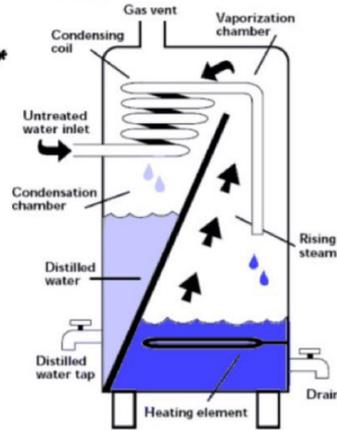
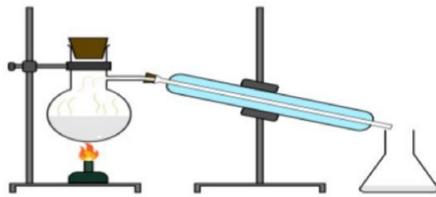


Methods for preparing Purified water:

1) Distillation method (Simplest)

- **Distillation** is a process of separating the component substances from a liquid mixture by selective evaporation and condensation

* للتجزير والتكثيف الإنتقائي ..



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Methods for preparing Purified water:

2) Ion- exchange method

- Advantages over distillation method:

- No heat is required ← ما يحتاج حرارة
- Ease of operation ← سهولة التشغيل
- Minimal maintenance ← صيانة أقل
- More mobile facility ← سهولة النقل

- The ion exchange equipment involves the passage of water through a column of cation and anion exchangers, consisting of water insoluble, synthetic, polymerized resins of high molecular weight

- ✓ 1- water insoluble.
- ✓ 2- Synthetic.
- ✓ 3- High M.w.

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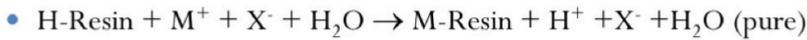
① أبخر الماء
 ② أطل تكثيف الماء
 ③ برقع ال temp ل 100
 لفضل إنه من أهم اللي تبخر
 بدين بتداهه وبكاشق
 وينتج لنسبها.
 ← ممكن يكون فيها ion

انايون.
 (ماء بنغوت وبتتفاعل مع د)
 Cation exchange
 وبتروح بقر بال
 Anion exchange
 ديهلج عندي
 Cation, anion
 وبتروح عندي
 Demineralized water
 ما فيها (Minerals).
 ما فيها ion إلا.

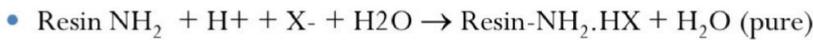
Methods for preparing Purified water:

- Water purified using this method is referred to as **demineralized** or **deionized water**.
 - 1- منزوعة الأيونات .
 - 2- منزوعة المعادن .
- These resins are mainly of two types:
 - A) The **cation** or **acid exchanger**, which permit the exchange of cations in solutions with hydrogen ion from the resin
 - B) The **anion** or **base exchangers** which permit the removal of anions

Cation exchange



Anion exchange

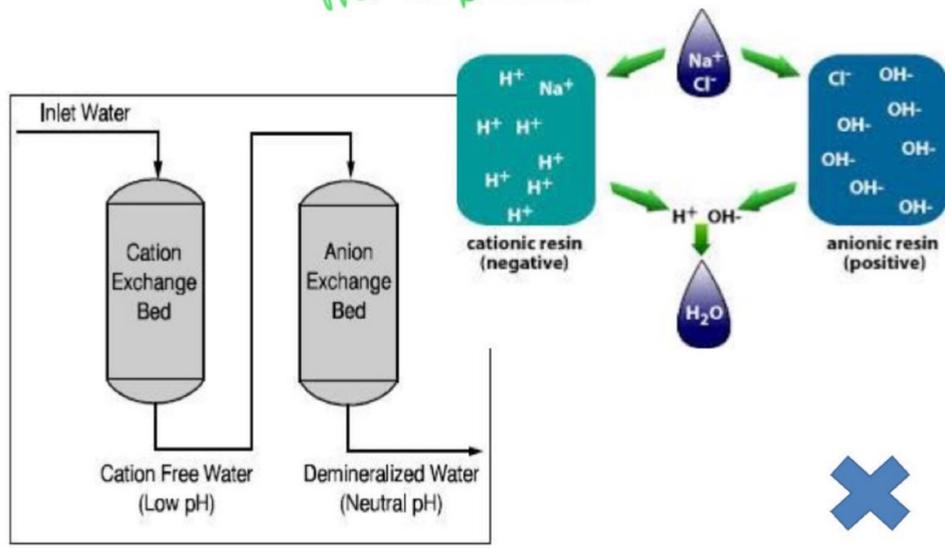


41

يجب الماء تصليحه من الـ salt
 الذي فيه تركيز Salt
 عايب لا part الذي فيه تركيز
 الـ Salt آتون .

⊕ Cation
 Positive
 بيطي مكانهم
 تسيل replacement

Not important



42

Methods for preparing Purified water: ✖

3) Reverse osmosis

- Formally, reverse osmosis is the process of forcing a solvent from a region of high solute concentration through a semipermeable membrane to a region of low solute concentration by applying a pressure in excess of the osmotic pressure.
- This is one of the processes referred to in industry as cross-flow (or tangential flow) membrane filtration
- In this process a pressurized stream of water is passed parallel to the inner side of a filter membrane core.
- A portion of the feed water permeates the membrane as filtrate
- In the normal osmosis process, the solvent naturally moves from an area of low solute concentration (high water potential), through a membrane, to an area of high solute concentration (low water potential).
- Whereas the flow in this crossflow system is from a more concentrated to less concentrated and therefore it is termed *reverse osmosis*.

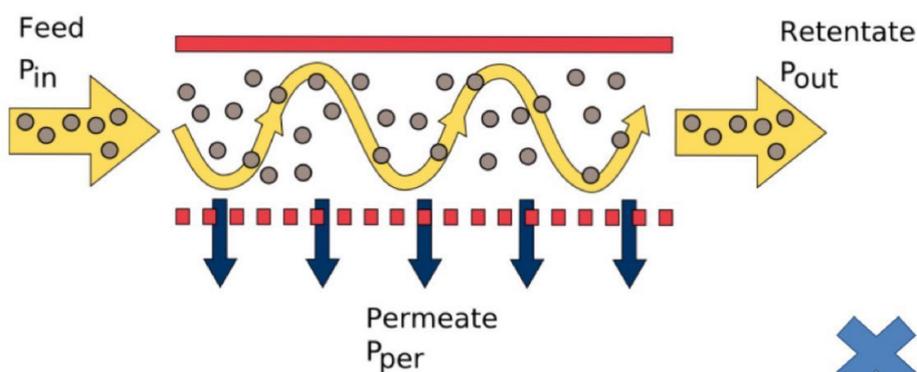
43

* ليس يكون بغير الضغط، (عكس) reverse

← باثر ضغط على ال Solvent
من منطقة ذات تركيز عالي
لمنطقة ذات ضغط منخفض
* جدار الضغط أعلى من ال osmotic pressure
* عن طريق غشاء شبه نافذ .

← بالوضع الطبيعي
ال Solvent يتحرك من
ال High Solute ← Low Solute
High potential → low potential

Cross-Flow Filtration



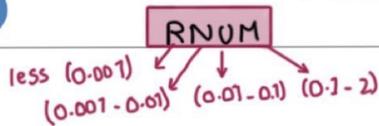
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Methods for preparing Purified water:

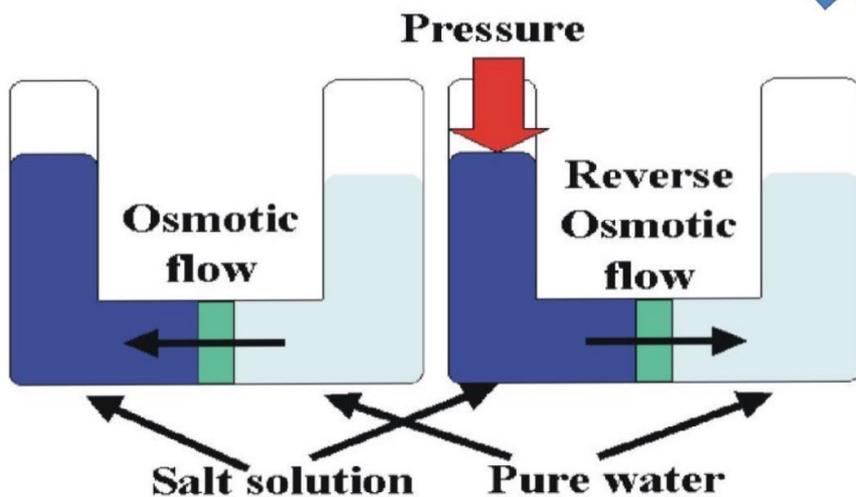
- Reverse osmosis can remove many types of **molecules** and **ions** from solutions, including **bacteria**
- The result is that the **solute** is retained on the pressurized side of the membrane and the pure **solvent** is allowed to pass to the other side
- Depending on their pore size, cross flow membranes can remove particles defined in the range of:
 - 1 • Micro filtration (0.1 – 2 microns)
 - 2 • Ultrafiltration (0.01 to 0.1 microns)
 - 3 • Nanofiltration (0.001 to 0.01 microns)
 - 4 • Reverse osmosis (Less than **0.001** microns) : Reverse osmosis removes virtually all viruses, bacteria, pyrogens, and organic molecules and 90% to 99% of ions

المذاب بضغط ضيق
 بالجانب المصنوع...
 والفذيب القوي يسمح له
 بالمرور..

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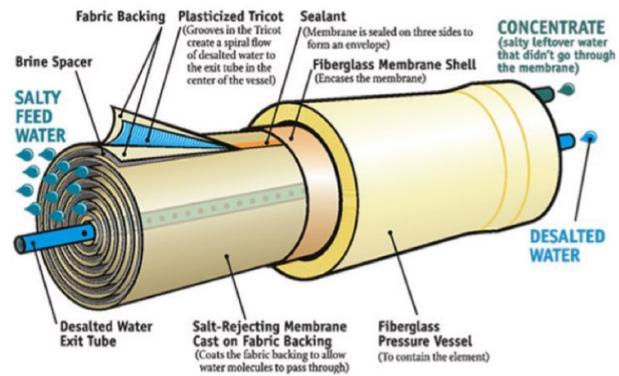
1. Virus
2. Bacteria
3. pyrogens
4. Organic Molecules.



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Reverse Osmosis Membrane Element inside a Pressure Vessel

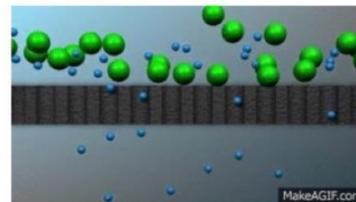


RO Membrane

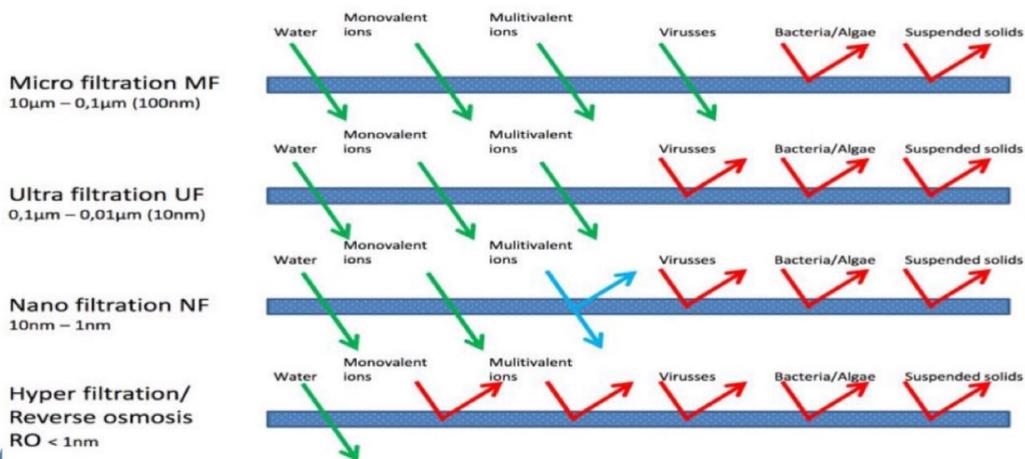
https://www.youtube.com/watch?v=rK7UVY_7K8w

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Membrane filtration



Comparison membrane techniques



© Logisticon Water Treatment b.v.

Ideal Excipients

- ✓ 1. Cheap
- ✓ 2. Commercially available
- ✓ 3. Non-toxic (safe), acceptable by regulation where the product will be marketed
- 4. Physiologically Inert :It does not exert any therapeutic effect. **e.g. sodium, sucrose, etc.**

* ما لا يؤثر علاجيًا ..
- 5. Physically and chemically stable.
- 6. Does not enhance microbial growth.
- 7. They must be color compatible, or color free

متوافق .. اللونان ..
- 8. Does not interfere the bioavailability of drug (dissolution, disintegration, etc)

* لا يتدخل ..
- 9. In case the drug was considered as food (Dietary supplement), the additives should be of Food grade (FD&C)

إذا اعتبرت الدواء مكمل غذائي ، لازم تكون الإضافات من الدرجة الغذائية (FD & C)

Isra Dmour

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Common Excipients (Additives)

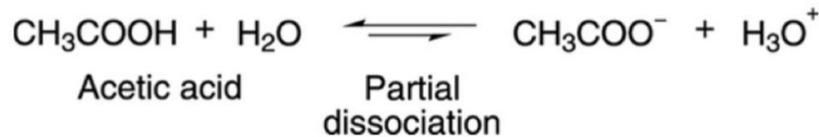
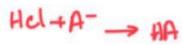
- 1. **Buffers** → بتايف التفرجاب (pH)
- 2. **Preservatives** ← مواد حافظة
- 3. **Antioxidants** ← مصهار أكسدة
- 4. **Viscosity enhancers** ← بتزويج من اللزوجة
- 5. **Sweetening agents** ← مواد حلوية
- 6. **Flavours** ← مضافات
- 7. **Others**

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Buffers

بتمتص الجزيء (pH)
(مقاومة)

- **Buffers** are compounds that resist changes in pH upon the addition of limited amounts of acids or bases.
- Buffer systems are usually composed of a **weak acid or base** and its **conjugate salt**.
- The components act in such a way that addition of an acid or base results in the formulation of a salt causing only a **small change** in pH.
- **Acetic acid, phosphate, citrate buffers**



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Buffers

- **Buffer capacity** is a measure of the efficiency of a buffer in resisting changes in pH.
- Conventionally, the **buffer capacity (β)** is expressed as the amount of **strong acid or base**, in gram-equivalents, that must be added to 1 liter of the solution to **change its pH by one unit**.
- Buffer capacities ranging from **0.01 - 0.1** are usually adequate for most pharmaceutical solutions.

إذا كان Capacity للBuffer
كثيرا فإنه يتأثر بالتغير
بالpH بدرجة كبيرة ويمنع
تغير الرقم بالدرجة
مناسبة.

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Buffers

- Once the optimal solution pH for the drug has been determined, buffers are needed to maintain that pH for the expected shelf life of the product
- The buffer capacity must be **large enough** to maintain the product pH for a reasonably **long shelf life**
- Change in product pH may result from the interaction of components with one another or with the package (glass, plastic, rubber, closure)
- On the other hand, the buffer capacity must be **low enough** to allow **rapid** adjustment of the formulation's pH to the **physiological pH** upon administration

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← أيّ تغيّر بال (pH) ممكن يسبب تفاعل الدواء مع العبوة ..

Buffers

- Buffer should have low toxicity and compatible with other ingredients.
 للسمية منخفضة + مناسبة مع المركبات الأخرى.
- As the pH of most body fluids is 7.4, products such as injections, eye drops and nasal drops should, ideally, be buffered at this value.
- Body pHs: 1.2, 6.8, 7.4
- Formulating a product at this pH is not always possible because of the drug's **solubility**, **chemical stability**, or **therapeutic activity**. Therefore, some compromise in the formulation pH may be necessary
 التنازلات ..

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→ الأسباب التي قد تمنع دواء بتلك الـ pH = 7.4 ..

Buffers



- However, many body fluids have a buffering capacity and when formulating low volume intravenous injections or eye drops a wider range of pH can be tolerated
- Ophthalmic solutions generally are buffered in a pH range from 4.5 to 11.5
- When a formulation is administered to the eye, it stimulates the flow of tears that is capable of quickly diluting and buffering small volumes of formulations
- Usually a compromise between a pH which is physiologically acceptable and a pH of optimum stability and solubility

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Preservation of oral solutions:

- Oral aqueous solutions can support growth especially if sucrose is present
- Preservatives are added to prevent microbial growth.
- Methods to preserve solutions:
 1. Add a known **preservative** in the **correct concentration** that is **soluble** in the formulation
 2. If absolute alcoholic content is high → alcohol can act as preservative: a minimum of 15% absolute alcohol is adequate to preserve products with pH 5, and 18% for neutral or slightly alkaline preparations (tinctures, spirits, and some elixirs require no preservatives)

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المواد الحافظة لتتبع النمو
البكتيري..

Preservatives * مواد حافظة :

- Ex. Benzoic acid, sodium benzoate, methylparabens, propylparabens and butylparabens.
- When choosing a suitable preservative the following points should be considered:
 - A. No adsorption of the preservative into the container occurs
 - B. The preservative is not impaired by the pH of the solution or by interaction with other ingredients (inert)

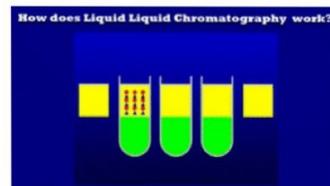
تراكم الجزيئات على السطح.

تضعف ..

57

Preservatives

- methyl-, ethyl-, propyl-, and butylparabens, frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils.
- This partitioning effect could reduce the effective concentration of the preservatives in the aqueous medium of a pharmaceutical product below the level needed for preservative action.



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Table 6 Preservatives used in pharmaceutical systems

Preservative	Usual concentration (%)
Acidic	
Phenol	0.2–0.5
Chlorocresol	0.05–0.1
α -Phenylphenol	0.005–0.01
Alkyl esters of <i>p</i> -hydroxybenzoic acid	0.001–0.2
Benzoic acid and its salt	0.1–0.3
Boric acid and its salts	0.5–1.0
Sorbic acid and its salts	0.05–0.2
Neutral	
Chlorobutanol	0.5
Benzyl alcohol	1.0
β -Phenylethyl alcohol	0.2–1.0
★Mercurial	
Thiomersal	0.001–0.1
Phenylmercuric acetate and nitrate	0.002–0.005
Nitromersol	0.001–0.1
Quaternary ammonium compounds	
Benzalkonium chloride	0.004–0.02
Cetylpyridinium chloride	0.01–0.02

(From Ref [16])

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Antioxidants

- Some drugs can be chemically degraded by oxidation.
- If such a drug is present in the formulation, an antioxidant should be added.
- These are materials added to **reduce the decomposition (oxidation) of pharmaceutical product.**
- These include:
 1. ascorbic acid,
 2. citric acid, $2 \text{ acid} + 2 \text{ Sodium..}$
 3. sodium metabisulfite
 4. sodium sulfite.

* Sulfites can cause allergic-type reactions in certain people and so patients should be questioned about this potential reaction before the antioxidant is included in the formulation.

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Flavoring agents:

- Most drugs have disagreeable tastes ^{كراهية}
- A formulation that is disagreeable in appearance and texture or taste ^{مظهر ملمس طعم} will not encourage patient compliance
- more attractive and palatable ^{جذابة مُتساففة} formulation → more acceptable to the patient → compliance will be improved



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Flavoring agents:

- Children prefer sweet, fruity, and candy-like tastes
- Adults tend to tolerate a reasonable level of bitterness or less sweet, tart, fruity flavors ^{تحمل المرارة}
- For infants under 3-6 months of age flavoring agents are unnecessary and are not recommended???
- In addition to the active drug, formulation components may produce characteristics tastes or odors:
 - ✓ alcohol: biting taste
 - ✓ Glycerin: sweet taste
 - ✓ Methylparaben: floral like aroma ^{رائحة تشبه الأزهار}
 - ✓ Propylparaben: produces a numbing feel in the mouth ^{* شعور بالتخدير بالفم ..}
 - ✓ Menthol and mannitol: impart a cooling sensation ^{* إحساس بالبرودة ..}

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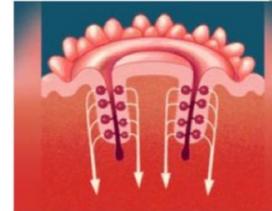
Flavoring techniques:

الذوق

A. blending: the use of a flavor that blend with drug tastes:

- Drugs with **acidic taste** can be blended with **citrus fruit flavors**

B. Overshadowing (masking, overpowering): involves using a flavor with a stronger intensity and longer residence time in the mouth (e.g. **wintergreen oil**)



C. Physical methods:

- Use **insoluble** form of drug
- Make an **o/w** emulsion of an oily drug and flavor the **external aqueous phase**

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Flavoring techniques:

D. Chemical methods: by adsorbing, complexing or making a pro-drug of the drug that eliminate the undesirable taste

E. Physiological techniques:

- Use additives that cause a cooling sensation (e.g. mannitol, menthol)
- Menthol, peppermint oil and chloroform mask the taste also by acting as desensitizing agents.

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Sweeteners

→ **Sucrose** .. * كربوهيدرات لها (Low mw) ..

- **Low molecular weight carbohydrates** and particularly **sucrose** are traditionally the most widely used sweetening agents in oral solutions.
- Polyhydric alcohols such as ^①glycerol, ^②sorbitol, ^③mannitol and ^④xylitol possess sweetening properties and can be used for diabetic patients.
- **Artificial sweeteners** (saccharin, aspartame and cyclamates) can be used. **Saccharin** and **cyclamates** are suspected to be carcinogenic and so **aspartame** is the most accepted one.
* ممكن تسبب سرطان.

← الفحطيات
الصناعية ..

65

Sweeteners

Advantages of sucrose:

- ✓ 1. colorless
- ✓ 2. very soluble in water
3. stable over a pH range of about **4 - 8**
4. It increases the viscosity of solutions which will give them a pleasant texture in the mouth
← يعطي نسيج لطيف في الفم ..
5. It masks the taste of both salty and bitter drugs
← يخفي طعم المالح والمر بالمواد ..
6. It has a soothing effect on the throat which makes it suitable for antitussive preparations
← مهم في علاج مناسبات المستحضرين
مضادة للسعال ..

- **The main disadvantages** of sucrose is that it initiates **dental caries** and is not suitable for **diabetic patients**.

تموس الإنسان

لأن بوضع نسبة السكر بالم ..



66

Coloring agents



- Colors are substances added to a formulation for the sole purpose of imparting color to promote patients' acceptance of a formulation via **visual appeal**

عزيمها الوصير اعطاء اللون
لتحز بز القبول -

* جازبية بصريّة..

- Coloring agents are not required in every formulations and they are **contraindicated in all sterile solutions**

عشان الحائل الحفمة
عتر صابة لازم ما يكون الصابون
عشان تاكد من توادها -

بملائن

- Pleasant fruity colors are generally preferred and should be coordinated with flavors and scents (yellow with lemon, red with cherry)

متناسقة ..

الطعّات .. الراجح ..



67

Coloring agents

Many are Salt → Sulfonic acid..

الآ.. الCationic
* Alkaloids..

- Physicochemical reactions with other formulation ingredients **must** be considered when choosing a colorant

- Many colors are **salts** of sulfonic acids and may be incompatible with large ⁺⁺⁺ cationic compounds such as **alkaloids**



- The pharmacists should also consider how **(pH changes) or (light exposure)** alters the color or stability of the product

كيف ال pH والبيتر
ميس والتعرض للضوء ممكن يغير
اللون أو ياتر على الstability

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Coloring agents

- Colors used in pharmaceutical preparations are either **natural colors** or **synthetic dyes** → أصباغ صناعية.
- Natural colors include **red ferric oxide**, **titanium oxide**
- The synthetic dyes are **certified by FDA** and are:
 - **FD&C dyes**: used in **food**, drug, and cosmetics
 - **D&C dyes**: used in drugs and cosmetics
 - **External D&C dyes**: used in externally applied drugs and cosmetics

F → food.
 O → drug.
 C → cosmetics.

* Natural → Oxide → red ferric
 → titanium

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♥ Viscosity Enhancers: increase viscosity → enhance palatability.. pourability..

- It is sometimes desired to **increase viscosity** to enhance **palatability and pourability**. + قابلية اللب.. الاستساغة..

- This can be achieved

1. by **increasing sugar concentration**
2. by **incorporating viscosity controlling agents** such as **polyvinylpyrrolidone (PVP)** or **various cellulose derivatives** مشتقات السيلوز..

- **Palatability (palatable)???** * مُستساغة: the fact or quality of being acceptable or agreeable to the taste.



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* سبب زيادة الـ Viscosity
 .. سكر من الـ Sugar
 (Cellulose + PVP ..) +
 agent

Isotonicity modifiers:

- Solution for injection, for application to mucous membranes and large volume solutions for ophthalmic use must be made iso-osmotic with tissue fluid to avoid pain and irritation.
- Other additives should be considered when adjusting tonicity because of their effect on the osmotic pressure of solution.

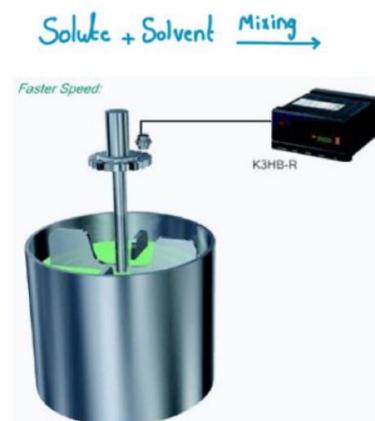
1 injection ← Mucous Membranes

2 ophthalmic ← large volume

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Preparations of solutions:

- Most solutions are prepared by simple mixing of the solutes with the solvent.
- On an industrial scale, solutions are prepared in large mixing vessels with ports for mechanical stirrers.
- When heat is desired, thermostatically controlled mixing tanks may be used.
- Heat jacketing



على نطاق صناعي ..

أوعية خلط كبيرة ..

لما يكون الحرارة مطلوبة
يقدر انتم استراتيجيات بجمع
بدرجات حرارة منخفضة.

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