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**REVIEW ARTICLE**
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# TOPICAL GELS FOR DRUG DELIVERY: RECENT ADVANCEMENTS IN FORMULATION AND FUTURE DIRECTIONS IN CLINICAL PRACTICE

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**Abstract**
The main intention behind this review is to provide updated information related to the recent developments in terms of novel topical preparations including the basic concepts of dermal drug delivery systems. Topical drug delivery systems especially gels have several advantages such as it provides prolonged application to the site of action ultimately improving the therapeutic effect. A gel is a semisolid combination of a three-dimensional matrix of cross-linked materials. The three dimensional matrix of gel is mainly composed of a gelling agent and water. This review highlights the fundamentals of gel formulation and the factors affecting, along with the classification, advantages, limitations, and applications of different types of pharmaceutical gels such as niosomal/proniosomal gel, emulgels, bigels, xerogels and aerogels, organogels and hydrogels.

**Keywords:** Classification, Gel applications, gel formulation, limitations, pharmaceutical gels.

## 1. INTRODUCTION

A gel is a semisolid combination of a three-dimensional matrix of cross-linked materials. Several substances create a matrix in a liquid dispersion medium and form a gel (Fig. 1.1.). Organic and inorganic macromolecules act as formational units in preparing gel (Larson, 1999). According to USP (2021), “A gel is solid or semisolid. Gels can be classified into two groups, chemical and physical gels. Chemical gels are usually covalently cross-linked gels, while physical gels consist of small molecules or molecular chains that are physically cross-linked into networks, or solutions, or colloidal dispersions that are stiffened by a gelling agent.” A gel is a two-phase system in which the inorganic particles are present in an insoluble state, but these particles are uniformly distributed throughout the external phase. However, the large organic particles are freely available in the external phase (Fig. 1.1.). These phases are then joined together in stretchable chains (Goyal et al., 2011).

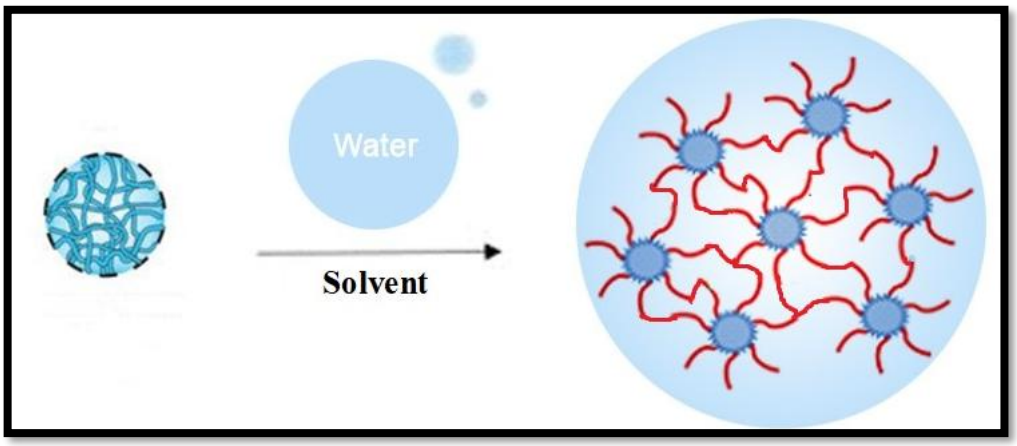


**Fig. 1.1.** Cross-linking of polymer in a solvent to form a gel matrix.

Gelling agent, also known as a gelator, is a natural, synthetic or semi-synthetic polymer or low molecular weight small molecule which is added to an organic, inorganic, or aqueous solvent or in a solvent system to prepare a gel (Fig. 1.2) (Jain, 2006; Murdan, 2005; Vintiloiu and Leroux, 2008; Allan, 2012).

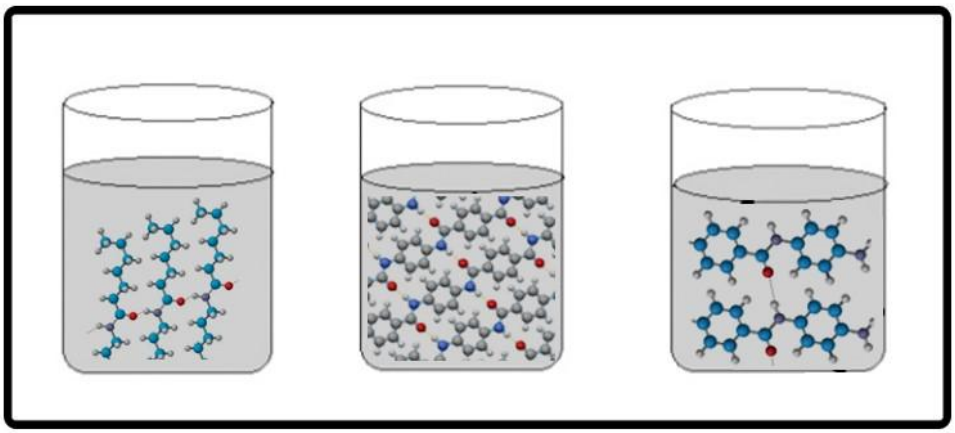

**Fig. 1.2.** Swelling of a polymer to form a gel.

## 1.2. TECHNICAL FEATURES OF GELS

Gels have been the topic of interest for the past few decades because of their potential for application in specific areas such as biomedical, cosmeceutical, energy-saving, etc. One of the recent features focused on is the adhesiveness of the gel on different surfaces (Sun et al., 2021). Some of the technical features that are important for gels are discussed below:

i. The gelling agent should be inert and should not produce any harmful effect on the formulation.
ii. Anti-microbial agents should be present in the formulation to stabilize it from microbial contamination.
iii. It should be safe and provide patient compliance.
iv. All rheological properties of the gel should be maintained.
v. The gel formulation should be economical.
vi. Gel intended to be used in eyes should be sterile and stored at the recommended storage condition to maintain stability.
vii. It should be neither greasy nor sticky and non-staining in nature.
viii. No physical change should occur in the formulation upon storage.
ix. It should have the capability of a high level of drug encapsulation.
x. The gel must be biodegradable without forming toxins.

## 1.3. ADVANTAGES OF GELS OVER OTHER DOSAGE FORMS

Recent advances in gel technology have proven crucial for their application, especially in topical drug delivery. Some of the advantages of gels that make them superior to other dosage forms are enlisted here (Jain, 2006; Florence and Attwood, 2007; Labarre et al., 2010; Rehman et al., 2014):

i. They produce a local effect; therefore, there are fewer chances of side effects.
ii. They provide a soothing effect on the skin.
iii. They are less greasy as compared to other dosage forms and easily washable.
iv. They are non-invasive and have a high retention time compared to other dermatological preparations, thus providing patient compliance.
v. They provide targeted and controlled drug delivery to the diseased tissue with the advantage of tissue repair by releasing the drug through chemical stimulation.
vi. They can incorporate hydrophilic as well as lipophilic drugs.

## 1.4. GEL LIMITATIONS / DISADVANTAGES

Apart from being advantageous, the gels also have some limitations, which are discussed as follows (Nabi et al., 2016):

i. If a drug with a large particle size is incorporated into the gel, it becomes difficult to get absorbed through the skin.
ii. Topical gels can cause allergic reactions.
iii. A high quantity of water may result in microbial or fungal growth.
iv. Syneresis is another issue that may occur on storage.
v. The release of the drug may be affected in gels with a covalent bond.
vi. Temperature, humidity, and other environmental factors may alter the rheological properties of the gels.
vii. Degradation of a drug may result from polymer interaction with the drug in some cases.

## 1.5. BASIC COMPONENTS OF A GEL FORMULATION

The main advantage of formulating a gel is the ease of preparation. The fundamental components include a polymer (gelling agent) and a solvent. Apart from these two, a gel may contain stabilizing agents, dispersing agents, buffer, preservatives, penetration enhancers, anti-oxidants, and flavoring agents/sweeteners. Preservatives are essential as they prevent the gel from microbial growth, especially in the case of hydrogel, due to the presence of a high amount of water (Nabi et al., 2016). Anti-oxidants are added in preparations that are sensitive to oxidative degradation, and their selection depends on the type of solvent used. Water-soluble anti-oxidants (e.g., sodium metabisulfite, sodium formaldehyde sulfoxylate, etc.) are preferred as a majority of the gels have an aqueous solvent (Rathod and Mehta, 2015).

### 1.5.1. Gelling Agents

The selection of a gelling agent depends on the gel type (e.g., hydrogel, organogel, etc.) and its affinity with the solvent. Fig. 1.3 enlists some of the commonly used gelling agents with their classification and percentages at which they act as a gelling agent (Attwood., 2002; Rathod and Mehta, 2015).

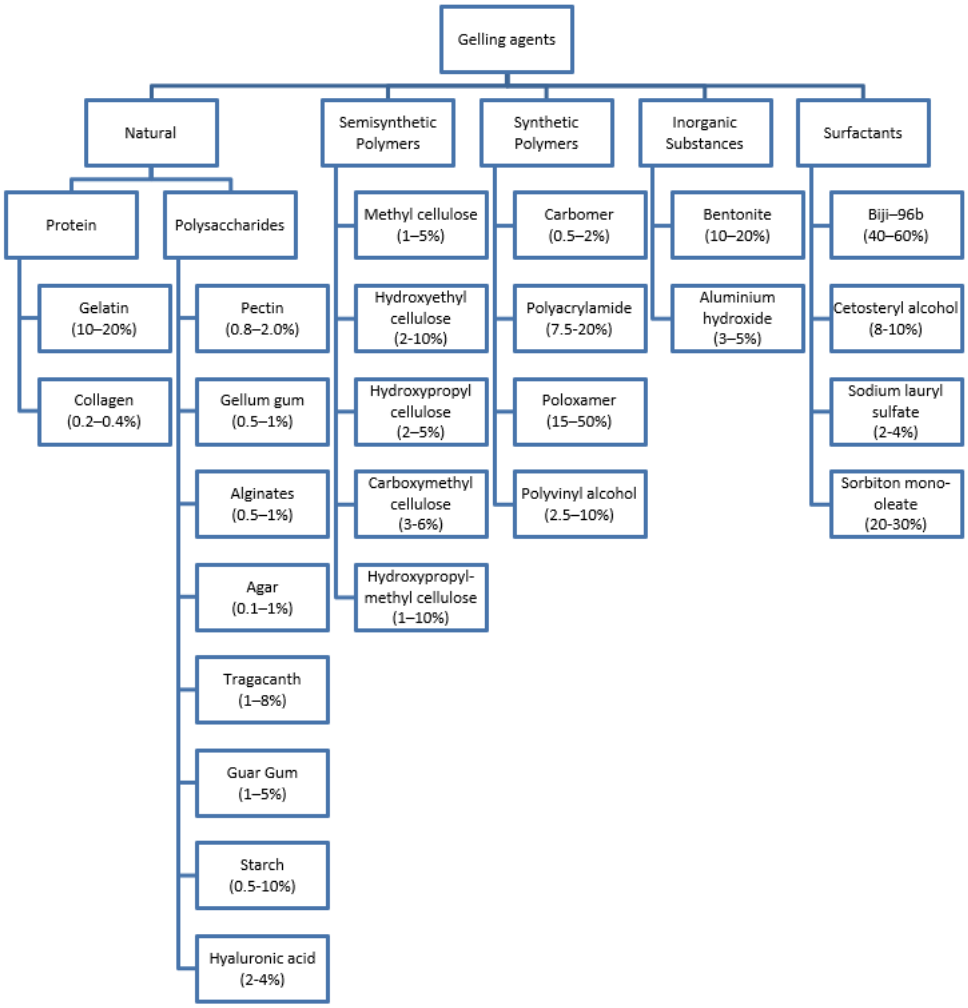


**Fig. 1.3.** The classification of gelling agents with origin and percentages.

### 1.5.2. Buffers

pH plays a vital role in the penetration of the drug through the skin. Buffers may be added, especially in topical drug delivery-based gels. The buffer selection is critical as it has some hydro-alcoholic-based solvents limitations. Examples of buffers include phosphate buffer, citrate buffer, etc. (Bhatia et al., 2000; Rathod and Mehta, 2015).

### 1.5.3. Penetration Enhancers

The penetration enhancer should be inert chemically and pharmacologically but must be acceptable pharmaceutically. They should be free from allergic reactions and non-irritant, colorless, odorless, and tasteless, having a known duration of action with a quick response. More importantly, it must be accepted cosmeceutically (Ojha et al., 2017).

### 1.5.4. Gel Preparation Medium

A solvent is often purified water but co-solvents (e.g., alcohol, glycerol, PEG, etc.) may be added to enhance drug solubility or increase the drug skin penetration (Rathod et al., 2015). In nature, a solvent can be hydrophilic or hydrophobic (lipophilic or organic). The selection of the vehicle-like gelling agent depends on the desired application of the gel. The solvent selected must be efficient, biocompatible, and not evaporate quickly (Nabi et al., 2016).

## 1.6. FACTORS AFFECTING GEL FORMULATIONS

Formulating a gel is easy as compared to other dosage forms. However, certain factors affect the gel formulations, which include (Nabi et al., 2016):

i. Gelling agent concentration and its molecular weight.
ii. Solubility and affinity of the polymer towards the solvent used.
iii. pH.
iv. Solvent nature.
v. Ion concentration of the solution.
vi. Temperature, humidity, and other environmental factors.

## 1.7. STRUCTURE AND CLASSIFICATION OF GELS

In recent drug developments, gels have become the most beneficial vehicle for localized, topical drug delivery. Advanced studies for the dermal application of the drug have reported some additional types of gels (i.e., niosomal gel, emulgels, bigels, xerogels), including hydrogels and oleogels (Rehman et al., 2014).

Conventional methods of gel formation are cost-effective and convenient to make. However, the advancement in the field of the gel makes it challenging to characterize the gel, especially the hydrogels having a variety of cross-linked networks (Peppas and Barr-howell, 2019). Khandan et al. (2017) characterized the gels as liquids having 3D cross-linked structure which behaves as solids. The interlinking of the fragments of the gelling agent strengthens the gel. Particle nature and the type of force involved in connecting these linkages relate to the gel's structure and properties. The attractive force involved in the pairing of gelling agents may vary from strong covalent or ionic bonds to weak hydrogen bonds and Vander Waal forces. A slight rise in temperature occurs due to liquefaction in gels due to weak interactions (Carter, 2000). A brief classification of gels is elucidated in Table 1.1.

**Table 1.1.** Classification of gels

| | |
|---|---|
| Physical Properties | •Smart<br>•Conventional |
| Ionic Charge | •Non-ionic<br>•Cationic<br>•Anionic<br>•Ampholytic |
| Cross-linking | •Physical<br>•Chemical |
| Biodegradeability | •Biodegradeable<br>•Non-biodegradeable |
| Size of Pores | •Non-porous<br>•Microporous<br>•Nanoporous<br>•Macroporous |
| Preparation Method | •Homopolymer<br>•Copolymer: Triblock and Multiblock<br>•Interpenetrating |
| Source | •Natural<br>•Hybrid<br>•Synthetic |

### 1.7.1. Niosomal or Proniosomal Gel

Niosomes are chemically stable, derived from liposomes having nonionic surfactants, capable of carrying both types of drugs, i.e., hydrophilic or lipophilic. They are more stable than liposomes and phospholipid carriers whereas proniosomes are more stable than niosomes (Masotti et al., 2010; Marianecci et al., 2011; Verma et al., 2020). Niosomes are easy to prepare and can also be formed through hydration from proniosomes which are niosomal hybrids having compact crystalline structures (El-Laithy et al., 2011). Apart from various advantages, niosomes are expensive, sensitive to moisture (hydrolysis), and quickly aggregate and sediment (Rehman et al., 2014). The targeted drug delivery of lipid-soluble vitamins and the non-invasive vaccines have been observed through noisome gels prepared by the oleogel technique (Gupta et al., 2005; Gonnet et al., 2010). In contrast, the hydrogel-based niosomes and proniosomes have been effective for the transdermal delivery of the drug (Marianecci et al., 2011; Shehata et al., 2021). Niosomal gels have several advantages over liposomes, such as improved skin permeation with controlled release of the drug, improved stability chemically as well as physically, and are cost-effective in production (Biswal et al., 2008; Mahale et al., 2012; Verma et al., 2020). To release the drug and permeate it from the skin, proniosome requires hydration; that is why dry niosomes are another name given to proniosome (El-Laithy et al., 2011). Comparatively, niosomal hydrogels are more physically stable than proniosomes and have more drug penetration in the transdermal drug delivery system providing a unique vesicle for delivery (Ibrahim et al., 2005; Rehman et al., 2014; Shah et al., 2021).

### 1.7.2. Emulgels

Despite recent developments in novel drug delivery systems, the delivery of lipophilic drugs has always been an area of concern. The answer to the question has been the emulgel, which converts water-in-oil emulsion to an emulgel by adding a gelling agent in the water phase. Both the emulgels, i.e., water-in-oil and oil-in-water, have been used to deliver the lipophilic drugs (Dhawas et al., 2020; Harshitha et al., 2020; Koshani et al., 2021; Salabat and Parsi., 2021). Emulgels also have various other advantages which are favorable dermatologically, such as:

i. Biofriendly
ii. Less greasy
iii. Greater spreadability
iv. Easy to remove
v. Improved shelf-life
vi. High patient acceptability due to the pleasant appearance
vii. Provides controlled release of drug
viii. Easy to prepare and are cost-effective

The only disadvantage of emulgel is skin irritation due to the presence of the surface-active agent(s). However, air bubbles can be formed in preparing an emulgel which are settled on standing (Rehman et al., 2014; Pawbake et al., 2020; Charyulu et al., 2021).

The novel topical drug delivery system has reached a new level as the researchers have moved to the advanced form of emulgels, i.e., microemulsion-based gels (MBGs) and nanoemulsion-based gels (NBGs) for the drug delivery. The advantages of MBGs and NBGs, apart from the one listed above, include their particle size, improved thermodynamic stability, targeted drug delivery, and avoidance of the first-pass effect (Chellapa et al., 2015; Choudhry et al., 2017).

### 1.7.3. Bigels

Bigels, as the name indicates, are a combination of hydrogel and oleogel (organogel), but they are free from any surfactant or stabilizer. They are prepared by mixing hydrogel and organogel at a high shear rate (rpm) (Di Michele et al., 2014; Lupi et al., 2016; Shakeel et al., 2018; Shakeel et al., 2019; Martins et al., 2020; Sreekumar et al., 2020). This homogenous system of bigels possesses properties of both gels and provides synergistic effects leading to increased drug penetration. The combined features of hydrogel and organogel make it unique with certain advantages such as they

are easy to prepare, provide a synergistic effect, are free from surfactant; therefore, no skin irritation is reported due to surfactant, and more importantly, they can deliver both types of drug, i.e., lipophilic and hydrophilic. However, sometimes it is not easy to maintain phase separation since the preparation is surfactant-free (Rehman et al., 2014). Moreover, the synergistic effect of the bigels increases its importance in the cosmetic and pharmaceutical industries (Rehman and Zulfakar, 2014; Rehman et al., 2014; Singh et al., 2014; Lupi et al., 2016). In the past few decades, bigels have been studied extensively for the topical delivery of drugs such as metronidazole, ciprofloxacin, ketoprofen, flurbiprofen, tenofovir, maraviroc, etc. (Andonova et al., 2017; Charyulu et al., 2018; Shakeel et al., 2018; Ilomuanya et al., 2020).

### 1.7.4. Xerogels and Aerogels

Aerogels and xerogels, commonly known as inorganic gels (because they are made up of silica), have also been studied extensively for the topical application of various drugs, especially for subcutaneous delivery (Uros et al., 2007; Guenther et al., 2008). Apart from the drying procedures, both the aerogels and xerogels are prepared by the sol-gel method. Xerogels are prepared by drying the wet silica gel at standard pressure. In contrast, the aerogels are prepared by avoiding the shrinkage at the supercritical level and preserving the porous structure, which ultimately forms aerogels. Compared with xerogels, the former is more effective because it has more drug solubility leading to increased bioavailability.

Additionally, the release kinetics can be controlled by modifying the aerogels structure using different functional groups. The main difference lies between the inner surface area, i.e., 400–1000 $m^2/g$ for aerogel and 300–600 $m^2/g$ for xerogel, and pore size, i.e., the aerogels have larger pores as compared to xerogels (Rehman et al., 2014). Aerogels have various advantages over xerogels. The drug loading at the supercritical stage provides uniform drug distribution at the molecular level, making it easy to incorporate the amorphous form of the drug. This system can also improve the bioavailability of BCS II drugs as the hydrophilic aerogel system collapses in the hydrophilic medium because of internal surface tension within the pores. Both the gels are thermally stable, having low thermal conductivity. The silica aerogels have a restriction that they are not biodegradable. Several studies have used polysaccharides to prepare biodegradable aerogels (Ollio and Ollio, 2009; Alnaief et al., 2011; Cheng et al., 2012; Stergar and Maver, 2016; Ganesan et al., 2018). However, the aerogel may be organic, inorganic, or hybrid; they have proven biocompatible ((Stergar and Maver, 2016).

### 1.7.5. Organogels

Organogels, one of the most common and well-known gel forms, contain lipophilic or non-polar liquid as the dispersion medium. Organogels are a network of a three-dimensional thermo-reversible gel consisting of an organogelator and a non-polar solvent. This three-dimensional network is formed by the physical or chemical interaction of gelators when used in less than 15% concentration, preventing the flow of external apolar solvent (Vintiloiu et al., 2008; Sahoo et al., 2011). The fundamental potential reason behind the study of organogels as the drug delivery system is their thermo-reversible property. These gels are thermodynamically stable, biodegradable, biocompatible, and possess high transdermal permeability, but they are greasy and difficult to wash (Murdan., 2005; Rehman et al., 2014). The applications of organogels are broader as they are used in the chemical, pharmaceutical, cosmeceutical, and food industries. Biotechnology is another field in which organogels are used predominantly as a vaccine delivery platform (Esposito et al., 2013, 2016, 2018). Edible oleogels are another interesting application of organogels to the health-promoting food industry, used to prepare different dairy and meat products (Co and Marangoni., 2018; Martin et al., 2020; Puscas et al., 2020).

### 1.7.6. Hydrogels

In the past few decades, synthetic functional polymers have been studied extensively for their biomedical application, especially as hydrogel, to overcome the disadvantages of conventional drug delivery and improve the efficacy of novel drug delivery systems (Kashyap et al., 2005; Vashist et al., 2014). Like organogels, hydrogels are also three-dimensional polymeric structures, but they contain a hydrophilic gelling agent (either synthetic or natural) that can hold a large amount of water (Rehman et al., 2014; Balakrishnan and Jayakrishnan, 2015). The hydrogels are mainly divided into physical and chemical hydrogels depending on the cross-linking. Physical hydrogels are reversible gels since weak bonds form their cross-linking. The chemical hydrogels, also known as permanent gels, are formed by covalent cross-linking (Campoccia et al., 1998; Shapiro, 2011; Allan, 2012; Peppas and Mikos, 2019). They are easy to prepare, cost-effective, biodegradable, adaptable to different compounds, and, more importantly, it serves as a base for other advanced forms of gels such as liposomal gel, emulgels, microgels, nanogels, nanocomposite hydrogels, etc. (Rehman et al., 2014; Khan et al., 2016; Esmaeely-Neisiany et al., 2020). However, it has some limitations towards transdermal drug delivery because of its hydrophilic nature. Microbial contamination is another disadvantage, especially in polysaccharide hydrogels (Rehman et al., 2014). Based on the size of pores, hydrogels can be characterized as non-porous (10–100 μm), macroporous (0.1–1 μm), microporous (100–1000 μm) and nanoporous (<100 nm) (Amin et al., 2009; Khan et al., 2016). Hydrogels are also classified based on cross-linking, i.e., physically cross-linked and chemically cross-linked hydrogels.

Bioadhesive hydrogel is another achievement in the field of hydrogel for novel drug delivery systems. It is formed when one of the phases is biological, resulting in adherence to the two phases and protecting the separation, resulting in increased bioavailability. Kashyap et al. (2005) discussed different routes of administration of bioadhesive hydrogels which are as follows:

i. Buccal
ii. Ocular
iii. Vaginal and cervical
iv. Peroral

Hydrogels have many applications, including vaccines, stimuli-responsive nanogels, tissue engineering, molecular imprinting, wound dressing, immunoisolation, and novel drug delivery (Kashyap et al., 2005; Ferreira et al., 2013; Hajebi et al., 2019). Nanotechnology has gained importance in the novel drug delivery system in the past few decades, and nanogels have been the focus, especially in transdermal drug delivery (Karg et al., 2019). The uptake of macrophages by nano hydrogels has been demonstrated by Gao et al. (2008), which brings the focus of researchers toward this novel nanohydrogel drug delivery system (Vashist et al., 2014). Nanogels, like hydrogels, consists of a three-dimensional network having physical or chemical cross-linking of the polymer (Soni and Yadav, 2016; Soni et al., 2016; Cuggino et al., 2019; Pinelli et al., 2020; Shah et al., 2020). A summary for all gel types with their definition, advantages, and limitations is given in Table 1.2.

## 1.8. CHARACTERISTICS OF GELS

### 1.8.1. Syneresis

Syneresis can be defined as the oozing of the fluid medium upon standing due to contractions. This phenomenon increases with the decrease in the concentration of the gelling agent and the other way round. It affects the stability of the gel and depicts that the gel became thermodynamically unstable. The contractions also cause the loosening of elastic stress during gel development. As soon as the stresses are mitigated, shortening of the space takes place within the solvent, which exudates the fluid (Carter, 2000; Zatz and Kushla, 2005).

### 1.8.2. Swelling

Swelling occurs when the gelling agent interacts with the liquid, initiating solvation. A considerable amount of liquid is absorbed in response to this interaction, thus increasing the volume (Fig 1.4). The size of swelling is dependent on the force of attraction present in the molecular linkages of the gelling agent (Carter, 2000; Zatz and Kushla, 2005).

**Table 1.2.** Definition, advantages, and limitations of different types of pharmaceutical gels

| Gel Type | Definition | Advantages | Limitations |
|---|---|---|---|
| **Niosomal or Proniosomal Gel** | Niosomal / proniosomal gels are simple gels containing Niosomes / proniosomes. | improved skin permeation with controlled release of the drug, improved stability chemically as well as physically, and are cost-effective in production | expensive, sensitive to moisture (hydrolysis), and quickly aggregate and sediment |
| **Emulgels** | Emulgels are gels in which water-in-oil or oil-in-water emulsions are added in a gel matrix. | Biofriendly, less greasy, greater spreadability, easy to remove, improved shelf-life, high patient acceptability due to the pleasant appearance, provides controlled release of drug, easy to prepare, cost-effective, improved thermodynamic stability, targeted drug delivery, and avoids of the first-pass effect | Skin irritation due to the presence of the surface-active agent(s) |
| **Bigels** | Bigels, as the name indicates, are a combination of hydrogel and oleogel (organogel), but they are free from any surfactant or stabilizer. They are prepared by mixing hydrogel and organogel at a high shear rate (rpm) | Easy to prepare, provide a synergistic effect, are free from surfactant; therefore, no skin irritation is reported due to surfactant, and more importantly, they can deliver both types of drug, i.e., lipophilic and hydrophilic | Phase separation |
| **Xerogels and Aerogels** | Xerogels are solid forms of a gel prepared by drying the wet silica gel at standard pressure with rapid shrinking of the gel, whereas in aerogels are compressible porous gel material from which liquid is removed conventionally. | More drug solubility leading to increased bioavailability, controlled release kinetics, Uniform drug distribution, easy incorporation of amorphous form, thermally stable | Silica aerogels are biodegradable |
| **Organogels** | Organogels are a network of a three-dimensional thermo-reversible gel consisting of an organogelator and a non-polar solvent | Thermoreversible, thermodynamically stable, biodegradable, biocompatible, and possess high transdermal permeability | Difficult to wash off |
| **Hydrogels** | hydrogels are also three-dimensional polymeric structures, but they contain a hydrophilic gelling agent (either synthetic or natural) that can hold a large amount of water | easy to prepare, cost-effective, biodegradable, adaptable to different compounds, and, it serves as a base for other advanced forms of gels such as liposomal gel, emulgels, microgels, nanogels, nanocomposite hydrogels, etc. | Microbial contamination |

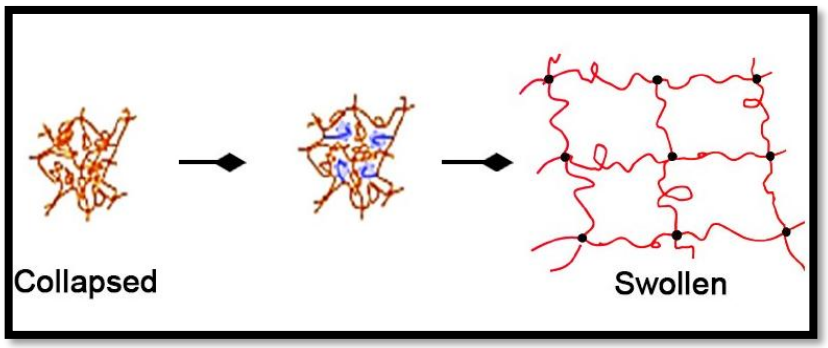


**Fig. 1.4.** Swelling of a gel.

### 1.8.3. Aging
When gelling agent forms a denser network with time, the phenomenon is known as aging (Carter, 2000; Zatz and Kushla, 2005).

### 1.8.4. Structure
The gelling agent forms a rigid network by interlinking its particles. The stress applied and the particles nature help in increasing the flow of gel (Patil et al., 2019).

### 1.8.5. Rheology
The gels obey non-Newtonian behavior as the solid dispersion in the gels follows pseudoplastic behavior, which indicates that the viscosity decreases as the shear rate increases (Patil et al., 2019).

## 1.9. APPLICATIONS OF GELS
Gel, a conventional dosage form, has various applications such as in cosmeceutical products (like shampoo, dentifrices, etc.), as catheter lubricant, as an adhering patch base, for electrocardiography suppository bases, etc. (Rathod and Mehta, 2015). Advancements in the field of the gels have remarkably increased the area of its application not only in the field of novel drug delivery systems (NDDS) but also for other purposes such as biomedical applications, hygiene (e.g., baby diaper, sanitary pads), in agriculture and horticulture, biotechnology, food packaging industry, cosmetic industry. Drug delivery through NDDS includes the controlled release of drugs, proteins, peptides, pesticides, nutrients, hormones, etc. However, drug delivery through the gel for any type of application requires the formation of gel that must be explicitly designed and must meet the desired properties (Ullah et al., 2015). Some of the examples of drugs recently incorporated into advanced gel formulations are listed in Table 1.3.
Gels, specifically hydrogels, in response to environmental changes, behave similarly to human organs, which direct their use towards medical implants, breast implants, artificial muscle diagnosis, bone implants, a decrease in thrombosis and intimal thickening in animals, etc. (Defail et al., 2006; Hill-West et al., 1994; Mendonça Munhoz et al., 2017). Thin films have also been prepared using organogels. They entrap the oil and hold it in a cross-linked network. This technique is used for a self-cleaning purpose and can also be used for different engineering metals (Liu et al., 2013).
Gels have a vast usage in sanitary pads to provide thinner pads with maximum absorbing power (Nagorski, 1994). The wastewater produced by the olive mill can be used as plant fertilizer, as hydrogel makes the wastewater immobilized, solving the polyphenolic issues (Davies et al., 2004).

**Table 1.3.** Example of drugs incorporated in different types of gels with their distinguish feature

| Gel Type | Drug | Distinguishing Feature | Reference |
|---|---|---|---|
| Chitosan gel | Doxorubicin | Increased cytotoxicity | Taveira et al., 2009 |
| Chitosan emulgel | Curcumin | Increased skin permeation | Thomas et al., 2017 |
| Lecithin organogel | Sumatriptan succinate | Increased drug release from the skin | Agrawal et al., 2010 |
| | Fenretinide | Improved stability and Shelf life | Esposito et al., 2013 |
| | Crocin | Increased skin penetration | Esposito et al., 2016 |
| | Metoprolol | Skin permeation enhancement | Varshosaz et al., 2013 |
| Pluronic lecithin organogel (PLO) | Cyclobenzaprine | Skin permeation enhancement | Bryson et al., 2015 |
| | Fluorescein | Increased transdermal permeation | Zhang et al., 2017 |
| | Melatonin | Improved transdermal and transbuccal release | Flo et al., 2016 |
| | Mefenamic acid | Topical controlled release | Jhawat et al., 2016 |
| Bigel | Ciprofloxacin | Controlled drug delivery | Singh et al., 2014 |

| | | | |
|---|---|---|---|
| | Vitamin E | Increased stability | Martinez et al., 2021 |
| | Diclofenac diethylamine | Improved drug delivery | Hamed et al., 2020 |
| Hydrogel, oleogel, bigel | Ibuprofen | Improved rheological and bioadhesive properties | Hamed et al., 2018 |
| Alginate based aerogel | Ketoprofen, nimesulide, loratidine | Improved pharmacokinetic properties | Lovskaya and Menshutina, 2020 |
| Dextran and dextran aldehyde coated silica aerogel | 5-Fluorouracil | Enzyme triggered targeted drug delivery to the colon | Tiryaki et al., 2020 |
| Silica aerogel | Celecoxib | Fast drug dissolution with controlled release | Jabbari-Gargari et al., 2021 |
| Silica xerogel | Nifedipine | Improved bioavailability | Zhang et al., 2020 |
| Alginate-methacrylate xerogel | Insulin | Improved wound healing | Rajalekshmy and Rekha, 2021 |
| Niosomal gel | Simvastatin | Enhanced anti-bacterial activity | Akbarzadeh et al., 2021 |
| | Diclofenac sodium | Improved therapeutic effect | Akbari et al., 2022 |
| | Pilocarpine hydrochloride | Suitable for ocular drug delivery | Jain and Verma et al., 2020 |
| Proniosomal gel | Rutin | Improved cytotoxic effect on melanoma cells | Pinzaru et al., 2021 |
| | Naproxen | Possible alternate for oral naproxen | Shah et al., 2021 |
| | Ciclopirox | Prolonged drug release | Mahajan et al., 2021 |

Biodegradable hydrogels have been prepared and used as an alternative to polyacrylic hydrogel for personal and biomedical applications. Hydrogels formed by cross-linking CMC-Na or hydroxyethylcellulose with divinyl sulfone have been studied to treat edema as super absorbent (Sannino et al., 2003). In addition, hydrogels having distinctive mechanical properties have become the area of interest for drugs with a narrow absorption window (Omidian and Park, 2008; Omidian et al., 2005; Omidian et al., 2007).

Organogels have simplified the transdermal delivery of drugs. Lecithin organogels have been studied vastly for topical and transdermal drug delivery. Various compounds such as vitamins, hormones, peptides, amino acids, pain killers, anesthetics, and antifungal drugs have been studied for transdermal drug delivery and found successful for their delivery through lecithin organogels (Patel and Patel, 2021; Rajiv and Om, 2005; Sanapalli et al., 2018; Shaikh et al., 2006; Sushi et al., 2012; Willimann et al., 1992; Zhang et al., 2018). Fish oil has been used to prepare polymer-fish oil bigel and studied for transdermal drug delivery. The polymer-fish oil bigels showed excellent spreadability with improved skin permeation compared to the conventional hydrogel (Rehman et al., 2014). A list of pharmaceutical formulations of gels recently patented is given in Table 1.4.

All the types of gels discussed have several advantages with some limitations. The literature suggests that the hydrogels are most convenient to use because they are easy to prepare with an exceptional advantage that they can further be utilized to formulate other types of gels. This serves as the basis of developing NS based hydrogels.

**Table 1.4.** Recently patented gel formulations

| S.No. | Patent No. | Formulation Title | Use | References |
|---|---|---|---|---|
| 1. | US20210137101A1 | Roach gel formulation | Insecticidal | Marwah et al., 2021 |
| 2. | WO2021034850A1 | In-situ gel forming ophthalmic formulations containing difluprednate | Pain killer | Liang et al., 2021 |
| 3. | US10507264B1 | Cross-linked hydrogel and method of making the same | Repairing, supplementing body tissue | Lowman et al., 2019 |
| 4. | US11026919B2 | Formulation for soft anticholinergic analogs | Anticholinergic | Bodor et al., 2021 |
| 5. | US10561606B2 | Injectable long-acting local anesthetic semisolid gel formulation | Controlled drug release | Shen and Gan, 2020 |
| 6. | US10881745B2 | Formulation of nanostructured gels for increased agent loading and adhesion | Increased loading capacity | Van der Poll et al., 2021 |
| 7. | EP3351599B1 | Corrosion-resistant adhesive sol-gel | Increased drug encapsulation | Schuette and Kinlen, 2019 |
| 8. | US10813882B1 | In situ gelling formulation for reduced initial drug burst | Treating hyperlipidemia | Ahmed et al., 2020 |
| 9. | EP3372221B1 | Hydrophobic gel based on vitamin E free from silicone products for topical application | Vitamin E free from silicone | Panin, 2019 |
| 10. | US11020410B2 | Self-assembled gels formed with anti-retroviral drugs, prodrugs thereof, and pharmaceutical uses thereof | Treating HIV/hepatitis | Karp et al., 2021 |
| 11. | US10975217B2 | Silica-based organogels via hexahydrotriazine-based reactions | Insulating materials | Boday et al., 2021 |
| 12. | EP3502779B1 | Inherently photodegradable hydrogels or organogels for microfabrication | Photodegradable gel | Levkin and Li, 2020 |
| 13. | US10603406B2 | Hydrogel for cell culture and biomedical applications | Cell culture and biomedical application | Huang, 2020 |
| 14. | US10500138B2 | Polyphenols/PEG based hydrogel system for a dental varnish | Dental varnish | Jha and Simonton, 2019 |
| 15. | US10973956B2 | Microporous hydrogel scaffolds for cell transplantation | Biomaterial implant (cell) | Kasputis et al., 2021 |

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