3. Colloidal Dispersion

تدريجي

هي نظام تكون فيه الجسيمات
ليست صغيره جداً مثل محلول
حقيقي
suspension وليست كبيره جداً مثل
بل تكون بحجم متوسط يجعلها موزعة
داخل وسط آخر

* حجم الجسيمات يكون بين 0.5µm - 1nm
اصغر يكون محلول حقيقي كل اكبر يكون suspension

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.

* اذا كان الطور المبعثر يحب الوسط وينجذب له يسمى Lyophilic أو محب للمذيب

* اذا كان الجذب ضعيف للطور المبعثر يسمى Lyophobic أو كاره للمذيب

Gel

شكله semisolid

يحتوي كمية كبيرة من السائل

Difinition

- 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.

- 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-liked system, which exhibits no flow when in the steady-state.

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.

* الجل اغلبه سائل لكنه بتعرف ك صلب
ذلك لانه بداخله شبكه ثلاثيه الابعاد متشابكه
وهاي الشبكه تعطيه: لزوجه ع تماسك ع قدرعلى الالتصاق

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

هذا يعطي الجل ٪-
١- قوام
2- صلابه نسبيه (تماسك)
3- الالتصاق بالجلد (حتى يضل في مكانه ويعطي مفعول دوائي)

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.

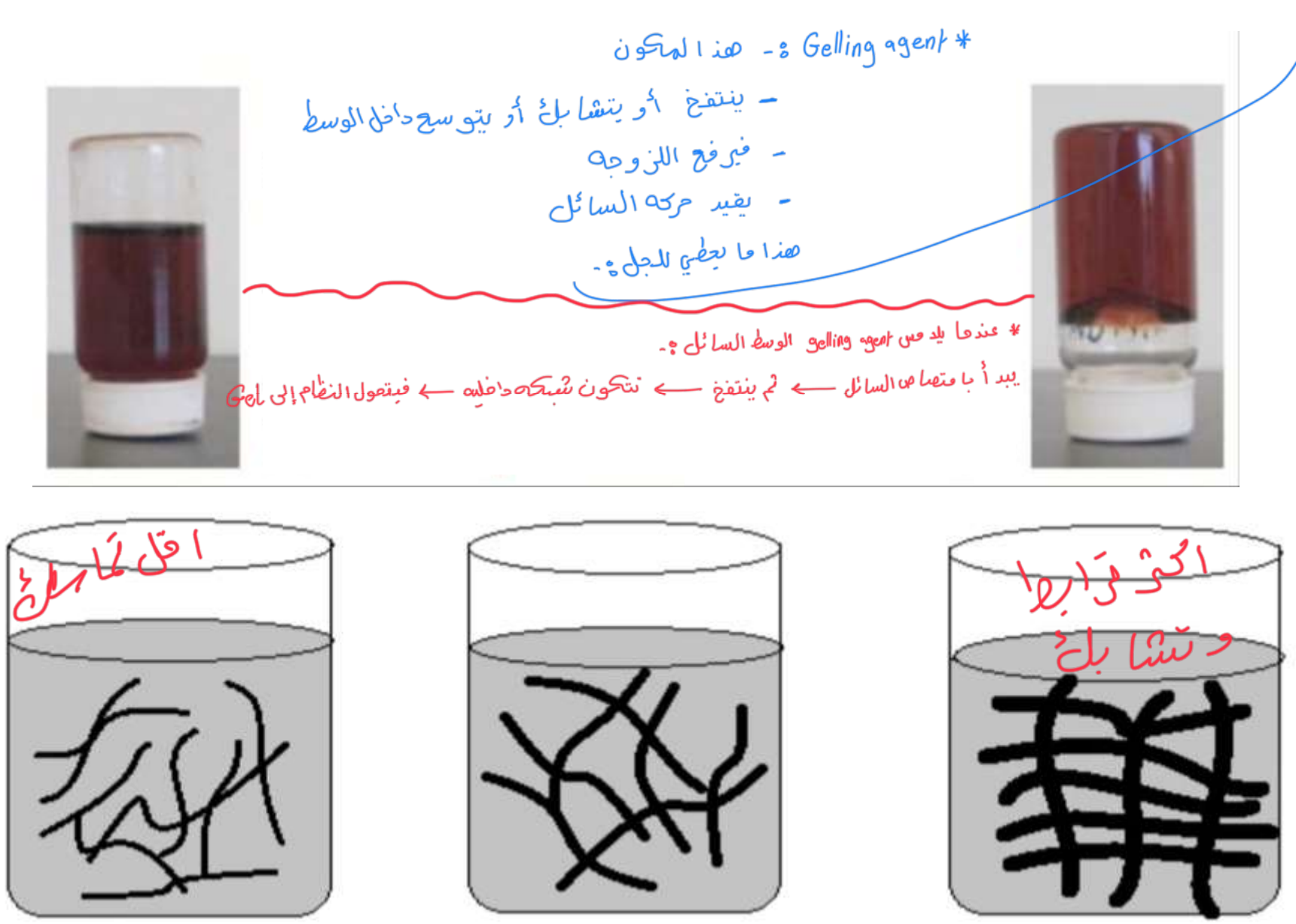


Figure 1. Gel formation due to swelling of gelling agent

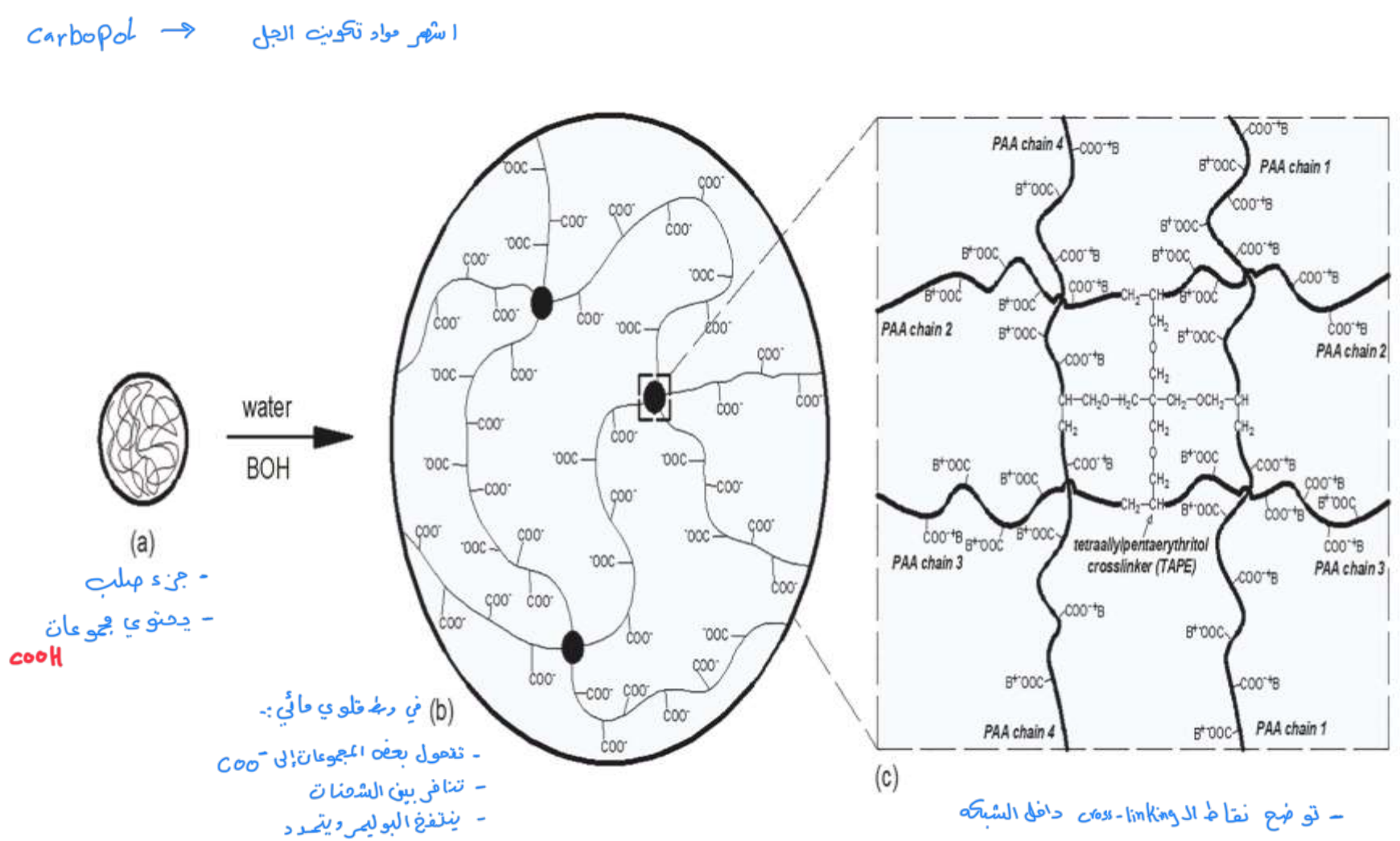


Figure 2. Schematic visualization of Carbopol particle, (a) Carbopol in solid state contains COOH groups, (b) after neutralisation in an alkali aqueous solution (notice the dissociated COO^- groups where solid circles represent one particular cross-linked node) shown in (c) in more detail.

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	

* نوعين رئيسيين:
Single Phase system
Two Phase system

* الجلات لا تعتبر نوع واحد بس ، بل يمكن تقسيمها حسب :-
- شكل الطور المبعثر
- اذا كانت المكونات ظاهره أو مش ظاهره
- طبيعه الشبكه الداخليه

Gel's classification:

1. Single Phase system

لا يحتوي جسيمات منفصلة واضحة
لا تتي ميه حدود تفصل بين الجسيمات والوسط

- 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 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.

هذا النوع عاده :- متجانس / ناعم / لا تشعر بوجود دقائق منفصله

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).

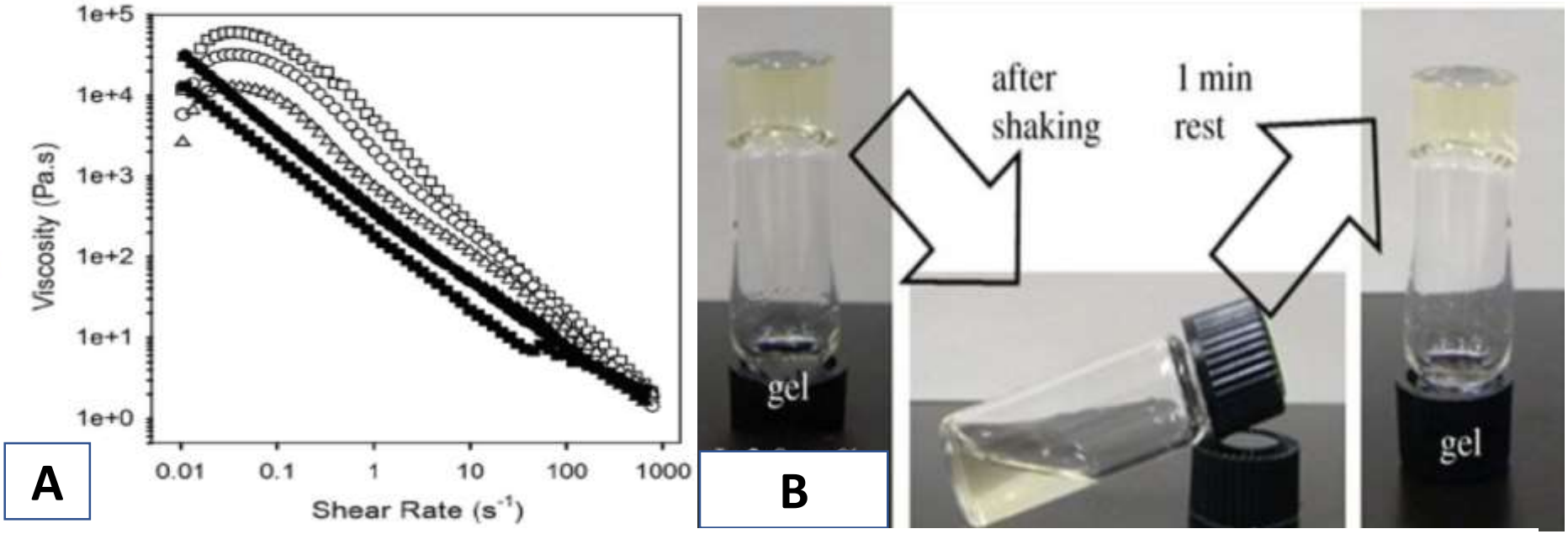
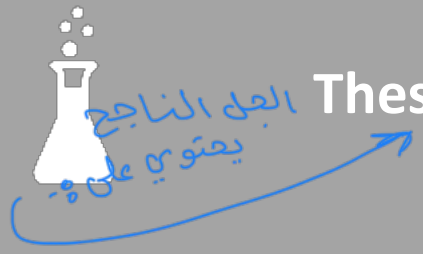


Figure 3. A) Viscosity curves showing thixotropic behaviour for fluid gels. B) Images for thixotropic gel before and after shaking.

Gel Formulation Considerations

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



These include:

- The gelling agent ← العامل المكون للجل
- The choice of vehicle ← اختيار الوسط أو المذيب
- The inclusion of buffers ← تنظيم PH
- Preservatives ← مواد حافظه
- Antioxidants ← مضادات الاكسده
- Flavours/sweetening agents ← نكهات ومحليات
- Colours ← الالوان (صبغه)

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.

ليش نستخدمه ؟
- اكثر ملاءمه للدواء
- افضل في الثبات
- مناسب من حيث اللزوجه

Common gelling agents:

* عند رفع PH :-
- ثابت المجموعات الحمضيه
- تتمدد السلاسل
- زياده اللزوجه
- تشكل الجل

أشهر مواد تشكيل الجل

1) Carbomers

- Carbomer is a generic name for a family of polymers known as Carbopol®.

اسم تجاري

- 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.

* Carbomer :- من اهم البوليمرات في الجلات الموضوعيه كانه :-
- يعطي قوام جيد
- شفاف
- ثابت نسبي

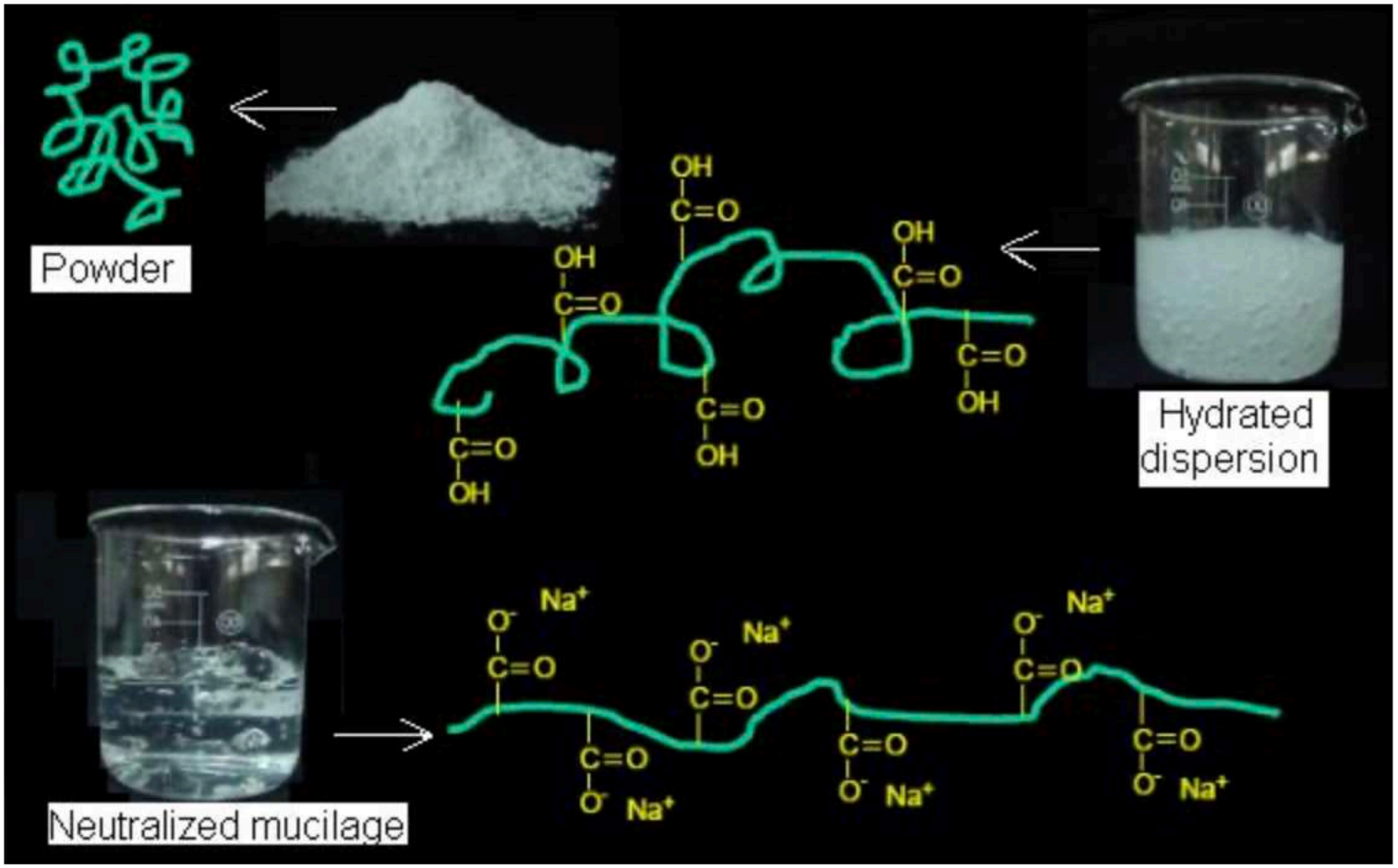


Figure 4. The process of the neutralisation and the Carbomer's molecule state

Carbomer grades:

* شو يعني اختلاف الدرجات ؟
يعني ان كل نوع يعطي لزوجه مختلفه ، استخدام مختلف ، شفافيه مختلفه

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

* مشتقات السليلوز ممتازه لانها:-
- مرنه
- مستقره نسبيًا عبر PH واسع
- شائعه في المستحضرات الدوائيه

2) Cellulose derivatives

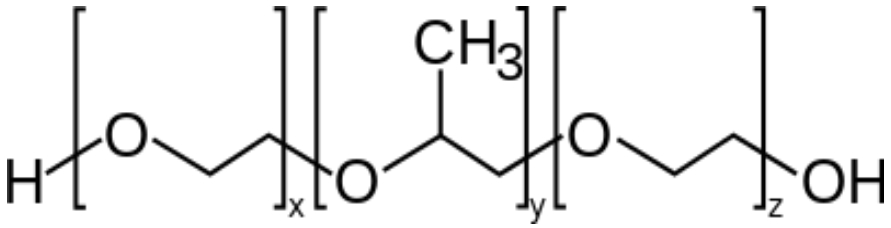
انوع من

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

- All cellulose derivatives except carboxymethyl cellulose (CMC) 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

3) Poloxamers



- Also called Pluronic®
- Are copolymers of polyoxyethylene and polyoxypropylene
- They forms reverse thermal gels in conc. ranging from 15-20%
- Liquids at cool temperature and gels at room or body temperature.

تكون سائله في الجو البارد ، تتحول إلى جل في حراره الغرفه

اهم ميزه لها انه تعطي ؛؛

* reverse thermal gels :-
هاي الخاصيه مهمه ومفيده ، لانها عند التحضير وهي باره تكون سائله و يسهل التعبئه ، عند وضعها بجراه الجسم او الغرفه تصبح جل .
و هاي الخاصيه تجمع بين سهوله التطبيق و الثبات بعد الاستعمال

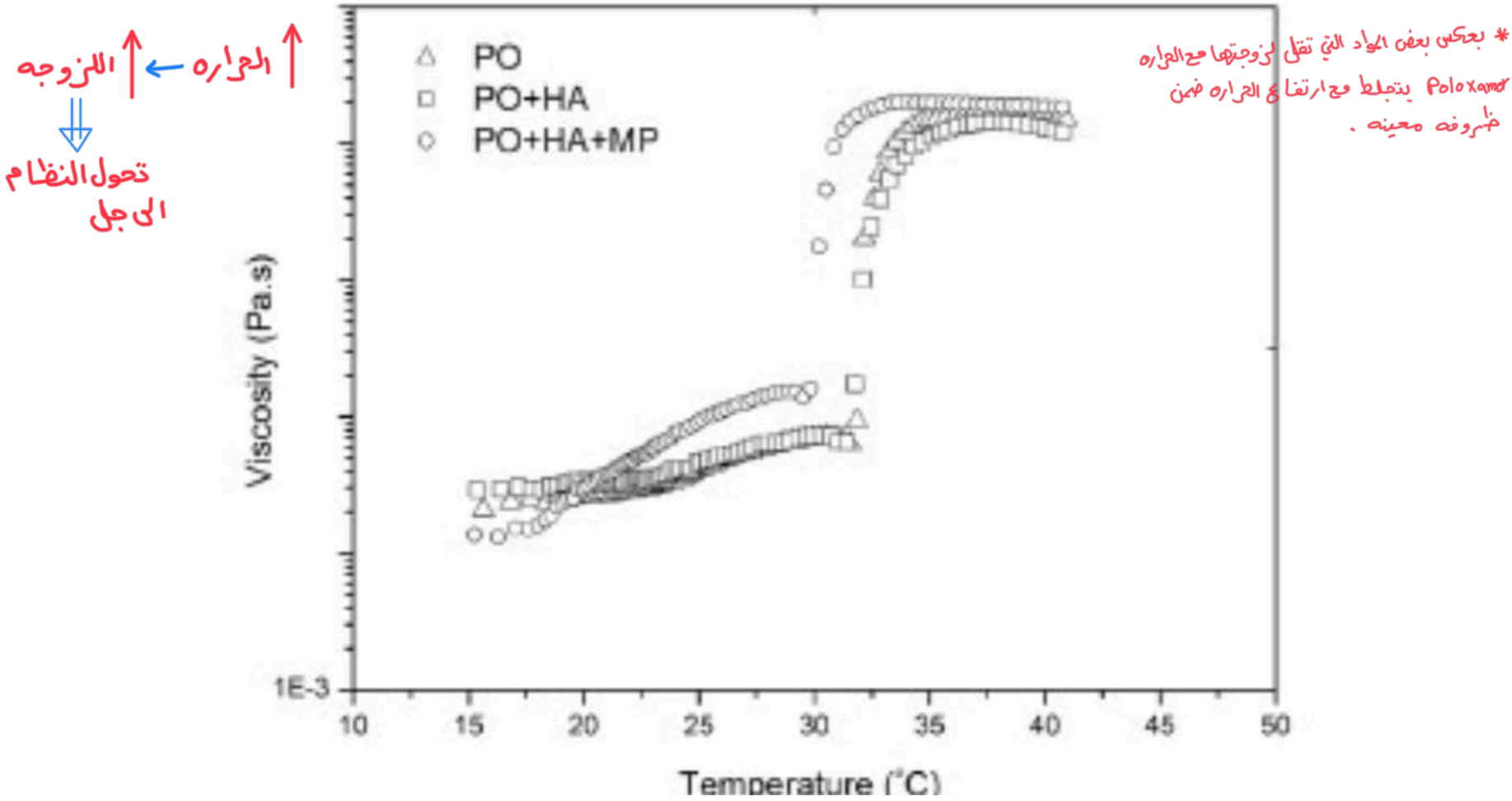


Figure 5. The viscosity temperature curve for three gel formulation containing Pluronic (PO).

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.

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

* درجه حراره الماء جزء اساسي من نجاح التحضير

* استعمال حراره غير مناسبه قد يسبب ...
- فشل في الذوبان
- تكتل
- لزوجه غير الصحيحه

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.

يعيق

* ليش اضافه الدواء قبل تكون الجل أفضل ؟ -
لانه إدخاله بعد تكون الجل راح يكون اصعب من ناحيه
التوزيع و التجانس و منع الفقاعات

تثبيت PH
و منع تغير بسهوله

The inclusion of buffers

- 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.

* PH مهم في الجلات ، ليش ؟
- ثبات الدواء
- لزوجه الجل

* في الانظمه المائيه الكحوليه ، تقل ذوبانيه املاح الbuffer
معنى ذلك ، اذا كان الوسط يحتوي كحول ؛-
- قد لا تذوب املاح الbuffer ، وهذا يسبب مشاكل في الثبات والتحضير

Preservatives

ليش بنحتاجها ؟
لان الجلات المائيه بيئه مناسبه لنمو الميكروبات خاصه البكتيريا والفطريات

- 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.

- Therefore, to compensate for this, the initial concentration of these preservatives should be increased. ⇒ حتى نحافظ على الفعاليه المطلوبه

* مش كل شي نضيفه من المواد الحافظه يبقى حرًا و فعالا ، لانه جزء منه رح يرتبط مع Polymer

ليش نضيفها ؟
لحمايه الادويه التي تتحلل من oxidative degradations
التعلل بالأكسده
التأكسد

Antioxidants

- Antioxidants may be included in the gel formulation to increase the chemical stability of therapeutic agents that are prone to oxidative degradation.

نختارها حسب الوسط المستحلل في الجل

- 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.

* الهدف النهائي :-
زياده الثبات الكيميائي
زياده العمر التخزيني
زياده الحفاظ على فعاليه الماده الدوائيه

ليش تستخدم ؟
حتى يكون المستحضر مقبول الطعم
اسهل استعمالا

➢ 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 ⟹

ليش ؟
تحسين المنتج ، تحسين المظهر

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

Preparation of gels

الجزء العملي

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.

* اذا حركنا الجل الكثير من اللازم ؟-
يدخل الهواء داخله ، فيتكون فقاعات
وهذه مشكله لانه تؤثر على النجانس ، وممكن تعطي قياس خاطئ للحجم

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.

Storage and Packaging

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

تمتص الرطوبه من الجو ، لذلك تحفظ بعيداً عن الرطوبه

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

عبوات الجل

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

Observing formulations for evidence of instability:

- Gels should be observed for:

1. Shrinkage
2. Separation of liquid
3. Discoloration
4. Microbial contamination

* اذا ظهرت هاي العلامات ، فالتركيبه قد تكون في مستقره
او حدث خلل في الحفظ ، أو فشل في نظام المواد الحافظه
او عدم توافق بين المكونات

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.

Examples gels

Lubricating Jelly formula

- Lubricating jellies are used:

جلا ن قُ لقه

1. To assist in medical procedures, مثل فحوصات (العين ، تنظير القلب)
2. To aid in insertion of various devices and drugs, including catheters and suppositories, ⇒ تعاميل
3. As a vehicle for some drugs products, especially in extemporaneous compounding.

1) ما هو النظام الغروي؟

هو نظام تكون فيه جسيمات متوسطة الحجم مبعثرة داخل وسط آخر.

2) ما هو الجل؟

شكل نصف صلب، يحتوي كمية كبيرة من السائل، لكن هذا السائل محبوس داخل شبكة ثلاثية الأبعاد.

3) لماذا الجل يبدو صلبًا رغم أنه غني بالسائل؟

بسبب وجود gelling agent الذي يشكل شبكة داخلية تزيد اللزوجة وتقيد الحركة.

4) ما أنواع الجلات؟

* Single phase
* Two phase

5) ما معنى Thixotropy؟

الجل يكون متماسكًا عند السكون، ويصبح أكثر سيولة عند الرج أو التحريك.

6) ما أهم عوامل تكوين الجل؟

* Carbomers
* Cellulose derivatives
* Poloxamers

7) ما الأمور المهمة عند تركيب الجل؟

* نوع العامل المجلّط
* الوسط
* pH
* buffers
* preservatives
* antioxidants
* طريقة التحضير
* التخزين

8) كيف أعرف أن الجل غير مستقر؟

من خلال:

* الانكماش