Colloidal Dispersion
Gel and magma

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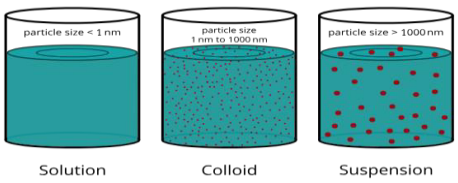
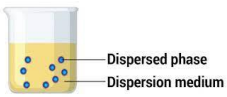
[Small particles]

← Colloidal Dispersion

- A colloidal dispersion is a system in which particles of colloidal size (1.0 nm-0.5 µm), of any nature (e.g. solid, liquid or gas) are dispersed in a continuous phase of a different composition (or state).
- **Magmas** 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.

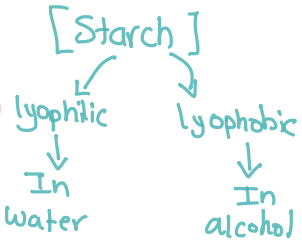




- lyophobic = Solvent hating
  * the degree of attraction → small
- Lyophilic = Solvent loving.
  * easier to prepar
  * greater Stability

(lyophilic) ← إذا عمل الماء interaction مع الماء

- These terms are more suitably used when reference is made to the specific **dispersion medium**, for a single substance may be lyophobic with respect to one **dispersion medium** and lyophilic with respect to another.
- For instance, starch is lyophilic in water but lyophobic in alcohol.
- Terms such as hydrophilic and hydrophobic, which are more descriptive of the nature of the colloidal property, have therefore been developed to refer to the attraction or lack of attraction of the substance specifically to water



lyo ← Solvent إذا بحكي عن *
hydro ← water إذا بحكي عن

lyo ← غالباً في [organic] *

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- Lyophobic colloids are generally composed of inorganic particles.
- When these are added to the dispersing phase, there is little if any interaction between the two phases.
- Unlike lyophilic colloids, lyophobic materials **do not spontaneously** disperse but must be encouraged to do so by special individualized procedures.
- Their addition to the dispersion medium does not greatly affect the viscosity of the vehicle

إضافتهم لا تؤثر على اللزوجة

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LYOPHILIC COLLOIDS
VERSUS
LYOPHOBIC COLLOIDS

Lyophilic colloids	Lyophobic colloids
Lyophilic colloids are solvent loving colloids	Lyophobic colloids are solvent hating colloids
Thermodynamically stable	Thermodynamically unstable
Precipitation in the lyophilic sol is a reversible process	Precipitation in the lyophobic sol is an irreversible process
There is a strong attraction force between colloids and the liquid	There is less or no attraction between colloids and the liquid
Highly viscous	Have the same viscosity as the solvent
Form a lyophilic sol	Form a lyophobic sol
Known as hydrophilic colloids when water is taken as the solvent	Known as hydrophobic colloids when water is taken as the solvent
A lyophilic sol can be prepared by the direct addition of colloids into the liquid	A lyophobic sol can be formed from special techniques such as mechanical agitation

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Definition

dispersions: small inorganic / large organic; liquid

- 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.

-restricted by ⇒ interlacing three dimensional network

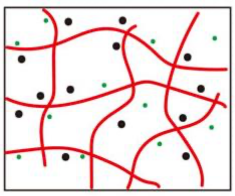
- Gels are also defined as semi-rigid systems in which the movement of the dispersing medium is restricted by an **interlacing three-dimensional network** of particles or solvated macromolecules of the dispersed phase.

نظام متقاطع خفيف إلى حد كبير

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

لا يظهر اي تدفق عندما يكون في الحالة الثابتة

F Nano/Micro-composite hydrogels



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Gels

Gels are transparent semisolid dosage forms that can be formulated for oral, opthalmic, 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**.

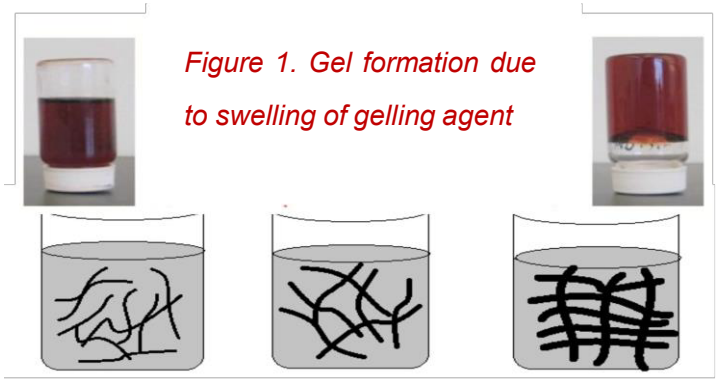

Figure 1. Gel formation due to swelling of gelling agent

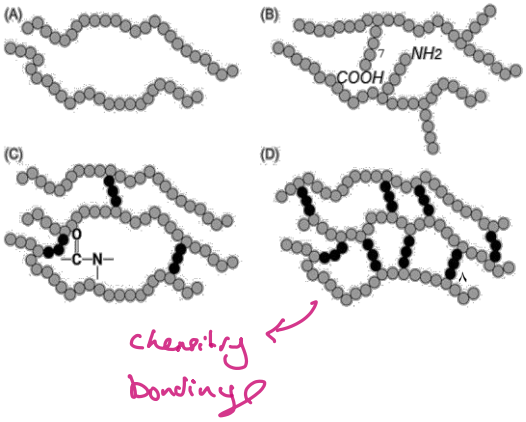

Figure 2. Gel formation due to crosslinking of gelling agent

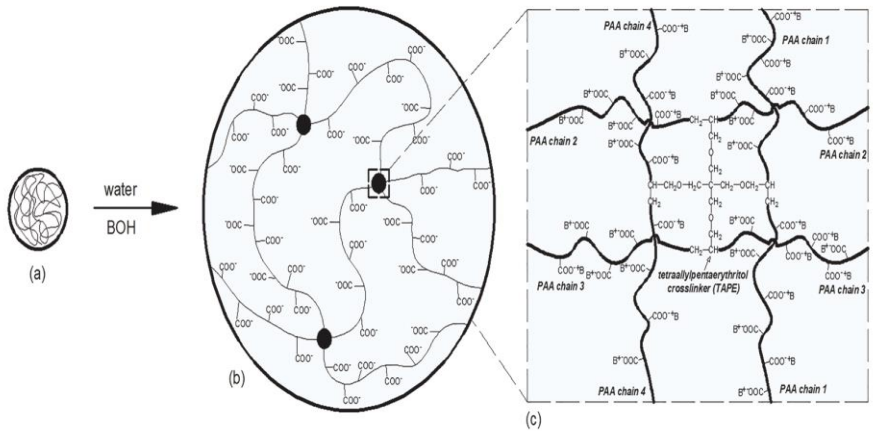

Figure 2. Schematic visualization of Carbopol particle, (a) Carbopol in solid state contains COOH groups, (b) after neutralisation in an alkali aqueous solution (notice the dissociated COO^- groups where solid circles represent one particular cross-linked node) shown in (c) in more detail.

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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	Pectin paste, Tragacanth jelly
	Natural and synthetic gums	Methylcellulose, sodium carboxymethylcellulose, Pluronic
	Inorganic hydrogels	Bentonite gel (10%–25%), Veegum, silica
Organogels	Hydrocarbon type	Petrolatum, mineral oil/polyethylene gel (Plastibase)
	Animal, vegetable fats	Lard, cocoa butter
	Soap base greases	Aluminum stearate with heavy mineral oil gel
	Hydrophilic organogels	Carbowax bases (PEG ointment)
	Polar	
	Nonionic	

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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.
- **Macromolecules are classified as:**

1. natural polymers (e.g. tragacanth),
2. semisynthetic cellulose derivatives (e.g. methylcellulose), or
3. synthetic polymers (e.g. carbomer polymers).

- Single phase gels made from natural macromolecules are called **mucilages**.

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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).

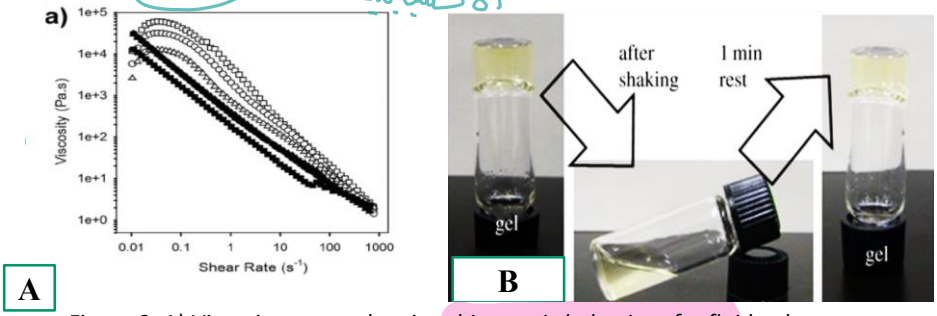

Figure 3. A) Viscosity curves showing thixotropic behaviour for fluid gels.

B) Images for thixotropic gel before and after shaking.

Gel Formulation Considerations

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

These include:

1. The gelling agent
2. The choice of vehicle
3. The inclusion of buffers
4. Preservatives
5. Antioxidants
6. Flavours/sweetening agents
7. Colours

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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.

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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:
  - A. polyhydroxy solvents, e.g. propylene glycol, glycerol, polyethylene glycol 400 as vehicles and
  - B. polyacidic polymers, e.g. poly (acrylic acid) as gelling agent.

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Common gelling agents:

1) Carbomers

- Carbomer is a 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.

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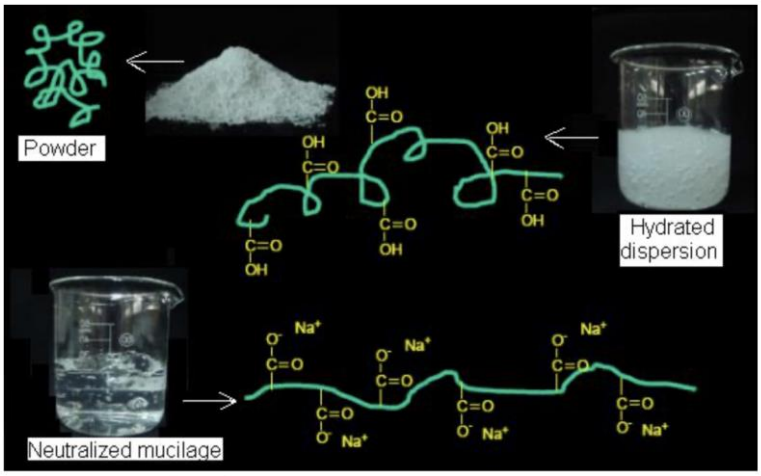

Figure 4. The process of the neutralisation and the Carbomer's molecule state

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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

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Common gelling agent.

2) Cellulose derivatives

- Methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and carboxymethyl cellulose).

كل المجموعات هاي الزوجية من (٣-١١) ما عدا Carboxymethyl

- 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

لـ يقلل من قدرة الميديا على الترطيب

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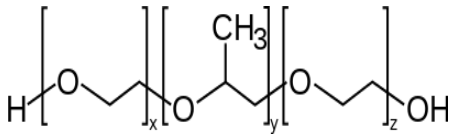
3) Poloxamers

منديج بين ٢ بوليمير



- Also called Pluronic®
- Are copolymers of polyoxyethylene and polyoxypropylene
- They forms reverse thermal gels in conc. ranging from 15-20%

مرتبة بالحرارة

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

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لئة في حالة حرارة الغرفة

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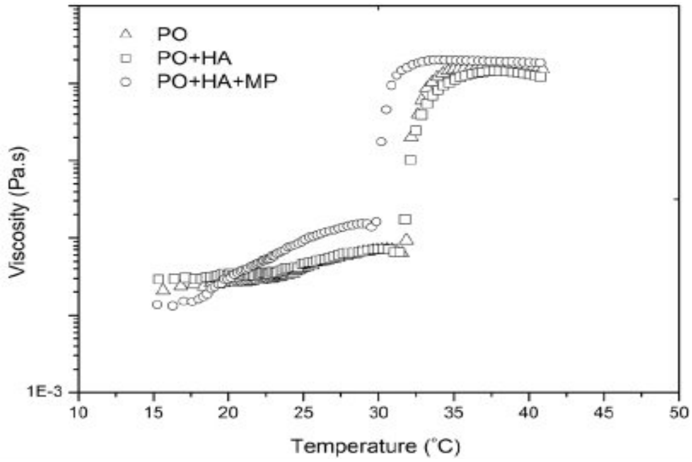

Figure 5. The viscosity temperature curve for three gel formulation containing Pluronic (PO).

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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.

- Levigate the powder with a water miscible non-solvent such as absolute alcohol or propylene glycol.
- Use a blender to mix the powder and solvent homogenously.

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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.

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3. Some gelling agents (e.g. carbomers) require a "neutraliser" or pH adjusting chemical to 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.

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The inclusion of buffers

للستخدمة عشان اعادل موضع درجة الـ (pH)

- 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.

مركبات الماء الكحولية

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مادة بستخدمها عشان مايتكون عندي ميكروبات في علبة الجل

Preservatives

للازم نعمله ادراج

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

- It should be remembered that 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.

مشكلة بتحنا كل ح ماده اخرى

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

حل : اعلى الكمية بزيد من التركيز شوية

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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. sodium metabisulphite, sodium formaldehyde sulphoxylate, are commonly used.

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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.

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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.

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.

3. Aqueous polymeric solutions, especially of cellulose derivatives, are stored for approximately 48 hours after dissolution to promote full hydration, maximum viscosity and clarity.

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4. It should be noted that excessive stirring of pharmaceutical gels results in entrapment of air.

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.

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التخزين والحفظ

Storage and Packaging

على حرارة الغرفة

- Gels generally are stored in tight containers refrigerated or room temperature.
- Carbomer polymers are quite hygroscopic→ store away from moisture.
- Gels are available in tubes, jars, squeeze bottles, pump dispensers.

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Observing formulations for evidence of instability:

- Gels should be observed for:
  1. Shrinkage   انكماش
  2. Separation of liquid   انفصال الماء عن المادة
  3. Discoloration   ظهور ألوان غريبة
  4. Microbial contamination   تلوث

• أي تكون خلال التصنيع على الاحصار شيء unstable

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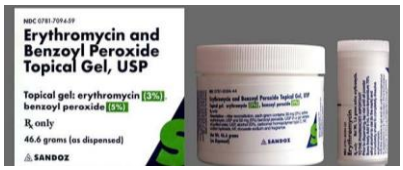
Example of gels

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



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Examples gels

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.

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