. Which is tough and elastic; the dermis is composed of collagen fibres interlaced with elastic fibres. The collagen fibres show flexible properties and are fit for holding water. The enzyme collagenase, which is liable for wound healing, is present in collagen fibres. There are mast cells and fibroblast in the dermis. Dermis comprises 2 layers.

1) Superficial papillary layer
2) Deeper reticular layer

Superficial papillary layer

This layer projects to epidermis pigment-containing cells. Which is called chromatophores and are present in this layer and which also consists of nerve fibres, blood vessels and lymphatics.

Deeper reticular layer

This is comprised of elastic and reticular fibres. These fibres are present near the sebaceous gland, sweat glands and hair bulbs. Glands are present in the dermal layer of the skin.

Hypodermis:

Layer of skin inside. The skin and the body's fundamental tissues, including the muscles and bones, are connected by this layer, also referred to as the contact layer. Sweat organs throw a weaker salt arrangement into the skin's outermost layer. The dissipation of the supplied weaker salt arrangement causes the outer layer of the skin to cool, which is crucial for maintaining proper body and skin temperature. Every portion of the body has sweat organs.

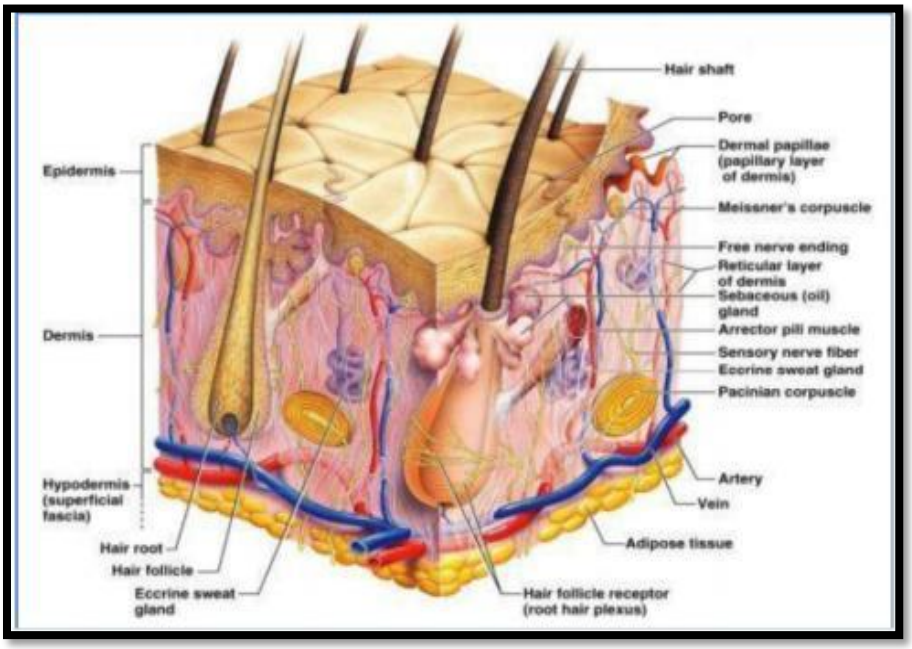

Fig :10 - Structure of Skin

Topical Drug Delivery System

Topical drug delivery systems transport particular medications when they come into touch with and pass through the skin. The problem with topical drugs is that they penetrate the epidermal barrier. There are two primary categories of topical medications: internal and external. Topical medicines used internally for local action on mucosal membranes, administered to anorectal tissues, orally, or vaginally. To cover the afflicted area, topical drugs are sprayed, applied, or otherwise dispersed onto skin tissue.

Advantages Of Topical Drug Delivery System

- Stay clear of first pass metabolism.
- Easy to use and convenient.
- More precisely deliver the medication to a certain location.
- Steer clear of intestinal incompatibility.
- A limited therapeutic window following the administration of medications with a short biological half-life. increased adherence from patients.
- Make self-medication appropriate.
-

Disadvantages Of Topical Drug Delivery System

- Some medications have poor skin permeability.
- Drugs with bigger particle sizes are more difficult to absorb through the epidermal layer.
- The potential for allergic responses.
- They can only be applied to medications that need a very low plasma concentration to work.
- The medication's route is inappropriate for medications that cause skin irritation or sensitisation.

Factors For Topical Drug Delivery System

The interaction of multiple elements determines the effectiveness of topical medication administration.

- Physiological factors,
- Physicochemical properties of the drug,

- Formulation components and their interactions.

The primary focus of physiological considerations is the skin's characteristics, including its thickness, degree of moisture, and density of hair follicles. These characteristics may show significant individual variation based on factors including age, gender, race, anatomical location, overall health, and environmental factors like humidity and temperature. The rate-limiting step for topical medication distribution should be located in the formulation rather than the biological barrier in order to reduce the impact of such physiological variability. The physicochemical characteristics of the medicine nearly always affect how easily it diffuses through the topical medium as penetration of the mucosal membranes or skin.Additionally, the formulation component affects the vehicle's viscosity and consistency, which in turn affect the vehicle's adhesion and retention qualities.

CONCLUSION:

Targeting the medicinal action directly to the site of disturbance is the main benefit of topical drug delivery, as it allows buildup of a high local drug concentration for improved drug activity both inside the tissue and surrounding it. It also has a high patient acceptance rate. Topical distribution is usually the preferable way of medicine administration when another technique has a lesser bioavailability. Clinical evidence suggests that topical gel is a safe and efficient treatment option for the treatment of skin-related conditions. Clinical data from its uses demonstrates that pharmaceutical gel offers a secure and efficient remedy for skin-related issues other topical illnesses. According to clinical data, topical gel is a safe and efficient therapy choice for managing skin-related conditions. It works locally to lessen the negative effects of other traditional dosage forms

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