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## 3. Colloidal Dispersion

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# Colloidal Dispersion

- A colloidal dispersion is a system in which particles of colloidal size (1.0 nm-0.5  $\mu\text{m}$ ), of any nature (e.g. solid, liquid or gas) are dispersed in a continuous phase of a different composition (or state).

← جزيئات صغيرة جدًا تتوزع في وسط مائل عندها (dispersed phase in continuous phase) ← تكون هذه الجزيئات صغيرة جدًا لكن أكبر من جزيئات المحلول

- **Magma**s and **gels**, are colloidal dispersion.

- If the disperse phase interacts appreciably with the dispersion medium, it is said to be lyophilic, meaning solvent loving. If the degree of attraction is small, the colloid is termed lyophobic, or solvent hating.

- Lyophilic colloidal systems are easier to prepare and have greater stability.

# Gel Definition

تعريف الجل

- Gels are defined as semisolid systems consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by a liquid.

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- Gels are also 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.

- Gels also are defined as a substantially diluted cross-linked system, which exhibits no flow when in the steady-state.

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بشكل كبير

الحالة الثابتة



# Gels

Gels are transparent semisolid dosage forms that can be formulated for oral, ophthalmic, nasal, topical, vaginal, or rectal administration.

Gels are mostly liquid; however, they behave as solids due to a three-dimensional cross-linked network within the liquid.

The essential additive or excipient to formulate a gel is called gelling agent.

Gelling agent undergo extensive cross-linking or enlargement when dissolved or dispersed in the dispersing medium. This cross linking increases the viscosity of the dispersing medium and restricts its movement which give the gel its structure (hardness) and make it adhesive to stick on skin.

Figure 1. Gel formation due to swelling of gelling agent

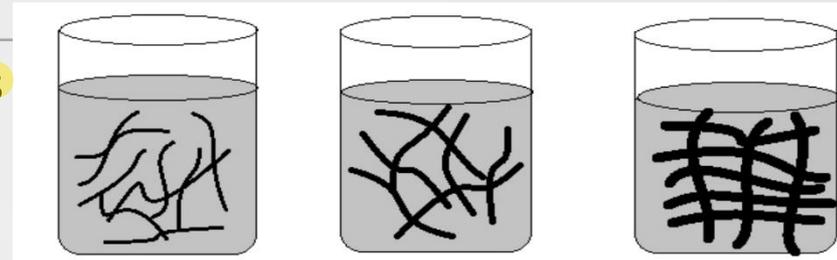
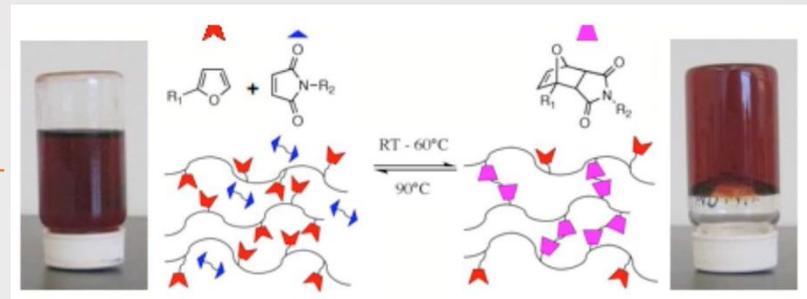


Figure 1. Gel formation due to swelling of gelling agent

→ or swelling

# Gel's classification

TABLE 14.4 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 carboxymethylcellulose, 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)

# Gel's classification:

## 1. Single Phase system

- If the gel does not appear to have discrete particles it is called a one-phase system.
- Single phase systems contain linear or branched polymer macromolecules that dissolve in water and have no apparent boundary with the dispensing medium. } → completely  
لا يمكن تمييز الوسط المنشأ عن الطور البعثر
- Macromolecules are classified as natural polymers (e.g. tragacanth), semisynthetic cellulose derivatives (e.g. methylcellulose), or synthetic polymers (e.g. carbomer polymers).
- Single phase gels made from natural macromolecules are called mucilages.

## 2. Two Phase system

- A two-phase system gel consists of floccules of small and distinct particles, these gels are frequently called a *magma* or a *milk* (e.g. milk of magnesia, aluminum hydroxide gel, bentonite magma).
- Two phase systems are thixotropic (semi solid on standing but liquefy when shaken).

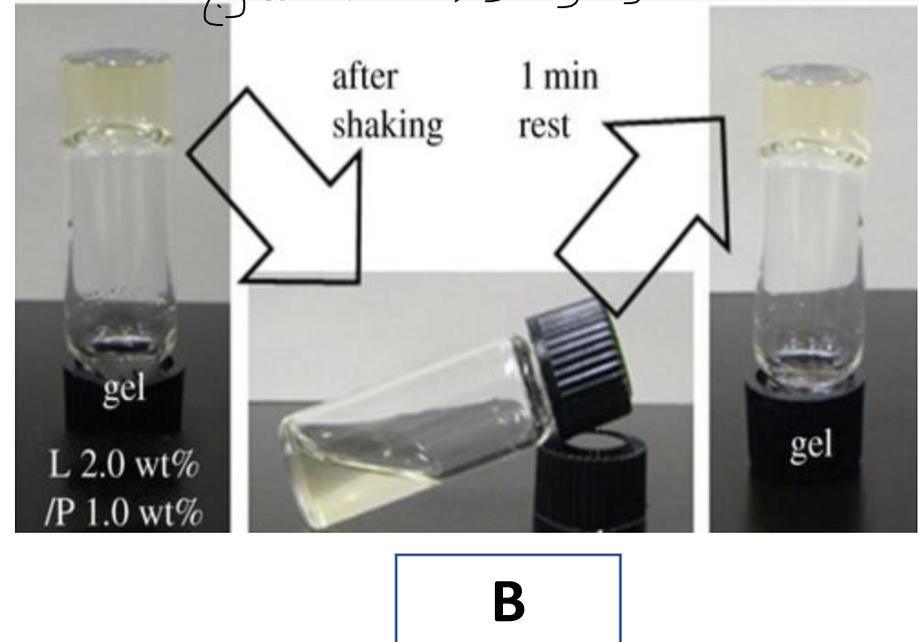
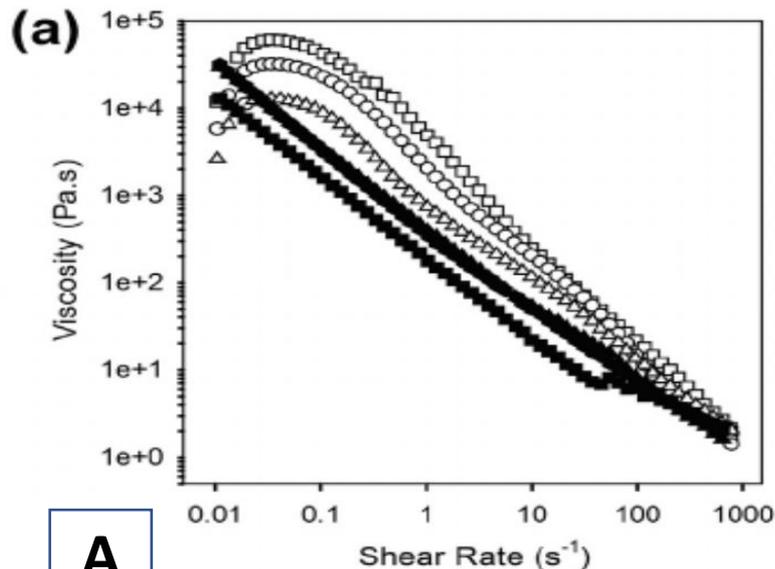


Figure 3. A) Viscosity curves showing thixotropic behaviour for fluid gels. B) Images for thixotropic gel before and after shaking.

# Gel Formulation Considerations

اعتبارات في تحضير الجيلات المرطبة



There are several formulation considerations open to the pharmaceutical scientist concerning the formulation of pharmaceutical gels.

The gelling agent ← يعطي القوام واللزوجة المطلوبة

The choice of vehicle ← مثل الماء أو الكحول

The inclusion of buffers ← مواد مستقرة pH



**These include:**

Preservatives

Antioxidants

Flavours/sweetening agents

Colours

# The choice of vehicle

Purified water is the normal solvent/vehicle used in the formulation of pharmaceutical gels.

However, co-solvents such as:

- Alcohol,
- Propylene glycol,
- Glycerol,
- Polyethylene glycol (usually polyethylene glycol 400)

may be used, to enhance the solubility of the therapeutic agent in the dosage form and/or (in the case of ethanol) to enhance drug permeation across the skin.

# The choice of vehicle

- ❑ If the drug has poor chemical stability and/or poor solubility in water or water-based vehicles, pharmaceutical gels may be formulated using polyhydroxy solvents, e.g. propylene glycol, glycerol, polyethylene glycol 400 as vehicles and polyacidic polymers, e.g. poly (acrylic acid) as gelling agent.

# Common gelling agents:

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## 1) Carbomers

- Carbomer is a <sup>poly</sup> generic name for a family of polymers known as Carbopol®.
- Form acidic aqueous solutions (pH around 3).
- Thicken at a higher pH (5 or 6) → swell as much as 1,000 times their original volume.
- A neutralizer (e.g. sodium hydroxide, triethanolamine) is added to increase the pH.

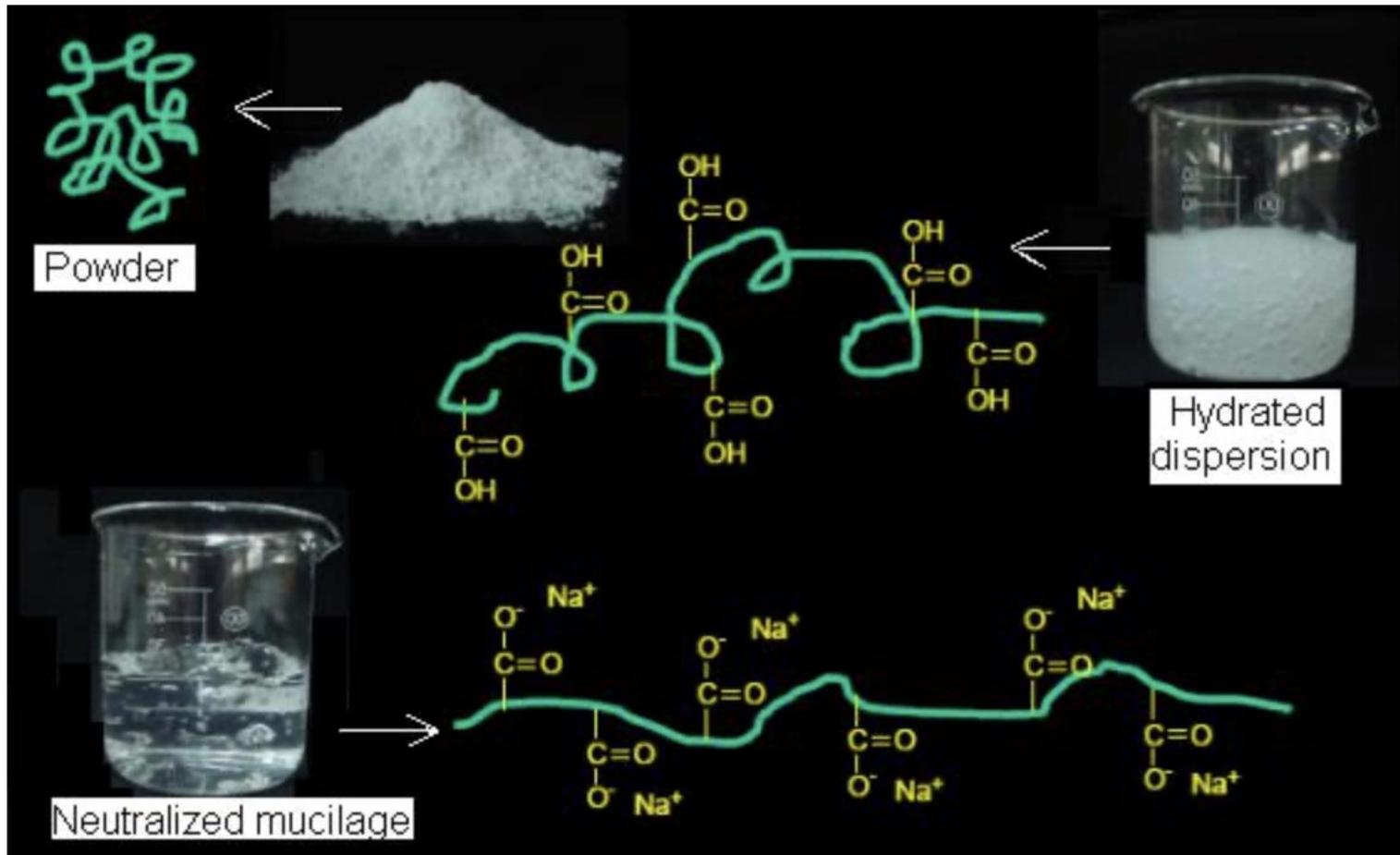


Figure 4. The process of the neutralisation and the Carbomer's molecule state

# Carbomer grades:

Polymer Name	Viscosity*	Properties
Carbopol® 910	3,000 - 7,000	Effective in low concentrations and will provide a low viscosity formulation.
Carbopol® 934	30,500 - 39,400	Effective in thick formulations such as emulsions, suspensions, sustained-release formulations, transdermals, and topicals. Forms clear gels with water.
Carbopol® 934P	29,400 - 39,400	Same properties as 934 but intended for pharmaceutical formulations. "P" = highly purified product
Carbopol® 940	40,000 - 60,000	Effective in thick formulations, very good clarity in water or hydroalcoholic topical gels. Forms clear gels with hydroalcoholic systems.
Carbopol® 941	4,000 - 11,000	Produces low viscosity gels, very good clarity.

\* 0.5% solution, pH 7.5

## 2) Cellulose derivatives

include:-

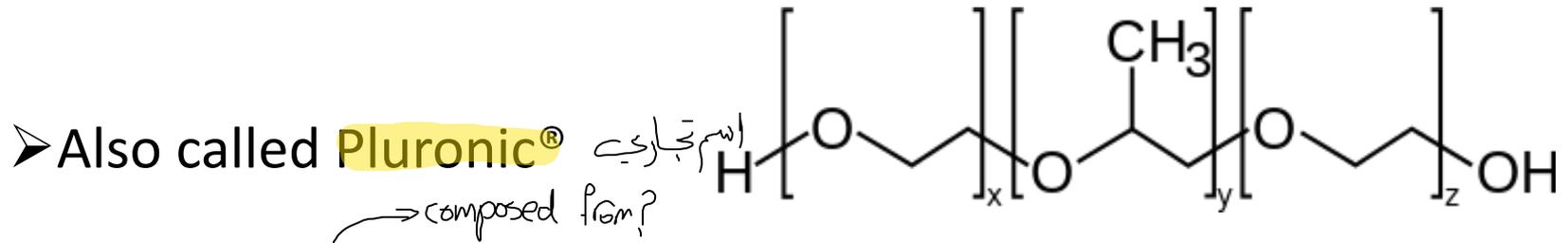
➤ <sup>1</sup>Methylcellulose, <sup>2</sup>hydroxyethylcellulose, <sup>3</sup>hydroxypropyl cellulose, <sup>4</sup>hydroxypropylmethyl cellulose, and <sup>5</sup>carboxymethyl cellulose).

➤ All cellulose derivatives **except** carboxymethyl cellulose maintain the viscosity of the gel over a wide pH range (3-11). CMC can maintain the viscosity between pH 7-9.

➤ The addition of salts to medium reduces the ability of cellulose to hydrate → <sup>ترطيب</sup>

← يقلل من قدرة السيليلوز على الإلتصاق والترطيب ← يؤثر على تكوين الجل وقوامه

### 3) Poloxamers



➤ Are **copolymers** of **polyoxyethylene** and **polyoxypropylene**

➤ They **forms reverse thermal gels** in **conc. ranging from 15-**

**20%** لے سائلہ عند التبريد تتحول إلى جل عند درجة حرارة الغرفة

➤ Liquids at cool temperature and gels at room or body temperature.

# Points to take in consideration regarding gelling agents

1. If the gelling agent is added to the dispersing medium too rapidly the agents tend to clump → layer with a gelled surface that is more difficult for the medium to hydrate.

## ➤ Some compounding techniques to minimise the problem:

- Sift the powders into the vortex of the rapidly stirring medium. لما فرقت الماء بشكل → تكون دوامة في المنتصف ← نضيف عليها (gelling agent) تدريجياً خلل
- Levigate the powder with a water miscible non-solvent such as absolute alcohol or propylene glycol. خلط powder مع محلول غير مائي قابل للذوبان في الماء تكون عجينة ناعمة
- Use a blender to mix the powder and solvent homogenously. يسهل خلطها مع الماء خلط

2. The solubility of some gelling agents is affected by water temperature , e.g.:

- Methylcellulose and poloxamers have better solubility in cold water.
- Bentonite, gelatin, and sodium carboxymethylcellulose are more soluble in hot water.
- Carbomers, tragacanth, and alginic acid gels are made with tepid water.

ماء فاتر

## Points to take in consideration regarding gelling agents

3. Some gelling agents (e.g. carbomers) require a “neutraliser” or pH adjusting chemical to <sup>تجویز</sup> create the gel after the gelling agent has been wetted in the dispersing medium.
4. Most gelling agents require 24 to 48 hours to completely hydrate and reach maximum viscosity and clarity.
5. Gelling agents are commonly used in concentrations of 0.5-2% but some may be used up to 10%.
6. It is easier to add the active drug before the gel is formed if the drug doesn't interfere with the gel formation.

← تداخل

# The inclusion of buffers

تعمل على تثبيت الرقم الهيدروجيني وهو خليط من حمض ضعيف وملكه أو قاعدة ضعيفة وملكها

- As in other pharmaceutical formulations, buffers (e.g. phosphate, citrate) may be included in aqueous and hydroalcoholic-based gels to control the pH of the formulation.
- The solubility of buffer salts is decreased in hydroalcoholic-based vehicles.

# Preservatives

المواد الحافظة

➤ Aqueous-based pharmaceutical gels require the inclusion of preservatives.

➤ It should be remembered that <sup>تذكر</sup> certain preservatives, e.g. parabens, phenolics, interact with the hydrophilic polymers used to prepare gels, thereby reducing the concentration of free (antimicrobially active) preservative in the formulation.

لجزء الفعالة لمقاومة الميكروبات

➤ Therefore, to compensate for this, the initial concentration of these preservatives should be increased.

# Antioxidants

- Antioxidants may be included in the gel formulation to increase the chemical stability of therapeutic agents that are prone to oxidative degradation.
- The choice of antioxidants is based on the nature of the vehicle used to prepare the pharmaceutical gel.
- Therefore, as the majority of pharmaceutical gels are aqueous-based, water-soluble antioxidants, e.g. <sup>①</sup> sodium metabisulphite, <sup>②</sup> sodium formaldehyde sulfoxylate, are commonly used.

## ➤ Flavours/sweetening agents:

- Flavours and sweetening agents are only included in pharmaceutical gels that are designed for administration into the oral cavity, e.g. for the treatment of infection, inflammation or ulceration.

## ➤ Colours

- Colours may be (but are not usually) added into pharmaceutical gels.

# Preparation of gels

1. In the manufacture of pharmaceutical gels, generally the water-soluble components/excipients are initially dissolved in the vehicle in a mixing vessel with mechanical stirring.   
﴿خلط مكوناتي﴾
2. The hydrophilic polymer must be added to the stirred mixture slowly to prevent aggregation and stirring is continued until dissolution of the polymer has occurred.   
لذوب
3. Aqueous polymeric solutions, especially of cellulose derivatives, are stored for approximately 48 hours after dissolution to promote full hydration, maximum viscosity and clarity.   
شفافية
4. It should be noted that excessive stirring of pharmaceutical gels results in entrapment of air.   
﴿احتباس الهواء داخله﴾

However, certain measures can be taken to prevent this:

- The mixing rate must not be excessive
- A mixing vessel may be used to which a vacuum may be pulled, thereby removing air.

﴿تحت ضغط فراغ﴾

# Storage and Packaging

➤ Gels generally are stored in tight containers refrigerated or room temperature.

لے عبوات محکمہ الا علاق

➤ Carbomer polymers are quite hygroscopic → store away from moisture.

لے شدیدہ احتیاط الرطوبه

الرطوبه

➤ Gels are available in tubes, jars, squeeze bottles, pump dispensers.

# Observing formulations for evidence of instability:

لے مراقبتہ التزکیمات لردہ حالات  
عدم الإستقرار

➤ Gels should be observed for:

1. Shrinkage الإنحماش
2. Separation of liquid انفصال الكل عن السائل
3. Discoloration
4. Microbial contamination التلوث الميكروبي



# Example of gels

- Fluocinonide Gel, USP, an anti-inflammatory corticosteroid.
- Tretinoin Gel, USP, stimulates epidermal cell turnover, causes peeling, and is effective in the treatment of acne. حب الشباب  
تقشر
- Erythromycin and benzoyl peroxide topical gel.
- Lubricating Jelly formula

Lubricating jellies are used: 

1. To assist in medical procedures,
2. To aid in insertion of various devices and drugs, including catheters and suppositories,
3. As a vehicle for some drugs products, especially in extemporaneous compounding.