

Pharmaceutical Gels



Pharmaceutical gels are semisolid systems consisting of **dispersions of small or large molecules in an aqueous liquid**, which has been **thickened with a gelling agent**. Gels can be **a single phase or a biphasic system**.

1. Single-phase gels use **high molecular weight hydrophilic polymers as gelling agents**. Examples of such polymers include **carbomers** (cross-linked acrylic acid polymers). These gels are considered to be **one-phase systems** because **no definite boundaries exist between the dispersed macromolecules and the liquid**.

2. Biphasic gels could contain a **gelatinous, cross-linked precipitate of one substance in the aqueous phase**. For example, **magma or milk of magnesia** consists of a gelatinous precipitate of magnesium hydroxide.

Gelling agents in single-phase gels could be:

- (a) **synthetic macromolecules**, for example, **carbomer 934**;
- (b) cellulose derivatives, such as **carboxymethylcellulose**; and
- (c) **natural gums**, for example, **tragacanth**.

» **Carbomers** are **high molecular weight water-soluble polymers** of acrylic acid cross-linked with allyl ethers of sucrose and/or pentaerythritol. Their viscosity depends on their polymeric composition. They are used as gelling agents at concentrations of **0.5%–2% w/w** in water.

» In addition to the gelling agent and water, gels may also contain a **drug substance**, **cosolvents** (such as **alcohol and/or propylene glycol**), anti-microbial **preservatives** (such as **methylparaben and propylparaben**, or **chlorhexidine gluconate**), and **stabilizers** (such as the chelating agent **edetate disodium**).

» Gels can be classified based on their gelling agent as **inorganic and organic**.

Inorganic gels use precipitates of inorganic salts, such as magnesium hydroxide, as gelling agents, whereas **organic gels** generally use a carbon-based hydrophilic polymer. Inorganic gels are generally **two-phase systems**, whereas organic gels are **generally single-phase systems**.

» Based on the **solvent phase of the gels**, they may be classified as **hydrogels or organogels**.

Hydrogels contain **water** as the main continuous phase solvent, whereas **organogels** may contain an **organic liquid**. Hydrogels contain significant amounts of water but remain as water insoluble.

» The diffusion rate of a drug from a gel depends on the **physical structure** of the polymer network and its **chemical nature**.

✓ If the gel is **highly hydrated**, diffusion occurs through the **pores**.

✓✓ In gels of **lower hydration**, the drug dissolves in the polymer and is transported between the chains.

✓✓✓ Polymer cross-linking **increases the hydrophobicity** of a gel and reduces the diffusion rate of the drug.

» Gels typically display **non-Newtonian flow characteristics**, that is, they show a **nonlinear relationship between shear stress and strain rate**, which can also be time dependent. Depending on their flow characteristics, gels may be:

1. shear thinning (pseudoplastic, i.e., viscosity decreases and flow increases on agitation),

2. shear thickening (dilatant, i.e., viscosity increases and flow decreases on agitation), or

3. thixotropic (e.g., requires decreasing stress to maintain a constant strain rate over time; or, in other words, viscosity decreases and flow increases over time under the same agitation rate).

Inorganic gels consist of floccules of small particles, as found in aluminum hydroxide gel or bentonite magma. Such gels may be thixotropic, displaying higher viscosity and a semisolid state on standing and becoming low viscosity liquids on agitation.

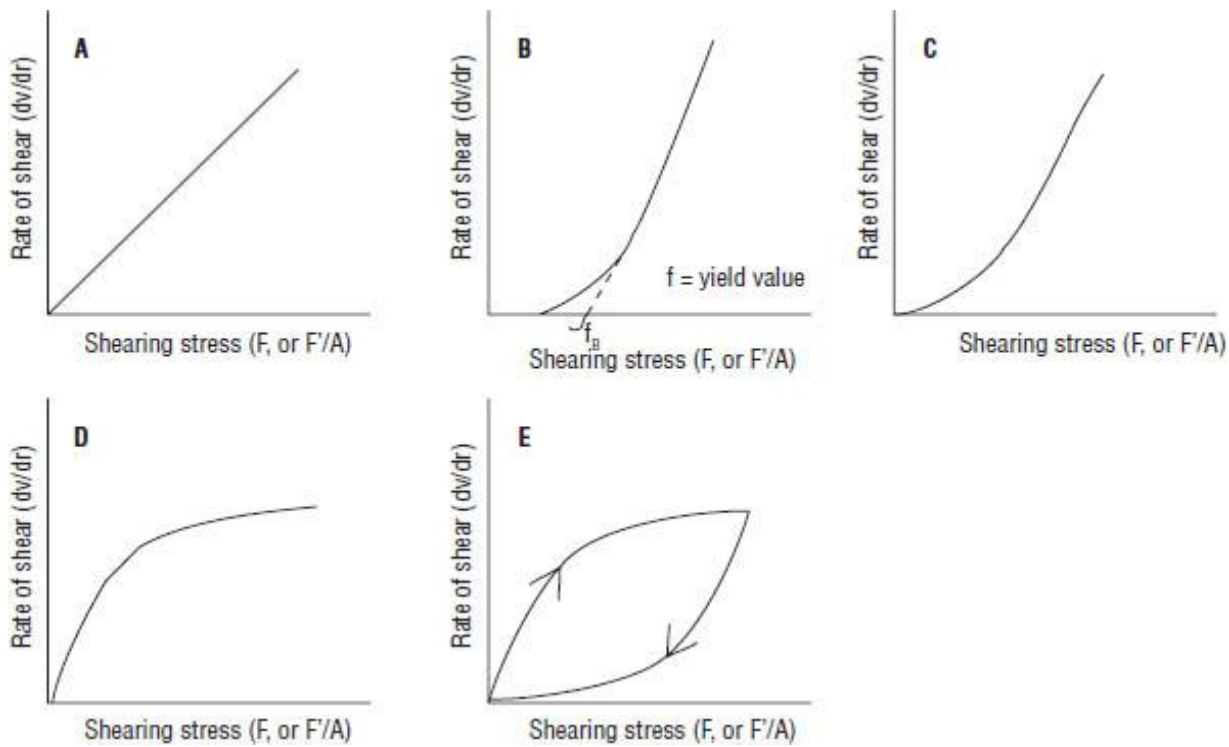


Figure 1: Plots of Rate of Shear as a Function of Shearing Stress for (A) **Newtonian**, (B) **Plastic**, (C) **Pseudoplastic**, (D) **Dilatant**, and (E) **Thixotropic Flow**

Methods of preparation:

- a. Fusion method.
- b. Cold method.
- c. Dispersion method.

Notes:

1. Gels and magmas are considered colloidal dispersions because they contain particles of colloidal dimension.
2. Some gel systems are as **clear as water**, and others are **turbid** because the ingredients may not be completely molecularly dispersed (soluble or insoluble), or they may form aggregates, which disperse light.
3. The **concentration of the gelling agents** is mostly <10%, usually in **0.5% to 2.0%** range, with some exceptions.

Terminology related to gels

- 1. Imbibition** is the taking up of a certain amount of liquid without a measurable increase in volume.
- 2. Swelling** is the taking up of a liquid by a gel with an increase in volume.
- 3. Syneresis** occurs when the interaction between particles of the dispersed phase becomes so great that on standing, the dispersing medium is squeezed out in droplets and the gel **shrinks**. **Syneresis is a form of instability in aqueous and nonaqueous gels.**
- 4. Thixotropy** is a reversible (gel–solution) formation with no change.

Table (1): General classification and description of gels

CLASS	DESCRIPTION	EXAMPLES
Inorganic	Usually two-phase systems	Aluminum hydroxide gel Bentonite magma
Organic	Usually single-phase systems	Carbopol Tragacanth
Hydrogels	Organic hydrogels Natural and synthetic gums Inorganic hydrogels	Pectin paste, tragacanth jelly Methylcellulose, sodium CMC, Pluronic Bentonite gel (10%–25%), Veegum, silica
Organogels	Hydrocarbon type Animal, vegetable fats Soap base greases Hydrophilic organogels Polar Nonionic	Petrolatum, mineral oil/polyethylene gel (Plastibase) Lard, cocoa butter Aluminum stearate with heavy mineral oil gel Carbowax bases (PEG ointment)

Preparation of magmas and gels

- ▶ Some **magmas and gels (inorganic)** are prepared by **freshly precipitating the disperse phase** to achieve a **fine degree of subdivision of the particles and a gelatinous character to those particles**. The desired gelatinous precipitate results when solutions of inorganic agents react to form an **insoluble chemical** having a high attraction for water. As in the **microcrystalline** particles of the precipitate develop, they strongly attract water to yield gelatinous particles, which combine to form the desired gelatinous precipitate.
- ▶ Other magmas and gels may be prepared by **directly hydrating the inorganic chemical**, which produces the disperse phase of the dispersion. In addition to the **water vehicle**, other agents as **propylene glycol (PG), propyl gallate, and hydroxypropyl cellulose (HPC)** may be used to enhance gel formation.
- ▶ Because of the **high degree of attraction between the disperse phase and the aqueous medium in both magmas and gels**, these preparations remain fairly uniform on standing, with little settling of the **disperse phase**. However, **on long standing, a supernatant layer of the dispersion medium develops**, but the

uniformity of the preparation is easily reestablished by moderate shaking. **To ensure uniform dosage, magmas and gels should be shaken before use**, and a statement to that effect must be included on the label of such preparations.

Examples of gelling agents

1. Alginic acid

It is used in concentrations of **1% to 5%** as a thickening agent in gels. It swells in water to about 200 to 300 times its own weight without dissolving. Cross-linking - the linking between polymers via a chemical bond(s)- with increased viscosity occurs upon the addition of a calcium salt, such as **calcium citrate**. Alginic acid can be dispersed in water vigorously stirred for approximately 30 minutes.

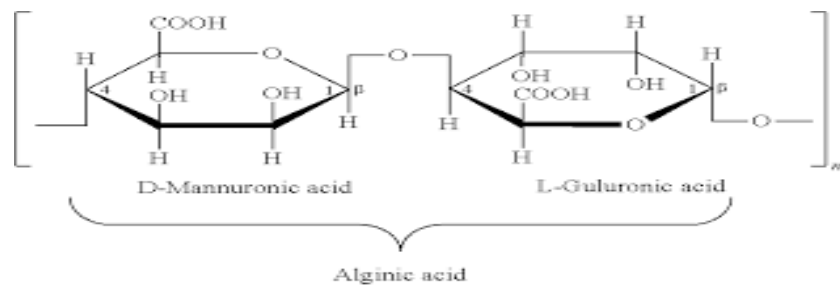


Figure 2: Alginic acid structure

2. Carbomer (Carbopol) resins:

They are fluffy white dry powders with large bulk density. The **0.5% and 1.0%** aqueous dispersions are pH **2.7 to 3.5** and **2.5 to 3.0**, respectively. There are many carbomer resins, with viscosity ranges from 0 to 80,000 cP such as **Carbomer 934** and **Carbomer 940**.

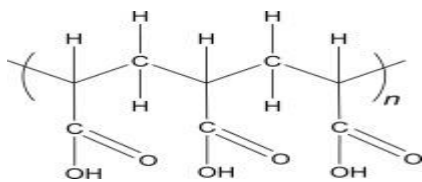


Figure 3: Carbomer structure

3. CMC in concentrations of **4% to 6%** of medium viscosity can be used to produce gels; glycerin may be added to prevent drying. Precipitation can occur below pH 2; it is most stable at pH 2 to 10, and maximum stability is at pH 7 to 9. It is incompatible with ethanol.

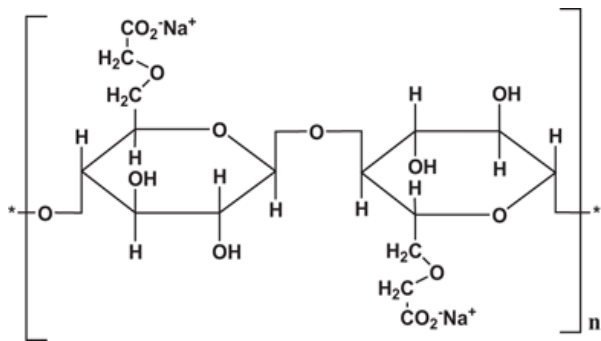


Figure 4: CMC sodium structure

4. CMC sodium is soluble in water at all temperatures. Once the powder is well dispersed, the solution is heated with moderate shear to about 60°C for fastest dissolution. These dispersions are sensitive to pH changes because of the carboxylate group.

5. Gelatin is dispersed in hot water and cooled to form gels.

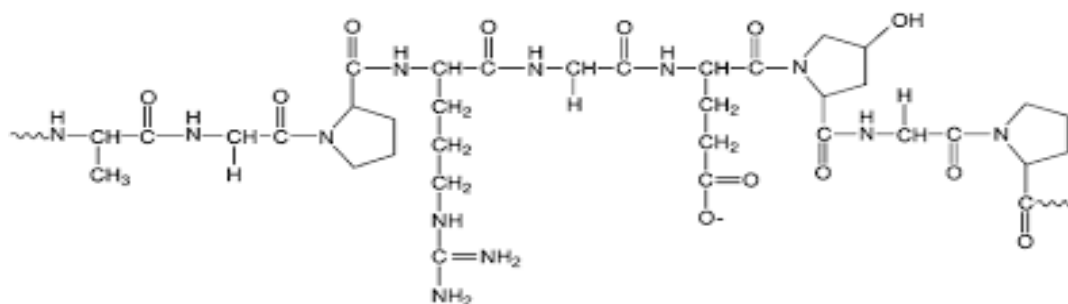


Figure 5: Gelatin structure

6. Methylcellulose is a long-chain substituted cellulose that can be used to form gels in concentrations up to about 5%. Because methylcellulose hydrates slowly in hot water, the powder is dispersed with high shear in about one-third of the required amount of water at 80°C to 90°C. Once the powder is finely dispersed, the rest of the water is added cold or as ice with moderate stirring to cause prompt dissolution. Maximum clarity, fullest hydration, and highest viscosity will be obtained if the gel is cooled to 0°C to 10°C for about an hour. A preservative should be added.

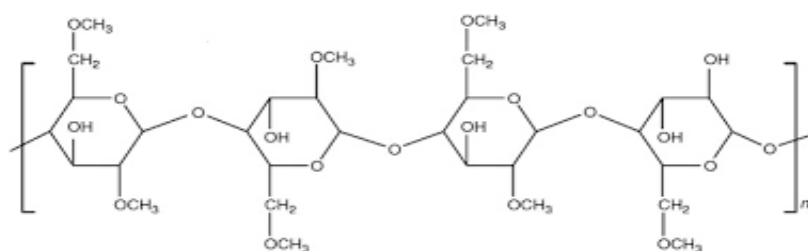


Figure 6: Methylcellulose structure

7. Plastibase, or Jelene, is a mixture of **5% low molecular weight polyethylene and 95% mineral oil**. A polymer, it is soluble in mineral oil above 90°C, close to its melting point. When cooled below 90°C, the polymer precipitates and causes gelation.

8. Poloxamer, or Pluronic, gels are made from selected forms of polyoxyethylene–polyoxypropylene copolymers in concentrations ranging from **15% to 50%**. Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the **124 (L-44 grade), 188 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade), and 407 (F-127 grade) types, which are freely soluble in water**. The “F” designation refers to the flake form. The “L” designation refers to the liquid form. The trade name **Pluronic**.

Pluronic F-127 has low toxicity and good solubilizing capacity and optical properties, and it is a good medium for topical drug delivery systems.

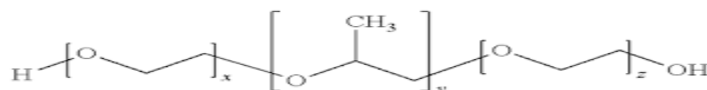


Figure 7: Poloxamer, or Pluronic structure

8. PVA is used at concentrations of about **2.5%** in the preparation of various jellies that dry rapidly when applied to the skin. For best results, disperse PVA in cold water, followed by hot water. It is less soluble in the cold water.

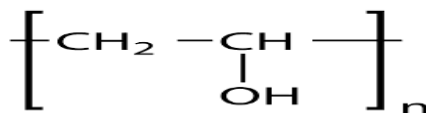


Figure 8: PVA structure

Examples of pharmaceutical gels

- 1. Sodium Fluoride and Phosphoric Acid Gel, USP**, is applied topically to the teeth as a dental care prophylactic.
- 2. Betamethasone dipropionate topical gel** anti-inflammatory and antipruritic agents.
- 3. Tretinoin Gel**, an irritant that stimulates epidermal cell turnover, causes peeling, and is effective in the treatment of acne.
- 4. Clindamycin topical gel, clindamycin and benzoyl peroxide topical gel and benzoyl peroxide gel** used in the control and treatment of acne vulgaris;
- 5. Hydroquinone gel** bleach for hyperpigmented skin;
- 6. Salicylic acid gel** a keratolytic;