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Recent Approaches and Applications of Topical Gel as a Novel Drug Delivery

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ABSTRACT

Topical formulations provide both systemic and local effects that are generally applied to the skin. A topical gel is one such formulation meant for topical use. They are defined as semisolid preparations where the drug is dispersed in the liquid medium. As it enhances the delivery of the drugs, they are used widely. Gels are 3D (3 dimensional) structures that are made of either natural or synthetic polymers which are interlinked by physical, chemical, or ionic interactions. Gels are classified based on the nature of the colloidal system, solvent system, rheological properties, and physical nature. As topical gels have gained their advantages, it raised to the development of novel approaches like hydrogel, emulgel, organogel, etc. There are different methods of preparing gels like- cold method, chemical method, dispersion method, flocculation method, and due to thermal changes. This review article deals with the information about the various aspects like classification, novel approaches, applications, mechanism of formation of gels, method of preparation, and evaluation parameters.

ABBREVIATIONS:

Table No. 1: List of abbreviations

Short-form	Abbreviations
3D	3 Dimensional
%	Percentage
USP	United States Pharmacopeia
pH	Potential of Hydrogen
m^2/g	Square meter per gram
nm	Nanometre
<	Less than
µm	Micrometre
i.e.;	That is
°C	Degree Celsius
h	Hour
o/w	Oil-in-water
w/o	Water-in-oil
TEA	Triethanolamine
UV radiation	Ultra Violet radiation
Da	Dalton
RPM	Revolutions per minute
g	Gram
ml	Millilitre
cm	Centimeter
sec	Second
mg	Milligram
±	Plus or minus

INTRODUCTION

Delivery systems are deliberate chemical entities that carry a chosen active component & delivers to the site of action[1]. Topical preparations are applied to the skin for both local and systemic effects. Topical drug delivery can be defined as the application of the

pharmaceutical dosage form to the skin for the direct treatment of cutaneous disorder or manifestation, by limiting the pharmacological effect of the drug to the skin's surface [2,3,4,5].

A topical formulation must have pleasing appeal, in addition to physical and chemical stability[6]. Topical application pertains to a particular surface area of the skin and affects only that area to which it is applied. Two major outcomes are desired as a result of the application of topical formulations. The first outcome is to support and restore the barrier function of the skin. The second outcome is to improve skin condition, by, not only transporting an active compound into the skin but by maximizing its effectiveness as well[1]. The topical preparations are more advantageous than other routes because they reduce the side effects, ease in the application, non-invasive and painless[3,6]. The USP defines gels as a semisolid system containing a dispersion made of either a large organic molecule or small inorganic particle surrounded and interpenetrated by a liquid. The inorganic unit forms a 3D structure that resembles "the house of cards". Therefore a gel is a two-phase system in which an inorganic particle is dispersed throughout the continuous phase and the organic particle is dissolved in the continuous phase that is randomly wound inflexible chains[7]. They are linked by either ionic or chemical or physical interactions. The gels have several advantages when compared to other topical preparations like - non-greasy, retention of gels are higher, have excellent spreadability, used for the formulation of controlled release dosage form by interlinking with polymers. The disadvantages include poor permeability across the skin, some gels are unstable due to the floccule present in them, temperature, humidity, other environmental factors may affect the rheology of the formulation, gelling agents may undergo precipitation which results in the salting-out effect, drying of the gels occur due to the solvent evaporation[8,9]. As the gels have a pronounced effect on the delivery of drugs, this is a major area for research. Hence, many are focusing on gels to enhance the delivery of drugs or have controlled release or enhance the bioavailability of the therapeutic agent. Teerasak D *et al.,* developed glutaryl melatonin niosome gel for topical oral mucositis and it showed mild anti-candidiasis and anti-inflammatory properties [10]. Aney SJ, Nida M prepared herbal topical gel containing alcoholic extract of leaves of *Andrographi spaniculata* using carbopol 934. The results inferred that the gel formulations are good in physical appearance, homogeneity, and spreadability[11]. Tawfeek HM *et al.* developed metformin hydrochloride hydrogel by using different gelling agents and was found that it showed good wound healing property[12]. Perinbam K *et al.,* formulated povidone-iodine loaded film forming a topical gel and found that the optimized formulation showed better consistency,

spreadability, and adhesiveness [13]. Kusuma SAF *et al.* formulated an anti-acne gel containing *Citrus aurantifolia* fruit juice by using carbopol as a gelling agent and found that carbopol used at 1 % concentration produced a stable gel with good Physico-chemical properties[14]. Kasar PM *et al.* developed topical gel containing itraconazole for treating both local and systemic fungal infections as oral formulation has pronounced side effects. They prepared topical gels using different polymers like carbopol 934P and HPMC in different ratios which then concluded that they showed better release profile aiding in treating fungal infections[15]. Shukr MH *et al.,* designed topical gel using carbopol 940 containing various essential oils possessing anti-bacterial actions. Further evaluated for the anti-bacterial activity by determining the minimum inhibitory concentration and concluded that gels containing lemongrass oil and thyme oil showed better antibacterial activity and possess no skin irritation[16]. Thakur V *et al.,* aimed at developing a gel containing fluconazole as an anti-fungal agent using different penetration enhancers like tween 80, oleic acid, propylene glycol. It was determined that tween 80 showed better penetration than oleic acid and propylene glycol and the change in pH was negligible[17]. Tanwar YS *et al.,* formulated prolonged-release diclofenac sodium gel with a high concentration of the gelling agent for prolonging the duration of the release of complete drug[18]. The present review focuses on the recent approaches, applications in the development of topical gels as drug delivery.

Properties of gels:

- It should be inert, non-toxic, and compatible with other ingredients.
- It should be convenient in handling and on application.
- It should maintain the rheological property during storage.
- It should be non-greasy and possess emollient and thixotropic property.
- The topical gel should not be gummy.
- The gelling agent incorporated in the preparation should produce a solid-like consistency during storage and should be easily destroyed when it is subjected to shear forces produced during the topical application, or by shaking the bottle or squeezing the bottle[3,7,9,19,20,21,22,23,24].

Characteristics of gel:

1. **Structure:** The formation of networks due to the interlinking of gelling agents are the reason for the rigidity of the gel. The nature of the particle and type of force is accountable for the property of the gel and the structure of the network.

2. **Rheology:** The dispersion of flocculated solids and the solutions of the gelling agents are pseudo-plastic which shows Non-Newtonian flow behavior. The weak structure of the inorganic particles dispersed in water will be disrupted on the application of shear stress due to the breaking down of inter-particulate association, having a greater tendency to flow.

3. **Syneresis:** Many gels frequently contract spontaneously and exudes the fluid medium which is collectively called syneresis. This is due to the relaxation of elastic stresses which are developed during the setting of the gels. When these stresses are removed, the interstitial spaces which are available for the solvent decreases, leading to the manifestation of the fluid. This effect is primarily noticed in organogels, inorganic hydrogels, but are absent in hydrogels. The degree of syneresis increases with the decrease in the concentration of polymer.

4. **Swelling:** If a gelling agent is kept in contact with the solvent, a significant amount of liquid is absorbed and there will be an increase in the volume (act as an initial phase of dissolution). This process is called as swelling. During this process, the solvent penetrates the gel matrix replacing the gel-gel interactions with gel-solvent interactions. The process of swelling is limited as the degree of cross-linking prevents the dissolution.

5. **Aging:** Colloidal systems typically show a slower rate of aggregation, which is collectively called as aging. This results in the gradual formation of a denser network of the gelling agent.[7,19,20,22,23,24,25]

Structure of gels:

A gel comprises either natural or synthetic polymer creating a 3D matric throughout the dispersion medium. On application, the liquid evaporates leaving behind the drug, which then gets entrapped in a thin film of gel-forming matrix covering the skin[25] (represented in Figure No. 1).

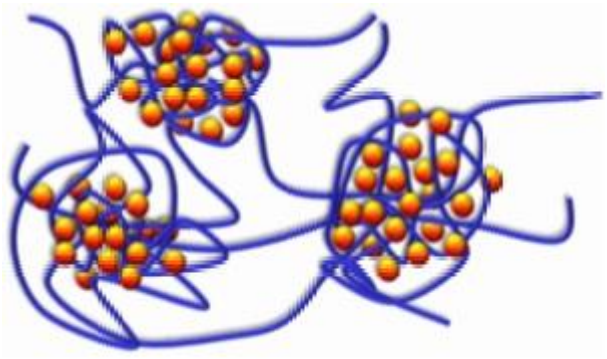

Figure No. 1: Structure of gel (drug being entrapped into the polymer)[25].

The interlinking of gelling agents creates networks that are responsible for the rigidity of the gel[20]. The nature of the particles and the type of force involved in the formation of linkages determine the structure and property of the gel[26]. If the polymeric particles are spherical or isometric aggregates of small molecules or single macromolecule, the arrangements of the particles can be represented in Figure 2 (a,b). If the macromolecules are linear, the networks formed are due to the entanglement of the molecules either relatively small or contains several molecules associated in a crystalline fashion, which can be depicted in Figure 2 (c,d). The different types of forces responsible for interlinking are; Vander Waals force, weak hydrogen bond, strong bonds. If the linkages are due to weaker forces, the increase in temperature often causes the liquefaction of the gel[22,26].

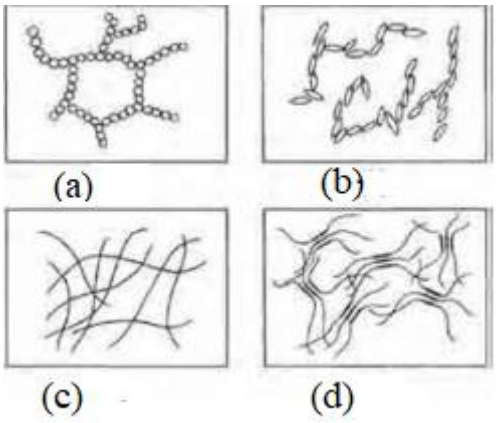

Figure No. 2: (a) Flocculated particles in 2 phase gel structure. (b) The network of elongated particles forming a gel structure. (c) Matted fibers found in soap gels. (d) Crystalline and amorphous regions in the gel of carboxymethylcellulose[22].

Classification of gel:

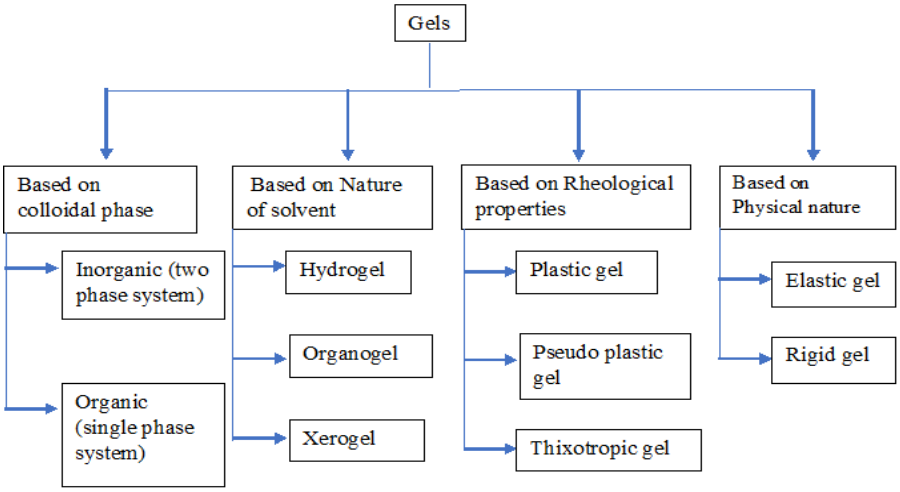

Figure No. 3: Classification of gels[25,26,27].

1. Based on Colloidal phase:

a) Inorganic (two-phase system): As the particle size of the dispersed phase is comparatively large, they form a 3D structure throughout the gel. As it consists of floccules of small particles rather than larger molecules, hence the gel structure is not stable. On standing they should be thixotropic-forming semisolids and on agitation, it should return to the liquid state.

Example: Aluminium hydroxide gel USP.

b) Organic (single-phase system): It is composed of larger organic molecules that exist as twisted strands dissolved in a continuous phase. These molecules are either natural or synthetic polymers which are collectively referred to as gel formers. They entangle with each other by Vander Waal's force of attraction.

Example: Carbopol, Tragacanth.

1. Based on the nature of the solvent:

a) Hydrogel: Water is the continuous liquid phase.

Example: Poloxamer gel, Cellulose derivatives, Gelatin, Bentonite magma.

b) Organogel: Non-aqueous phase acts as the continuous phase. These are generally non-glossy, non-crystalline, thermo-reversible solid material in which the liquid organic phase is being trapped in a 3D cross-linked network. These liquids can be a vegetable oil, mineral oil, or organic solvent.

Example: Dispersion of metallic stearate in oils.

c) Xerogel: These are generally gels that are composed of solid components obtained on drying with shrinkage. It regularly retains a large surface area ranging from 150-900 m^2/g with a porosity of 15-50 % having a very small pore size of about 1-10 nm. If the solvent is removed under supercritical conditions, the network doesn't shrink rather highly porous, low-density material is obtained which is known as aerogel.

Example: Acacia tear, polystyrene, β-cyclodextrin, Tragacanth ribbons, and Dry cellulose.

2. Based on the Rheological properties (follow Non-Newtonian flow properties):

a) Plastic gel: They generally exhibit plastic flow. The plot of rheogram predicts that the yield value of the gels above the elastic limit alters the flow properties.

Example: Bingham bodies, flocculated suspensions of Aluminium hydroxide.

b) Pseudo plastic gel: They exhibit a pseudo-plastic flow. As the rate of shear increases, the viscosity of the gel decreases.

Example: liquid dispersion of tragacanth, sodium alginate, sodium CMC, etc.

c) Thixotropic gel: As the linkages between the particles are very weak and gets broken on shaking. This is due to the reversible isothermal gel-sol-gel transformation. This occurs in colloidal systems having non-spherical particles.

Example: Kaolin, Agar, Bentonite.

3. Based on Physical nature:

a) Elastic gel: They show elastic behavior.

Example: Alginate, Guar gum, Gels of agar, Pectin.

b) Rigid gel: This is formed by macromolecules, the linkages are due to the primary valence electron.

Example: In silica the pores are due to Si-O-Si-O bond[3,7,9,19,20,21,22,23,24,25,26].

Novel approaches in topical gel preparation:

1) Hydrogel: Hydrogels are also called as hydrophilic gels. They are the polymeric networks of 3D crosslinked structure that can absorb large amounts of water nearly 10-20 times its molecular weight and gets swollen[21]. They can be either chemically robust or ultimately disintegrate and dissolve. The hydrogels swell by molecular entanglements and /or secondary forces of attraction such as hydrogen bonding or ionic bonding, hence they can be termed as 'reversible gel' or 'physical gel'. The water-absorbing property of the hydrogels is due to the presence of the hydrophilic functional group which is being attached to the polymer backbone, and the resistance to dissolution is due to the cross-linkers between the particles. The water present inside the hydrogel allows the dissolution of solute molecules, while the polymer serves as the matrix to hold the water together[28,29].

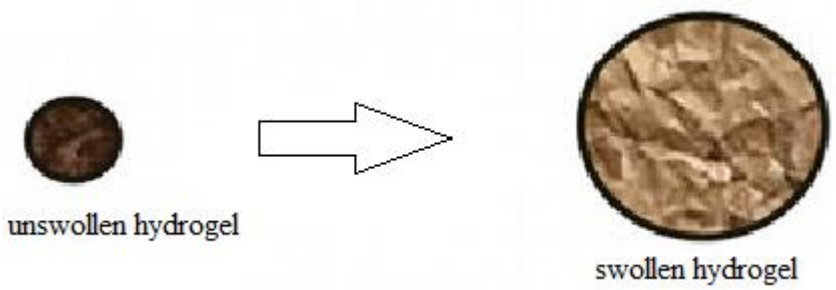

Figure No. 4: Diagram of the hydrogel[28].

The advantages of hydrogels are as follows:

- They are easy to modify.
- They are biocompatible.
- Environmentally sensitive hydrogels can sense the changes of pH, temperature, the concentration of the metabolite, release pattern due to these changes.
- They have applications in tissue engineering.

The disadvantages of hydrogels are as follows:

- Difficult in sterilizing.
- Possess low mechanical strength.
- It is difficult to load the drug.
- They are non-adherent.
- High cost[21,29,30,31].

2) Emulgel: Emulgels is basically the combination of emulsions and gels. They were developed for the delivery of hydrophobic drugs. The emulsion can be either o/w or w/o emulsions, where o/w systems directly entrap the lipophilic drugs whereas the w/o systems encapsulate the hydrophobic drugs[2,7]. The emulsion encountering for the emulgels are biphasic systems where one immiscible liquid is dispersed into other. This arises the stability issues which can be stabilized by the use of emulsifying agents. The gels encountering emulgels can swell in the presence of fluid within its structure[33].

The advantages of emulgel are:

- Site-specific drug delivery.
- Used for drugs having shorter half-life to prolong its release.
- Low production cost.
- It has better stability and loading capacity.
- Improves patient compliance.
- Used for the delivery of hydrophobic drugs.

The disadvantages of emulgel are:

- Drugs with larger particles don’t absorb.
- Some drugs possess poor permeability through the skin.
- It causes skin irritation or an allergic reaction.

- Formation of bubbles during the preparation of emulgel.[2,7,32,33]

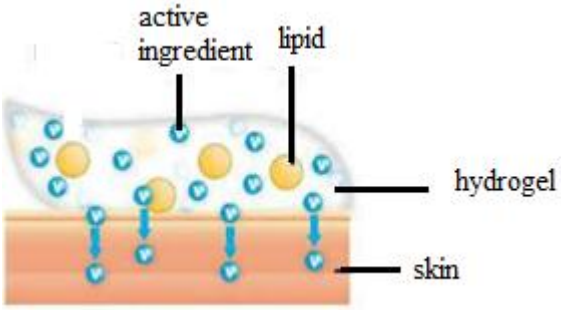

Figure No. 5: Structure of emulgel[34].

3) Organogel: Organogels are viscoelastic system which contains an immobilized external non-polar phase. This non-polar phase gets immobilized inside the spaces to form a 3D network by physical interactions among the gelators[2]. Generally, organogels are thermodynamically stable and can be used for the delivery of bioactive agents. Organogels are bi-continuous systems containing gelators and non-polar solvent which may or may not contain water molecules entrapped in the structures of the gelators[36]. The concentration of the gelators with < 15 % may result in the formation of the 3D structure. The formed 3D structure may prevent the flow of the external phase[2,35].

The advantages of organogels are:

- Have a longer shelf-life.
- Ease of preparation.
- They are chemically and thermodynamically stable.
- The structural integrity is maintained for a longer period.
- Both hydrophilic and lipophilic drugs can be incorporated as they are composed of both hydrophilic and lipophilic components.
- They improve skin permeability[2,35,36].

4) Solid lipid nanoparticle-based gel (SLN): SLN is a novel potential colloidal carrier system. They are composed of the solid hydrophobic core having a monolayer of

phospholipid coating with size ranging from 10-1000 nm. The hydrophobic chains in phospholipids have the potential to carry lipophilic and hydrophilic drugs.

The advantages of solid lipid nanoparticles are:

- They possess better stability than liposomes.
- They enhance the bioavailability of the entrapped molecules.
- They have a site targeted action.
- They enhance the permeation of the drugs across the skin.
- They enhance the bioavailability of poorly soluble drugs[21,37,38].

5) Ethosomes based gel: Ethosomes are also called as ethanolic liposomes. They can be defined as non-invasive carriers that are composed of lipid vesicles containing phospholipids, water, alcohol is the relatively very high concentration (final product contains alcohol of about 20 % - 30 %), whose size ranges from 10 nm – 1 µm[2,39,41].

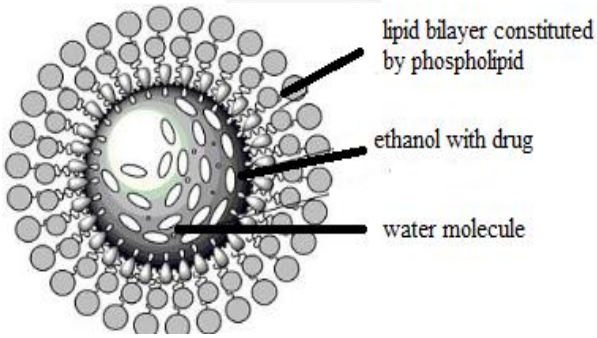

Figure No. 6: Structure of ethosome[39].

The advantages of ethosomes based gels are:

- Better patient compliance.
- Enhanced solubility and stability of the components.
- Improved permeation of the drug[2,21,39-41] .

6) Liposomes based gel: Liposomes are concentric bilayered vesicles which phospholipids arranged in the form of shells. Topical liposomes are more effective and have considerably low toxicity. They can be used for both hydrophilic and lipophilic molecules. These gels can have prolonged and controlled release, hence has better patient compliance.

The advantages of liposomes based gels are:

- Has enhanced stability as the drug is encapsulated.
- It provides passive targeting to tumor cells.
- Reduces the toxicity of encapsulated drugs[21,42].

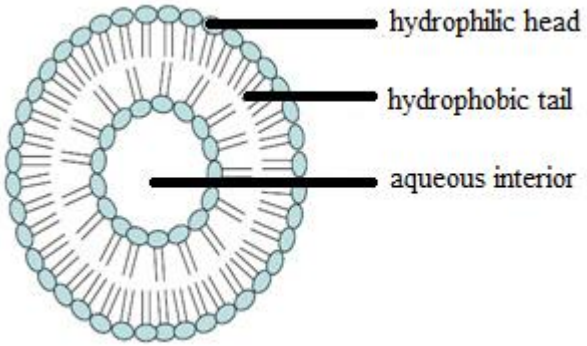

Figure No. 7: Structure of liposome[43].

7) Solid dispersion based gel: It is composed of 2 or more components, mainly a hydrophilic carrier and a hydrophobic drug that are in solid-state. This technique is mainly used for enhancing the solubility and bioavailability of poorly water-soluble drug i.e.; when the solid dispersion is exposed to aqueous media, the drug is released as a result of the dissolution of the carrier.

The advantages of solid dispersion based gels are:

- Enhanced rate and extent of absorption.
- Improves the wettability of the drugs.
- As they are metastable polymeric form, they increase the solubility of the amorphous form particles[21,44].

8) Niosomes based gel: Niosomes are the vesicles which are composed of non-ionic surfactant and cholesterol whose size ranges from 10 nm - 100 nm. They have improved penetrating capacity. They are more stable than liposomes.

The advantages of niosomes based gels are:

- The drug releases in a controlled fashion.
- It can apply to drugs possessing a wide range of solubility.
- They have enhanced the stability of the entrapped drug.
- Improved patient compliance.
- Ease in handling[21].

9) Microsphere based gel: Microspheres are also called as micro-particles. They are generally small spherical particles, which are free-flowing powders consisting of proteins or synthetic polymers which are generally biodegradable. Their size ranges from 1 µm -1000 µm.

The advantages of microsphere-based gels are:

- Reduces the side effects.
- Shows controlled release of drugs.
- Show prolonged therapeutic effects[2].

10) Microsponge based gel: Microsponges are spherical, uniform and porous microspheres having numerous voids, whose particle size ranges from 5 µm – 300 µm. When microsponge based is formulated and applied to the skin, the release of the drug can be controlled through diffusion or by rubbing, pH, moisture, skin temperature.

The advantages of microsponge based gels are:

- It can be used for extended-release.
- They can absorb the oil up to 6 times its weight without drying.

- Have lesser irritation.
- Improved patient compliance[2,21].

Gel forming substances:

The criteria for selecting the polymer for topical preparations are:

- They should be inert, should not react physically or chemically with the drug.
- Should be non-toxic.
- It should be stable and should not undergo decomposition in the presence of the drug and other excipients.
- Should be used for loading a large amount of drugs.
- The properties of the polymer-like molecular weight and chemical functionality should allow the diffusion and release of a specified amount of drug[3,8,19,20].

The polymers can be classified as follows;

1. Natural polymers: These are found naturally and can also be synthesized by living organisms.

a. Proteins: Gelatin, Collagen.

b. Carbohydrates: Tragacanth, Agar, Gillum gum, Alginic acid, Guar gum, Xanthine, Cassia tora.

2. Synthetic polymers: These polymers are prepared under *in vitro* conditions. They are also called as manmade polymers.

a. Carbomer: Carbopol – 940, Carbopol – 934, Carbopol - 941

b. Polyacrylamide

c. Poloxamer

d. Polyvinyl alcohol

e. Polyacrylamide

f. Polyethylene and its copolymer.

3. Semi-synthetic polymers: They are prepared by the chemical modification of the natural polymers. They collectively include cellulose derivatives.

Example: Hydroxypropyl cellulose, Hydroxyethylcellulose, Hydroxypropylethyl cellulose, Carboxymethylcellulose.

4. Inorganic polymers:

Example: Bentonite and Aluminium hydroxide.

5. Surfactants:

Example: Sodium lauryl sulphate, Sebrotearyl alcohol, Cetostearyl alcohol, Brij - 96, Dodecyl pyrinium iodide[3,8,19,20,25,26,45].

Preparation of gel:

They can be prepared on a large scale with 5 different methods. Namely,

1. Cold method: All the ingredients are mixed at a low temperature of about 5 °C to form a homogenous mass. To this, polymer and penetration enhancers are mixed to form solution A. The drug is mixed with the solvent to form solution B. On stirring, solution B is poured into solution A.

2. Dispersion method: The polymer is dispersed completely in water for about 2 h, after which the other excipients are added upon stirring until a homogenous mass is formed.

3. Thermal changes: When lipophilic colloids are subjected to thermal changes, it produces gel i.e.; cooling of the concentrated hot solution will yield gel. The process of gel formation occurs because as the temperature decreases, the degree of hydration is reduced.

Example: Agar sodium oleate, Gelatin, Cellulose derivatives, Guar gum.

Some materials like cellulose ether have their solubility towards water due to the formation of hydrogen bonds with water molecules. As temperature increases, the hydrogen bonds are

disrupted in turn reducing the solubility, which is responsible for the formation of a gel. Therefore, this method cannot be used to prepare gels.

4. Chemical reaction: Gels are produced by the chemical interaction between the solute and solvent molecules. By increasing the concentration of the reactants, the gel structure can be obtained.

Example: a) Aluminium hydroxide gel is produced by the interaction of aluminum salt and sodium carbonate in the aqueous medium.

b) Silica gel is produced by the chemical interaction between sodium silicate and acids in an aqueous medium.

5. Flocculation method: In this method gels are produced by precipitation as a result of the addition of an appropriate quantity of salt to produce age state, but they are inadequate to bring about complete precipitation. The rapid mixing can avoid the locally high concentration of the precipitant. This can be depicted by the help of an example; a solution of ethyl cellulose and polystyrene in benzene can be gelled by rapid mixing using a non-polar solvent like petroleum ether. The addition of salts to hydrophobic substances causes coagulation and gelation can be observed rarely, thus produced gels show thixotropic behavior. On the addition of salts to hydrophilic substances like gelatin, acacia, proteins don't produce gel as a result of the salting-out effect[3,7,9,19,20,21,26].

Method of preparation of:

a. **Hydrogel**:

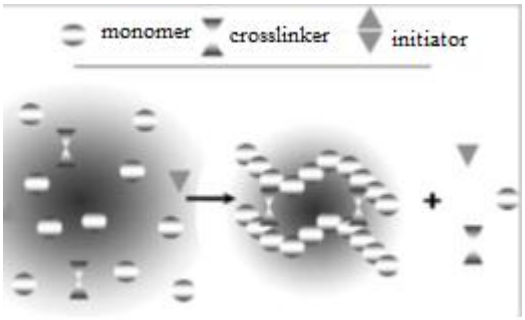

Figure No. 8: Preparation of hydrogel[28].

There are 4 different methods of preparing a hydrogel, namely;

❖ Solution polymerization or cross-linking: This method involves the polymerization of the ionic or neutral monomer with multifunctional crosslinking agents by the use of UV radiation or by the redox initiator system. After the gels are prepared they are washed to remove the unreacted solvents, monomers, initiators by allowing it to swell in the presence of water. The solvent used in this method is – ethanol, water, a mixture of ethanol-water, benzyl alcohol. Heterogeneous hydrogels are formed when the amount of water used during polymerization is more than the amount of water required for swelling.

❖ Bulk polymerization: It is the simplest technique to produce hydrogels, which involves the use of vinyl monomers along with a suitable initiator. The initiator will be selected based on the type of monomer used and the solvent used. The bulk polymerization of the monomer yields a glassy matrix that is hard, and when immersed in water swells to become soft and flexible. The polymerization can be achieved by the use of a chemical catalyst or UV radiation.

❖ Polymerization by radiation: The hydrogels of unsaturated compounds are prepared by ionizing at high energy radiations like gamma rays, electron beam which acts as an initiator. Due to the application of radiation to the aqueous polymer solution, it produces radicals on the polymer chains. The radiolysis of water molecules produces hydroxyl radicals, which attacks the polymer chain to yield macro radicals. The recombination of the formed macro radicals on different chains of the polymer produces a cross-linked structure by the formation of covalent bonds.

Example for the polymers which can be used in this technique is; polyacrylic acid, polyvinyl alcohol, polyethylene glycol. This method is more advantageous than others, as the hydrogels produced are pure and are initiator-free hydrogels.

❖ Suspension polymerization or inverse-suspension polymerization: Instead of using w/o (water-in-oil) process, o/w (oil-in-water) technique is employed, hence indicated as inverse-suspension. The monomers, initiators are dispersed in the hydrocarbon phase until a homogeneous mixture is obtained. The particle size depends on the speed of agitation, viscosity, rotor design, and the medium. As the dispersion is thermodynamically unstable, it requires the use of a low HLB (Hydrophilic-Lipophilic Balance) suspending system[28,30].

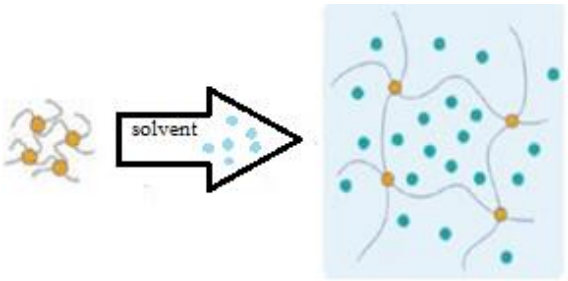

Figure No. 9: Swelling of hydrogel[23].

b. **Emulgel**:

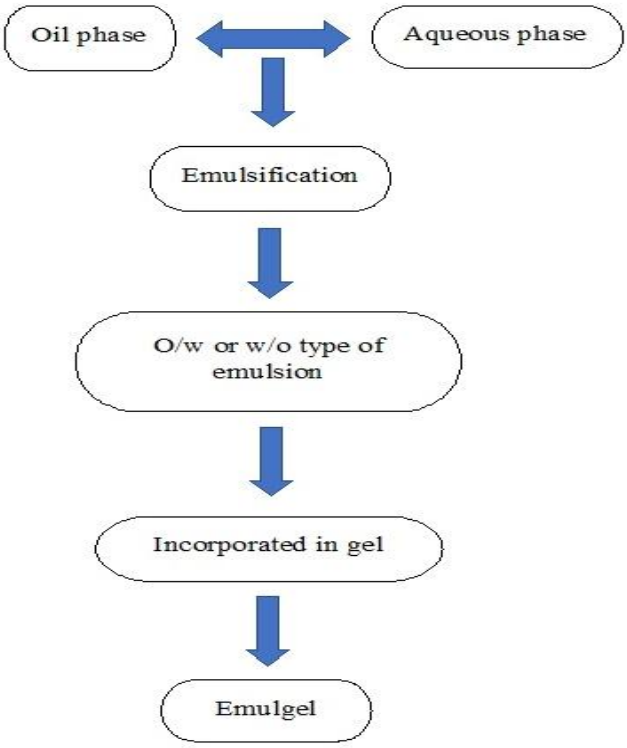

Figure No. 10: Representation of the steps involved in the preparation of emulgel[32,33,34,46,47].

1. Formulation of o/w or w/o emulsion:

a. Preparation of oil phase: The oil phase is prepared by dissolving the oily portion in the emulsifier i.e.; light liquid paraffin is dissolved in span 80.

b. Preparation of aqueous phase: Aqueous phase is prepared by dissolving the aqueous portion in the emulsifier i.e.; tween 80 is dissolved in purified water.

c. Preparation of the drug solution: The drug solution is prepared by dissolving the drug in ethanol.

The drug solution is incorporated into the aqueous phase or oily phase depending on the solubility. Both the phases which are previously heated are mixed by continuous stirring and cooled at room temperature.

2. Formulation of gel base: Polymer is dispersed in purified water by stirring using a mechanical shaker. The pH of the gel is adjusted to 6-6.5 by using TEA.

3. Incorporation of the prepared emulsion into the gel base: The prepared emulsion will be mixed with the gel in the ratio of 1:1 using glutaraldehyde[32,33,34,46,47,48].

Mechanism of gel formation: The gels are formed by 3 types of cross-linking, namely;

1) Ionic cross-linking: The gels are formed due to the ionic bond formation. Ionic bonds are a result of the interaction between the charges present on the polymer and the solvent.

Example: Polysaccharide alginate forms a gel in the presence of the calcium ions which can encapsulate enzymes.

Change in the pH can also yield gel, this can be depicted by the use of an example; pectin at acidic pH produces gel[8].

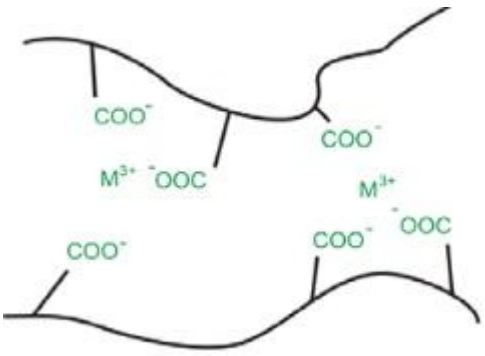

Figure No. 11 A: Ionic cross-linking[8].

2) Chemical cross-linking: When dual or multifunctional monomers are added to a polymer, which results in the formation of a covalent bond between them which are irreversible having large molecular mass. These polymers are insoluble and on the addition of certain solvent causes the swelling of the polymer to yield gel. Chemical cross-linking may be seen in

polymers having unbound groups or free groups in their structure. Due to the irreversible binding they increase the viscosity of the polymer. This can be depicted by the use of an example: Polyacrylic acid with multiple carboxylic acid groups and glycols with hydroxyl groups forms chemical cross-linking[8].

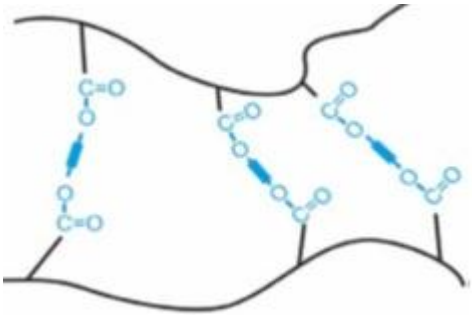

Figure No. 11 B: Chemical cross-linking[8].

3) Physical cross-linking: The gels may be formed due to hydrogen bond, solubilization of the crystalline component, variation in temperature, variation in concentration, hydrophobic interaction. Examples for such gels are; cellulose gels, poly (N-isopropyl acrylamide) gel, dextran gel[8].

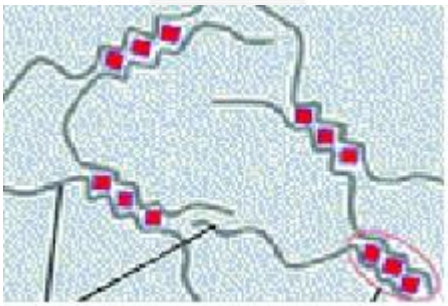

Figure No. 11 C: Physical cross-linking[8].

Transport across the skin and kinetics:[25,49,50,51,52]

The drugs can penetrate through the dense lamellar lipoid matrix of stratum corneum based on their partition coefficient of the drug having complementary physicochemical nature. The rate of permeation across the skin will be given by the equation:

$$\frac{dQ}{dt} = Ps \quad (Cd - Cr)$$

Where;

P_s = permeability constant of the skin penetrant.

C_d = concentration of the skin penetrant in the donor compartment.

C_r = concentration in the receptor compartment.

$$Ps = \frac{KsDss}{hs}$$

Where;

K_s = partition coefficient of the drug.

D_{ss}= apparent diffusivity for the steady-state diffusion.

h_s= thickness of the skin.

At $C_d >> C_r$, the drug permeates at a constant rate and the concentration of the drug at the stratum corneum is greater than the concentration of the drug in the body. At this condition,

$$\frac{dQ}{dt} = PsCd$$

The transport can also be favored by the incorporation of phospholipids. The transport of the drugs will be greatly affected by the molecular size of the particles i.e.; drugs with a molecular size of more than 500 Da cannot penetrate. The topical permeation of the drugs includes the following steps, namely;

1. Sorption by stratum corneum
2. Penetration of drug through the epidermis
3. Uptake of a drug by a capillary system in the dermal papillary layer.

The major process for drug absorption through the skin is passive diffusion. Kinetics of drugs applied topically follows Fick's law of diffusion. As the concentration gradient reaches zero, the diffusion of the drug stops. During passive diffusion, the flux can be expressed as;

$$J = \frac{DPA\Delta C}{h}$$

Where;

J = flux

D = diffusion constant

A = surface area

ΔC = concentration gradient of the drug across the stratum corneum

h = thickness of the stratum corneum.

Practically, the concentration of the drug in the receiver compartment is low than the donor compartment. Hence the above equation can be written as;

$$J = PmAC$$

Where;

P_m = permeability constant

C = concentration of the drug at the site of absorption

Permeability constant can also be written as;

$$Pm = \frac{DP}{h}$$

Evaluation parameters of the topical gel:

1. Physical examination
2. Determination of pH
3. Viscosity
4. Spreadability
5. Extrudability study
6. Homogeneity

7. Grittiness

8. Consistency

9. Percentage yield

10. Drug content

11. *In vitro* diffusion studies

12. Skin irritation study

13. Stability

14. Kinetic study

I. Physical examination: The prepared gels should be evaluated for the organoleptic characters, washability, and occlusive.

II. Determination of pH: The prepared gel will be measure with the help of a digital pH meter. 1 g of the gel should be dissolved in 100 ml of distilled water and will be stored at 4 ˚C for about 2 h. The electrode should be dipped in the diluted gel and the readings should be recorded. The measurements will be done in triplicate form and average values are noted.

III. Viscosity: The viscosity of the gels will be measured by using a viscometer. The gels will be rotated at 0.3, 0.6, 1.5 RPM, at each speed the readings will be noted. The viscosity of the gels will be determined by multiplying the dial reading with that of the factor given in the Brookfield Viscometer catalog.

IV. Spreadability: It specifies the extent of the area to which the gel spreads readily on the application to the skin. It will be measured based on "slip and drag characteristics" of the gel which can be defined as the time (in terms of secs) taken by the 2 glass slides to slip off from the gel when placed between the slides towards the direction of the load applied. The spreadability will be better if the time taken by the slides to separate is lesser. It can be calculated by applying the formula;

$$S = \frac{ML}{T}$$

Where;

S = spreadability

M = weight tied to the upper slide (g)

L = length of the glass slide (cm)

T = time taken for the separation of the slides (sec).

V.Extrudability study: The prepared gels will be filled in the collapsible tubes. The extrudability will be evaluated in terms of weight (g) required to extrude a ribbon of gel about 0.5 cm in 10 sec.

VI.Homogeneity: The gels will be tested for homogeneity by visual inspection based on the appearance and the presence of any aggregates.

VII.Grittiness: It will be determined microscopically using a light microscope. The absence of the particulate matter determines that the prepared gel is free from grittiness.

VIII.Consistency: The gel will be filled in the glass cup. A cone that is attached to a holding rod will be dropped from a distance of about 10 cm towards the center of the glass cup. The stabbing by the cone will be measured from the surface of the gel till the tip of the cone which is inside the gel. The extent travelled by the cone will be noted after 10 secs.

IX.Percentage yield: The empty container will be weighed and is then filled with the formulation. The practical yield will be measured by subtracting the weight of the empty container with the weight of the filled container. The percentage yield can be calculated by using the formula below;

$$\%\ yield = \frac{\text{practical yield}}{\text{theoretical yield}} \times 100$$

X.Drug content: 1 g of the prepared gel should be mixed with 100 ml of suitable solvent and are filtered. Aliquots of different concentrations will be prepared by suitable dilutions of the stock solution and the absorbance will be measured. The equation below is obtained by linear regression analysis of the calibration curve.

$$\text{Drug content} = \frac{\text{absorbance}}{\text{slope}} \times \text{dilution factor} \times \frac{1}{1000}$$

XI.*In vitro* diffusion studies: The diffusion studies will be carried out by using Franz diffusion cell which is mounted with the cellophane membrane. The donor compartment will be containing a fixed amount of the formulation. The donor compartment will be immersed in the receptor compartment containing phosphate buffer (pH 7.4) maintained at 37±1 ˚C. The sample will be withdrawn from the receptor compartment periodically at a specified interval of time. After withdrawing the sample at each interval the same amount of the fresh medium will be replaced. The drug content will be determined spectroscopically using phosphate buffer as blank.

XII.Skin irritation study: They are performed on Guinea pigs (400- 500 g) of either sex. The animal should be maintained under standard conditions. Before the application of the gel, the hair will be shaved with an area of about 4 cm^2 and marked for the easy identification between the test and the control group. The gel of about 500 mg/ Guinea pig will be applied twice a day for 7 days. The site will be periodically checked for the sensitivity reaction and will be graded as per the sensitivity reaction standard based on conditions like slight patchy erythema, slight or moderate patchy erythema, severe with or without edema.

XIII.Stability: The stability studies for the prepared formulation will be carried out by the freeze-thaw cycle. The product will be subjected to varying temperatures ranging from 4 ˚C for 1 month, 25 ˚C for 1 month, 40 ˚C for 1 month, exposed to even room temperature.

XIV.Kinetic study: The release kinetics can be determined by using zero order. Higuchi's equation, Korsmeyer-Peppa's equation. Based on the comparison of correlation coefficient and linearity the selections will be made to interpret the data[7,9,15,16,17,19,20,22,23,26,45,53,54,55].

CONCLUSION

In recent days, gel formulations have gained popularity than other topical preparations as they are easily washable, method of preparation is easy and simple, provides stability, controlled release when compared to other preparations, patient acceptability, reduced side effects, bypasses the gastrointestinal system, increases the absorption which enhances the bioavailability. They enhance the drug absorption with active targeting providing lesser side

effects. The gel formulations require optimization to enhance stability and efficacy. Recent studies show that topical gels are very safe and sound when used.

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