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A Comprehensive Review on Gel as Transdermal Drug Delivery

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ABSTRACT

The goal of this review was to compile recent literature with a special emphasis on a rational approach to topical formulation and basic components of topical drug delivery systems. Topical drug delivery systems include a wide range of pharmaceutical dosage forms such as semisolids, liquid preparations, sprays, and solid powders. A gel is a cross-linked polymer network that has swollen in a liquid medium. Its properties are heavily influenced by the interaction of the solid-state polymer and the liquid component. The semisolid state is caused by increased viscosity as a result of interlacing and the resulting internal friction. Because they are less greasy and can be easily removed from the skin, topical gel formulations are an ideal drug delivery system. In comparison to creams and ointments, gel formulations have superior application properties and stability.

INTRODUCTION:

Topical drug delivery is the application of a drug through the skin to treat or cure skin disorders. These topical drug delivery systems are typically used for local skin infections such as fungal infections or when other routes of administration are ineffective. [1] It can penetrate deeper into the skin, resulting in better absorption. The topical application offers no advantages over traditional dosage forms. Because of their bilayered composition and structure, they are generally thought to be more effective and less toxic than conventional formulations. Attempts have been made in the formulation of topical dosage forms to use drug carriers that ensure adequate localization or penetration of the drug within or through the skin to enhance the local and minimize the systemic effects or to ensure adequate Percutaneous absorption. [2] Topical preparations reduce GI irritation, inhibit drug metabolism in the liver, and increase drug bioavailability. Topical preparations act directly at the site of action. A gel is a two-component, three-dimensional network of structural materials that is cross-linked. The gel network's structural materials can be made up of inorganic particles or organic macromolecules, primarily polymers. [3]

Topical Drug Delivery System: The substance that brings a specific drug into contact with and through the skin is referred to as a topical delivery system. The transport of topical drugs across the skin barrier is a challenge. There are two basic types of products used in topical delivery:

✓ External topical that is spread, sprayed, or otherwise dispersed onto cutaneous tissues to cover the affected area.

✓ Internal topical that is applied to the mucous membrane orally, vaginally, or on anorectal tissues for local activity.

The majority of topical preparations are used for localized effects at the site of application due to drug penetration into the underlying layers of skin or mucous membranes. Although some unintended drug absorption may occur, it is in subtherapeutic quantities and is generally of minor concern.

Advantages:

✓ Easily terminate the medications, when needed.

✓ Avoidance of the first-pass metabolism.

✓ Avoidance of gastro-intestinal incompatibility.

✓ Convenient and easy to apply.

✓ A quite large area of application in comparison with the buccal cavity.

✓ Prevents fluctuation in drug levels, inter-and intrapatient variations.

✓ Improved patient compliance.

✓ Avoidance of risks and inconveniences of the intravenous therapy and of diverse conditions of absorption like pH changes, presence of enzymes, gastric emptying time.

✓ Deliver drugs more selectively to a specific site.

✓ Achievement of effectiveness with a lower total daily dose of the drug by continuous drug input.

✓ Providing utilization of drugs with a short biological half-life, narrow therapeutic window.

✓ Provide suitability for self-medication.

✓ Ability to deliver drugs more selectively to a specific site. [1, 4]

Disadvantages:

- Drugs with larger particle sizes can't be easily absorbed through the skin.
- Can be used only for those drugs which need very small plasma concentration for action.
- Skin irritation or dermatitis may occur due to the drug or excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergic reactions.
- The route is not suitable for those drugs that irritate or sensitize the skin[1, 4, 5].

Anatomy of Skin: The skin is a complex organ that covers the entire body's surface. It serves as a physical barrier between the body and the environment, preventing the loss of water and electrolytes, reducing chemical penetration, and protecting against pathogens and microorganisms. The skin is important for thermoregulation and immunological monitoring

because it contains sensory and autonomic nerves as well as sensory receptors that detect incoming stimuli such as touch, vibration, pressure, temperature, pain, and itching.

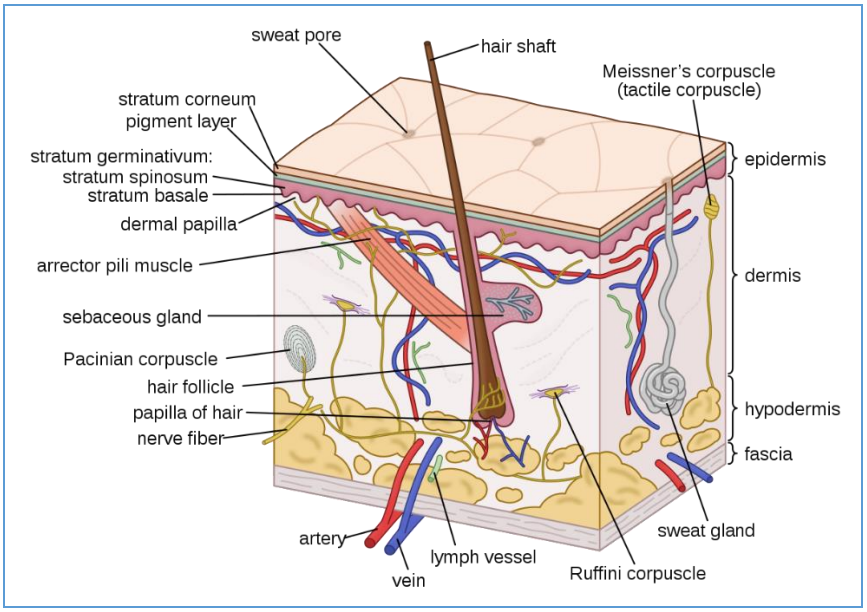

Figure 1: Structure of Skin

The skin is an important aspect of one's appearance, and it is the primary focus of many surgical and non-surgical skin procedures. Patients who experience chronological skin changes or photoaging skin changes such as wrinkles, laxity, and pigmentation are more likely to undergo cosmetic procedures to improve the appearance of their skin[6].

The layer of Skin:

Epidermis: The epidermis is the most superficial layer of the skin and consists of keratinized stratified squamous epithelial which varies in thickness in different parts of the body. The palms and soles of the feet are the thickest there are no blood vessel or nerve endings in the epidermis but the deeper layer penetrates the interstitial fluid of the dermis providing oxygen and nutrients and draining the asymptotes epidermis are the several layer of the cell and that prolong from the deep of the embryonic layer and to the superficial stratum corneum superficial cells are flat, thin nuclear free dead cells or squamous cells in which the cytoplasm is replaced by protein keratin these cells are constantly being erased and replaced by cells originating from the cotyledon and gradually migrate to the surface it takes about 40 days to completely replace the epidermis hair sebum and sweat ducts pass through the epidermis and reach the surface the surface of epidermis protrudes from the cellular projection of the dermis called papillae the pattern of bridges very from person to person and the impression they give

a fingerprint the down word protrusion of the germ layer between the papillae is believed to support the nutrition of the epidermal cells and stabilize the two lays to prevent shear damage acute trauma causes dermis and epidermis to separate and accumulation of serous fluid leads to blistering [7].

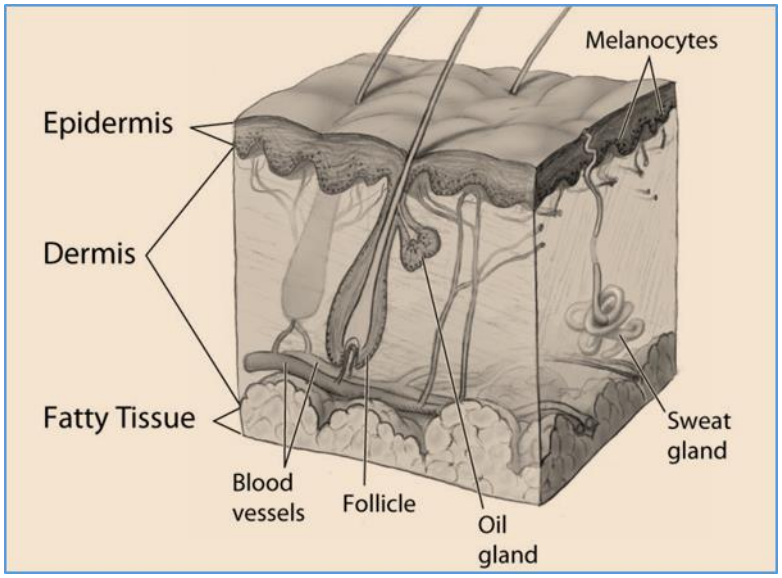

Figure 2: Layers of Skin

Classification of epidermis

- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basale

Dermis: The dermis is flexible and elastic; it is made up of a matrix that contains connective tissue and collagen fibers that are woven into elastic fibers. When the skin is overstretched, elastic fiber breaks occur, resulting in permanent stretch marks and obesity. Collagen fibers bind to water, giving the skin tension, but as this ability declines with age, wrinkles appear. The most important cells in the dermis are fibroblasts, macrophages, and mast cells. The areola and varying amounts of adipose tissue are located at the base of the innermost layer (fat).

- The dermis is divided into some structure.

- Blood vessel
- Lymph vessel
- A sensory (somatic) nerve ending
- Sweat gland and their ducts
- Hairs Arrector Pilli muscles and sebaceous gland

Hypodermic or Sub- Cutaneous Tissue: The hypodermic or subcutaneous tissue supports the epidermis and dermis, acts as a store and fat, and this layer helps regulate temperature, provides nutritional support, and mechanical protection, transports major blood vessels and nerves to the skin and contains the senses. Drugs must pass through three layers to reach the systemic circulation [8].

GELS

Gels are defined as semi-rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of the dispersed phase.

The word ‘‘gel’’ is derived from ‘‘gelatin,’’ and both ‘‘gel’’ and ‘‘jelly’’ can be drawn back to the Latin gelu for ‘‘frost’’ and gel are, 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. The use of the term ‘‘gel’’ as a classification originated during the late 1800s as chemists attempted to classify semisolid substances according to their phenomenological characteristics rather than their molecular compositions. At that time, analytical methods needed to determine chemical structures were lacking [9].

Gels are more rigid than jellies because they have more covalent crosslinks, a higher density of physical bonds, or are simply less liquid. Gel-forming polymers generate materials with varying degrees of rigidity, beginning with sol and progressing to mucilage, jelly, gel, and hydrogel.

Some gel systems are as clear as water, while others are turbid because the ingredients are not completely molecularly dispersed (soluble or insoluble) or form aggregates that scatter light. With a few exceptions, the concentration of the gelling agents is typically less than 10%, typically in the 0.5 percent to 2.0 percent range[10].

Structure of Gel: The rigidity of a gel arises from the presence of a network formed by the interlinking of particles' gelling agent. The nature of the particles and the type of force that is responsible for the linkages, which determine the structure of the network and the properties of the gel.

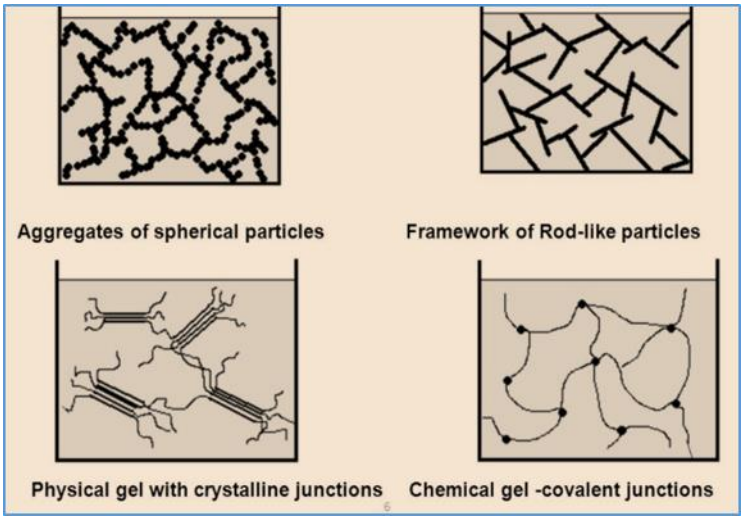

Figure 3: Structure of Gel

The individual particles of the hydrophilic colloid may consist of either spherical or an isometric aggregate of small molecules, or single macromolecules. Possible arrangements of such particles in a gel network [11]. In linear macromolecules the network is comprised of entangled molecules, the point of contact between which may either be relatively small or consist of several molecules aligned in a crystalline order, as shown in Figure 1 (c) and (d), respectively. The forces of attraction responsible for the linkage between gelling agent particles may range from strong primary valencies, as in silicic acid gels, to weaker hydrogen bonds and Vander Waals forces. The weaker nature of these latter forces is indicated by the fact that a slight increase in temperature often causes liquefaction of gel.

Properties of Gels [10, 12, 13, 14]

✓ It should have a suitable anti-microbial agent.

✓ Ideally, the gelling agent must be inert, safe, and cannot react with other formulation constituents.

✓ The topical gel must not be sticky.

✓ The gelling agent should produce a sensible solid-like nature at the time of storage which is easily broken when exposed to shear forces produced by squeezing the tube, trembling the bottle, or at the time of topical application.

✓ They exhibit the mechanical characteristics of the solid-state.

✓ 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.

✓ There is a high degree of attraction amongst the dispersed phase and water medium so the gels remain equally uniform upon standing and don't freely settle.

✓ Each component is continuous throughout the system.

Characteristics of Gels:

A) Swelling: When a gelling agent is kept in contact with a liquid that solvates it, then an appreciable amount of liquid is taken up by the agent, and the volume increases. This process is referred to as swelling. This phenomenon occurs as the solvent penetrates the matrix. Gel-gel interactions are replaced by gel-solvent interactions. The degree of swelling depends on the number of linkages between individual molecules of gelling agent and on the strength of these linkages.

B) Syneresis: Many gels often contract spontaneously on standing and exude some fluid medium. This effect is known as syneresis. The degree to which syneresis occurs, increases as the concentration of gelling agent decreases. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. The mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels. As these stresses are relieved, the interstitial space available for the solvent is reduced, forcing the liquid out.

C) Ageing: Colloidal systems usually exhibit slow spontaneous aggregation. This process is referred to as aging. In gels, aging results in the gradual formation of a denser network of the gelling agent. Theimer suggests that this process is similar to the original gelling process and continues after the initial gelation since the fluid medium is lost from the newly formed gel.

D) Structure: The rigidity of a gel arises from the presence of a network formed by the interlinking of particles of the gelling agents. The nature of the particle and the type of force that is responsible for the linkages determine the structure of the network and the properties of the gel.

E) Rheology: Solutions of the gelling agents and dispersion of flocculated solid are pseudoplastic i.e. exhibiting Non-Newtonian flow behavior, characterized by a decrease in viscosity with an increase in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by applied shear stress due to the breaking down of interparticulate association, exhibiting a greater tendency to flow. Similarly, for macromolecules the applied shear stress aligns the molecules in the direction of stress, straightening them out and lessening the resistance to flow [15, 16].

Classification of Gels [14,17]: Gels can be classified based on colloidal phases, nature of the solvent used, physical nature and rheological properties, etc.

Colloidal Phases: They are classified into:

a) Inorganic (Two-Phase System): If the partition size of the dispersed phase is relatively large and forms the three-dimensional structure throughout gel, such a system consists of floccules of small particles rather than larger molecules and gel structure, in this, the system is not always stable. They must be thixotropic-forming semisolid on standing and become liquid on agitation.

b) Organic (Single Phase System): These consist of large organic molecules existing on the twisted strands dissolved in a continuous phase. These larger organic molecules either natural or synthetic polymers are referred to as gel formers, they tend to entangle with each other in their random motion or are bound together by Vander walls forces.

Based on Nature of Solvent: They are classified into:

Hydrogels (Water-based): A hydrogel is a network of hydrophilic polymer chains, infrequently found as a colloidal gel in which water is a dispersion medium. They are highly absorbent natural or synthetic polymeric networks. They also have a degree of flexibility likely to the natural tissue, due to their significant water content.

Organogels (With a Non-Aqueous Solvent): An organogel is a non-crystalline, non-glassy thermoreversible solid material composed of a liquid organic phase trapped in a 3D cross-

linked network. The liquid can be, E.g., vegetable oil, an organic solvent, or mineral oil. The solubility and particle sizes of the structurant are significant characteristics for the elastic properties and firmness of the organogel. Frequently, these systems are based on the self-assembly of the structurant molecules.

Xerogels: It is a solid formed from a gel by drying with unrestricted shrinkage. It frequently retains high porosity (15-50%) and a huge surface area (150-900 m2/g), along with a very small pore size (1-10 nm). When the solvent is removed under supercritical conditions, the network doesn't shrink and a highly porous, low-density material is known as an aerogel is produced. Heat treatment of a xerogel at higher temperature produces viscous sintering and efficiently transforms the porous gel into a thick glass. E.g., Tragacanth ribbons, β-cyclodextrin, dry cellulose and polystyrene, gelatin sheets, and acacia tears.

Based on rheological properties: Usually, gels exhibit non-Newtonian flow properties. They are classified into:

a. Plastic gels: E.g., Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow, and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

b. Pseudo plastic gels: E.g., Liquid dispersion of tragacanth, sodium alginate, Na CMC, etc. exhibits pseudo-plastic flow. The viscosity of these gels decreases with an increasing rate of shear, with no yield value. The rheogram results from a shearing action on the long-chain molecules of the linear polymers. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with the release of solvent from the gel matrix.

c. Thixotropic gels: The bonds between particles in these gels are very weak and can be broken down by shaking. The resulting solution will revert to gel due to the particles colliding and linking together again (the reversible isothermal gel-sol-gel transformation). This occurs in a colloidal system with non-spherical particles to build up a scaffold-like structure.

E.g., Kaolin, bentonite, agar, etc.

Based on Physical Nature: They are classified into:

Elastic gels: Gels of agar, pectin, Guar gum, and alginates exhibit elastic behavior. The fibrous molecules are linked at the point of the junction by comparatively weak bonds like hydrogen bonds and dipole attraction. If the molecule possesses a free -COOH group then additional bonding takes place by a salt bridge of type -COO-X-COO between two adjacent strand networks. E.g., Alginate and Carbopol.

Rigid gels: This can be formed from macromolecule in which the framework is linked by primary valence bonds.E.g., In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

Preparation of Gels [18, 19]: Gels are normally in the industrial scale prepared under room temperature. However, few polymers need special treatment before processing. Gels can be prepared by following methods:

1. Thermal changes: Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reduced, the degree of hydration is decreased and gelation takes place. (Cooling of a concentrated hot solution will produce a gel). E.g., Gelatin, agar sodium oleate, guar gummed, cellulose derivatives, etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduce solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

2. Flocculation: Here gelation is produced by adding just a sufficient quantity of salt to precipitate to produce an aging state, but inadequate to bring about complete precipitation. It is essential to ensure quick mixing to avoid local high concentrations of precipitant.E.g., a Solution of ethylcellulose, polystyrene in benzene can be gelled by quick mixing with suitable amounts of a non-solvent such as petroleum ether. The adding of salts to hydrophobic solution brings about coagulation, gelation is infrequently observed. The gels formed by the flocculation method are Thixotropic in behavior. Hydrophilic colloids such as gelatin, proteins, and acacia are only affected by high concentrations of electrolytes, when the effect is to “salt out”, the colloidal and gelation doesn’t occur.

3. Chemical reaction: In this method gel is produced by chemical interaction between the solute and solvent. E.g., Aluminium hydroxide gel can be prepared by interaction in an

aqueous solution of an aluminum salt and sodium carbonate an increased concentration of reactants will produce a gel structure. Few other examples involve chemical reactions between PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), methane diphenyl isocyanide (MDI) that cross-links the polymeric chain.

Uses: In the pharmaceutical and cosmetic industry, the gel may be enumerated to have the following uses [16]

1. As delivery systems for orally administered drugs.
2. To deliver topical drug applied directly to the skin, mucus membrane, or the Eye.
3. As long-acting forms of drug injected intramuscularly.
4. As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid, and suppository bases.
5. In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations.
6. The bulk property of swelling is of particular interest for swelling implants, which can be implanted in a small, dehydrated state via a small incision and which then swell to fill a body cavity and/or to exert a controlled pressure.

CONCLUSION:

Gels are becoming increasingly popular because they are more stable and can provide controlled release than other semisolid preparations such as creams, ointments, pastes, and so on. The gel formulation may provide better absorption characteristics, increasing the drug's bioavailability. A thorough investigation into the gel formulation's stability characteristics over an extended period may provide scope for its therapeutic use in patients. Because the polymer is water-soluble, it forms a water washable gel and has a greater potential for use as a topical drug delivery dosage form. The clinical evidence indicates that topical gel is a safe and effective treatment option for the treatment of skin diseases.

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