تفريغ تعقيم

محاضرة: Ophthalmic Part 1

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لجان الدُّفعات

Soul Academy

Ophthalmic Preparations

Modified by Dr. Saja Hamed from slide share by

Srikanth A.V.N

Pharmaceutical Technology

بالحقن السائل بالمنطقه الخلفيه للعين (intra-vitreal injection)

Ophthalmic preparations

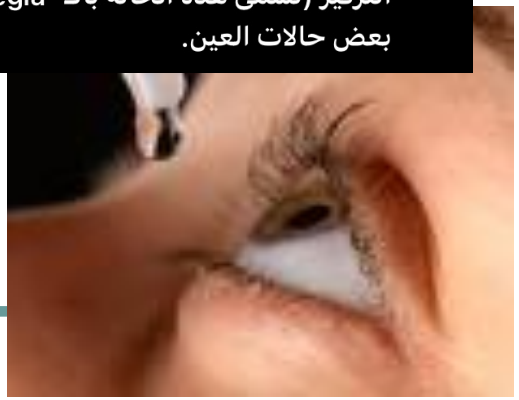
1. Prescription → وصفه طبيب
2. OTC
3. Product for care of contact lenses
4. Products used in conjunction with ocular surgery

Drugs used in the eye:

- Miotics e.g. pilocarpine Hcl
- Mydriatics e.g. Atropine
- Cycloplegics e.g. Atropine
- Anti-inflammatories e.g. corticosteroids
- Anti-infectives (antibiotics, antivirals and antibacterials)

كلمة **Cycloplegic** (سايكلوبليجك) تعني **مُسبب شلل مؤقت لعضلة البؤبؤ (عضلة العين المسؤولة عن التحكم في تركيز العدسة)**.

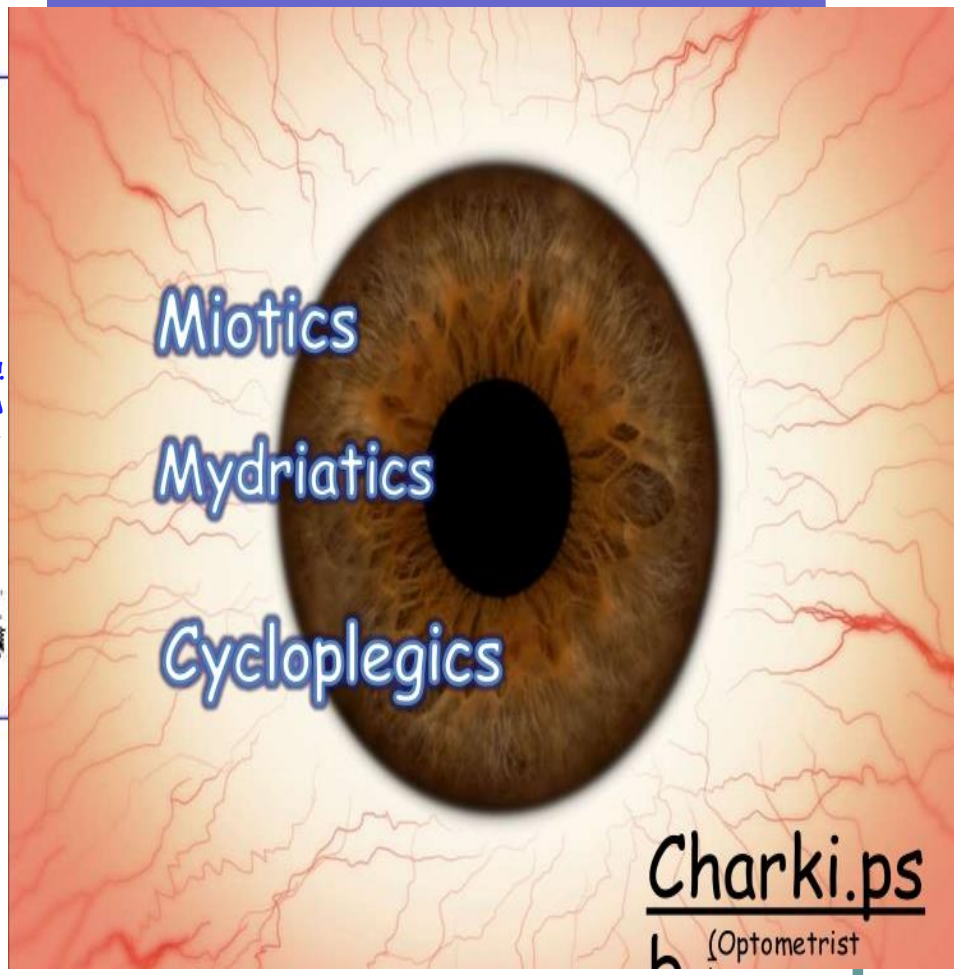
عادةً تُستخدم أدوية سايكلوبليجك في الطب لتوسيع حدقة العين (البؤبؤ) ووقف قدرة العين على التركيز (تسمى هذه الحالة بالـ "Cycloplegia") مؤقتًا، غالبًا خلال فحوصات العين أو لعلاج بعض حالات العين.



What is Cycloplegia?

- It is the paralysis of the ciliary muscle of the eye, resulting in the loss of visual accommodation. عدم القدرة على رؤية الاشياء القريبة
- Accommodation is the ability of the lens to change its refractive power to view the near objects clearly.
- It is brought about by the contraction of the ciliary muscles.

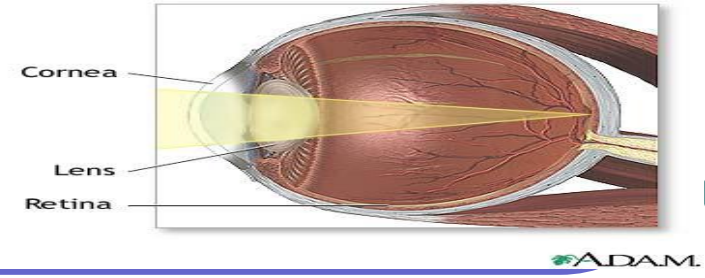
رح يتحطموا بتوسيع الحدقة
إذا عملت لها شلل ما رح تقدر تشوف الرؤية القريبة



Drugs used in the eye:

- Anti-glucoma drugs e.g. pilocarpine Hcl
- Adjuncts e.g. Irrigating solutions
- Diagnostic drugs e.g. sodium fluorescein
- Anesthetics e.g. Tetracaine

Anatomy and Physiology o



- The inside of the eyeball is divided by the lens into two fluid-filled sections.

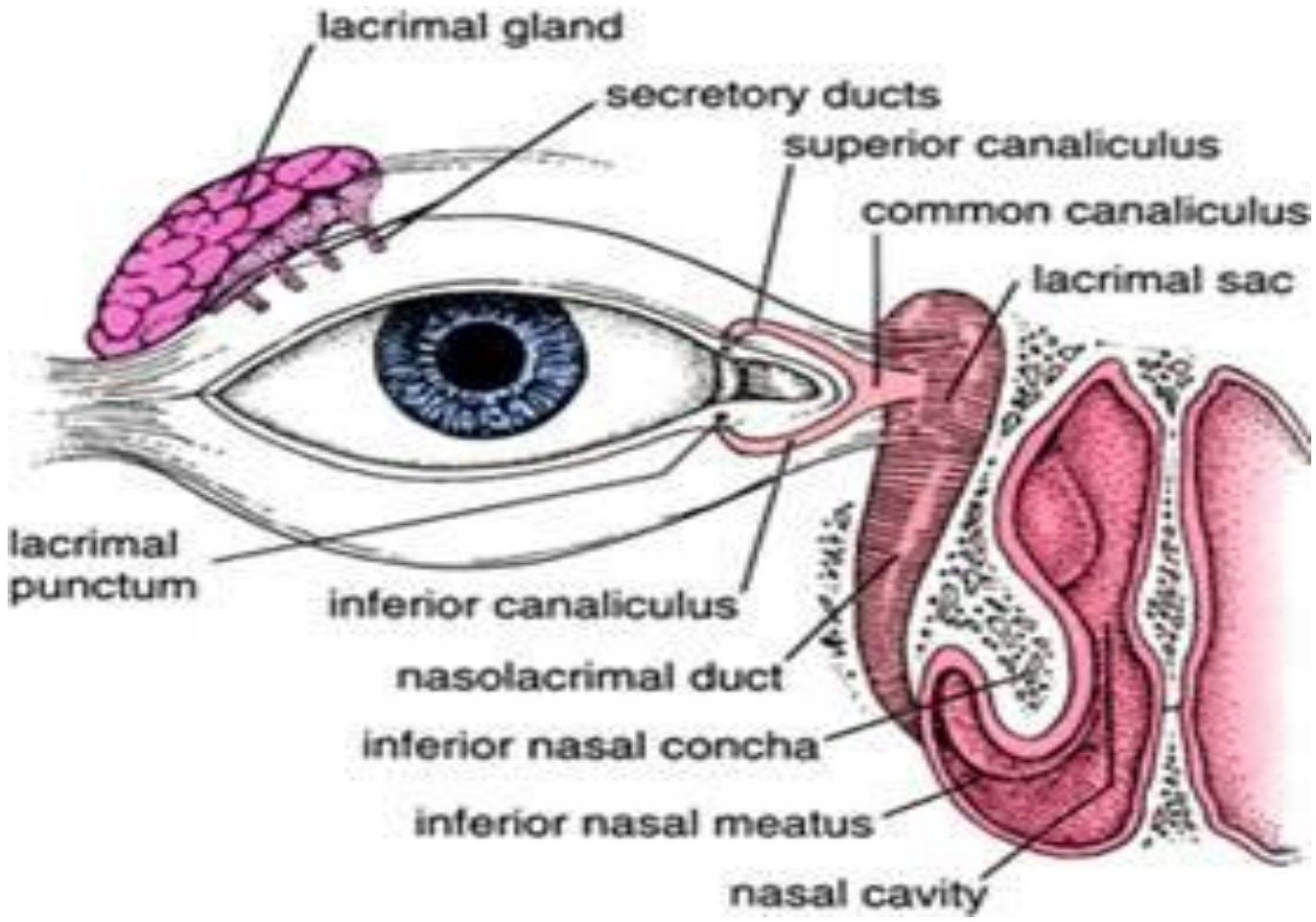
- The larger section at the back of the eye is filled with a colorless gelatinous mass called the **vitreous humor.** → موجود بالجزء الخلفي من العين
- The smaller section in the front contains a clear, water-like material called **aqueous humor.** → بالجزء الامامي
- The **conjunctiva** is a mucous membrane that begins at the edge of the cornea and lines the inside surface of the eyelids and sclera, which serves to lubricate the eye.
- Lacrimal gland: secret clear water secretion that contains numerous salts, glucose, other organic compounds, 0.7% protein including lysozyme

الاشياء الموجودة بالدموع
1 2 3 4

Tear films

- Compatible with both aqueous and lipid ophthalmic preparations
- Renewed during blinking → كل ما اعمل blinking رح يتجدد الدمع
- A pH below 4 or above 9 causes derangement of the film → acid اقل ٤ — اذا كانت القطرة حمضية كتير او كتير basic رح تخرب هذا الـ film لـ اعلى من ٩

lacrimal nasal drainage:



Corneal absorption:

احنا ناه بالفيزكال

J = The flux rate of drug across the membrane

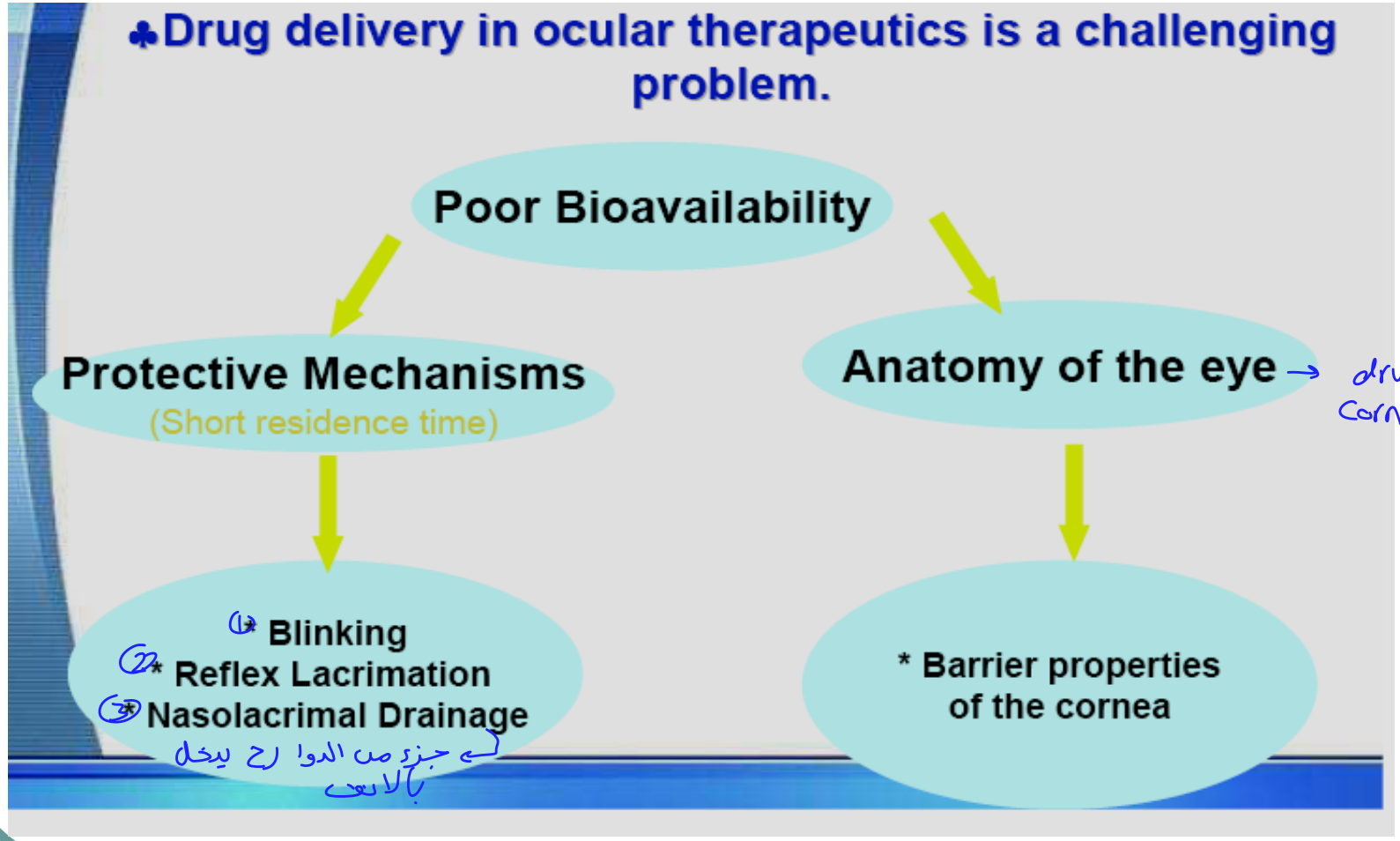
D = diffusion coefficient

- The diffusion coefficient ⇧ , as the molecular size of the drug ⇩

C_m = concentration gradient

- As the drug solubility ⇧ , the gradient ⇧ , the driving force for drug entry into the aqueous humour ⇧

Corneal absorption:



لانه مش كل الـ drug رح يدخلوا بالـ Cornea

لـ جزء من الدوا رح يدخل بالانف

General safety considerations:

A. Sterility:

- Ideally, all ophthalmic products would be terminally sterilized in the final packaging.

ideal هذا يعني ما رح نقدر نحققه

- Only a few ophthalmic drugs formulated in simple aqueous vehicles are stable to normal autoclaving temperatures and times (121°C for 20-30 min).

A. Sterility (cont.):

- Most ophthalmic products, however cannot be sterilized by heat due to the active principle or polymers used to increase viscosity are not stable to heat. يقدر اعرضهم للحرارة Preparation يعني مش كل ال
- Most ophthalmic products are aseptically manufactured and filled into previously sterilized containers in aseptic environments using aseptic filling-and-capping techniques.

General safety considerations:

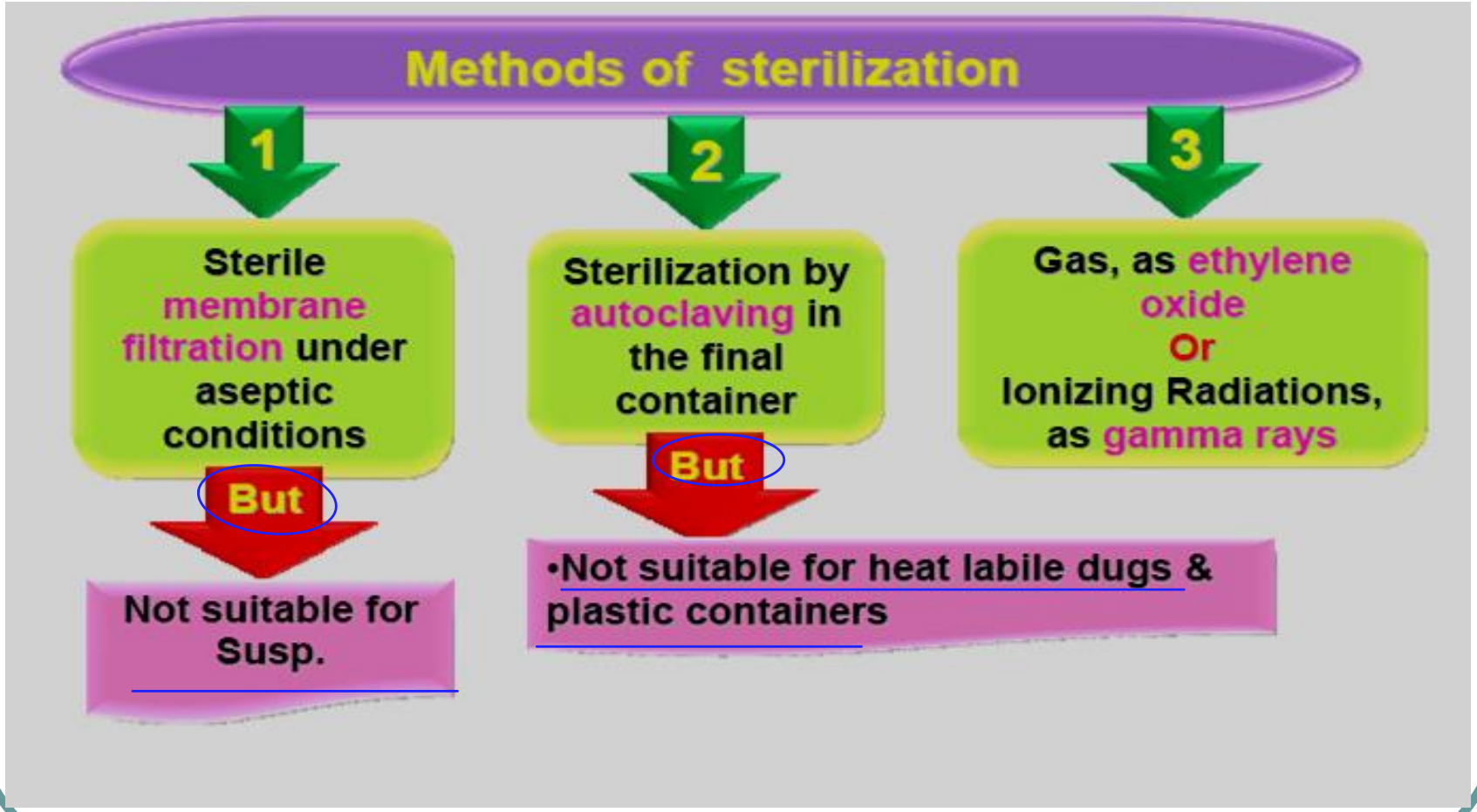
- 42 cases of epidemic keratoconjuctivitis were caused by one bottle of virus-contaminated tetracaine solution
- Virus contamination difficult to control why:
- None of the preservative is virucidal
- Not removed by filtration

إذا الطبيب ما انتبه لطريقة وضع القطرة بحيث إنها ما تلمس عين المريض رح يسبب Viral-infection لكل المرضى عنده

مخدر موضعي

لانها صغيرة كتير

A. Sterility (cont.):



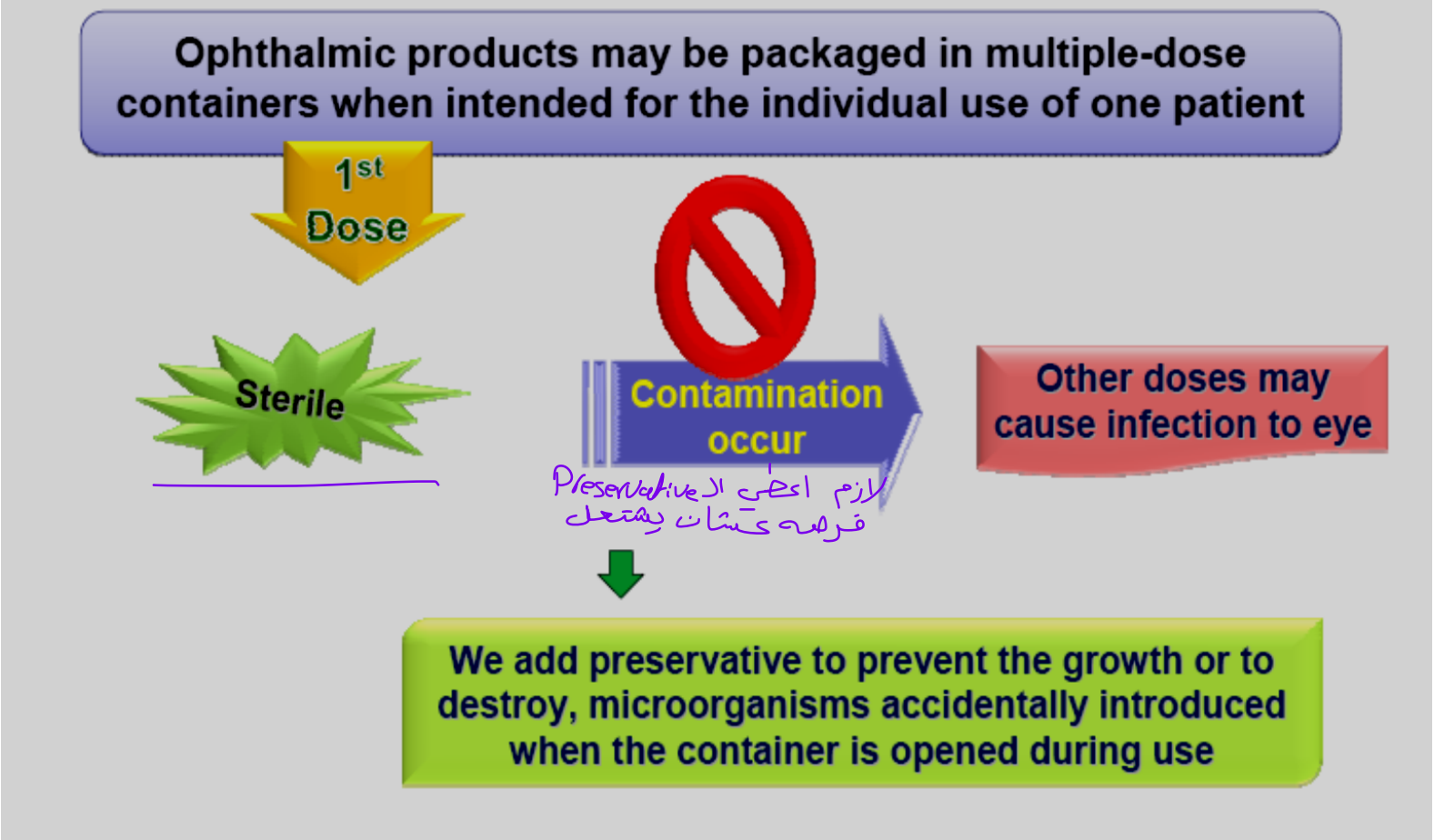
C.Preservation and preservatives:

- Preservatives are included in multiple-dose eye solutions for maintaining the product sterility during use.
- Preservatives are not included in unit-dose package.
- The use of preservatives is prohibited in ophthalmic products that are used in eye surgery because, if sufficient concentration of the preservative is contacted with the corneal endothelium, the cells can become damaged causing clouding of the cornea and possible loss of vision.

So these products should be packaged in sterile, single use containers.

- The most common organism is **Pseudomonas aeruginosa** that grow in the cornea and cause loss of vision.

C.Preservation and preservatives:



Manufacturing considerations:

A. Manufacturing Environment:

The environment should be sterile and particle-free through:

-*Laminar-flow* should be used throughout the manufacturing area.

-Total particles per cubic foot of space should be minimum.

- Relative humidity controlled between 40 and 60%.

- Walls, ceilings and floors should be constructed of materials that are hard, non flaking, smooth and non-affected by surface cleaners or disinfectants.

A. Manufacturing Environment:

A. Manufacturing Environment:

- Ultraviolet lamps provided in flush-mounted fixtures to maintain surface disinfection

- Separate entrance for personnel and equipment should be provided through specially designed air locks that are maintained at negative pressure relative to the aseptic manufacturing area and at a positive pressure relative to the noncontrolled area

Clean room الى نفس شيء

A. Manufacturing Environment:

. *Manufacturing Techniques:*

- ***Unpreserved formulations of active drug (s):***

The blow/fill/seal method

للدوا اي رح استخدمه مرة وحدة preservative فقط وما فيه

It is used for manufacture of unpreserved ophthalmic products , especially for artificial tear products.

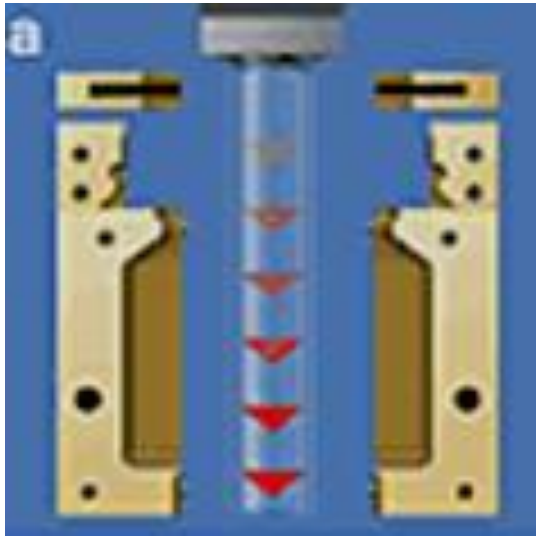
First step is : To extrude polyethylene resin at high temperature and pressure and to form the container by blowing the polyethylene resin into mold with compressed air. The product is vented out, and finally the container is sealed on the top.

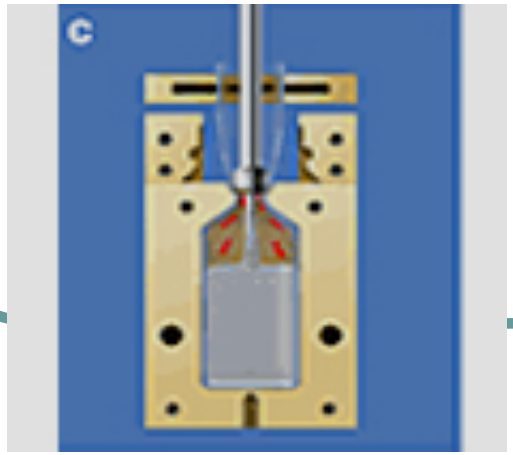
يستخدم لتحضير small + large volum

The blow /fill/seal method:

Watch: **Weiler — "ASEP-TECH: It's Safer Inside" Campaign**

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





C. Equipment:

All tanks, valves, pumps and piping must be of best available Grade of corrosion – resistant stainless steel.

All products-contact surface should be polished either mechanically or be electropolishing to provide a surface as Free as possible from scratches or defects.

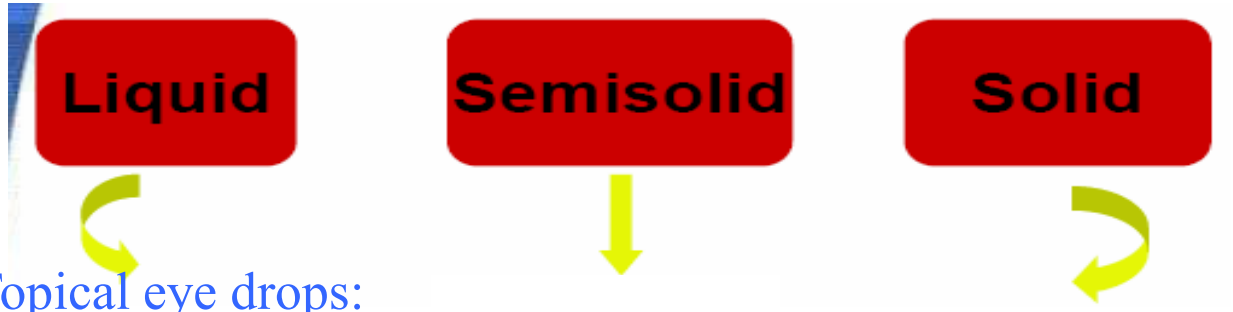
Care should be taken in the design of such equipment to Provide adequate means of cleaning and sanitization.

Ideal ophthalmic delivery system:

Following characteristics are required to optimize ocular drug delivery system:

- Good corneal penetration.
- Prolong contact time with corneal tissue.
- Simplicity of instillation for the patient.
- Non irritative and comfortable form
- Appropriate rheological properties

Classification Of Ocular Drug Delivery Systems:



Topical eye drops:
-Solutions

- Suspensions

- Powders for reconstitution

- Sol to gel systems

-Ointments

- Gels

- Ocular inserts

Intraocular Dosage Forms

* Injections
*irrigating solutions
* Implants

ح تكون injection بالملتحمه

Powder يكون ← steril-water وبحطه د عشان يصير Liquid (زي الدوا اللي بحطه بعين)

زيادة

A. Topical Eye drops:

1- Solutions:

- Ophthalmic solutions are sterile solutions, essentially free from foreign particles, suitably compounded and packaged for instillation into the eye.
- Most common dosage forms
- Dose uniformity is not an issue
- Little physical interference with vision

A. Topical Eye drops:

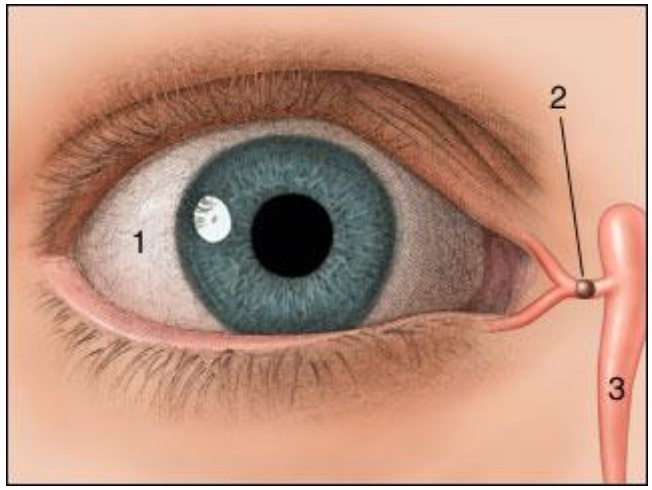
- ***Administration:***

- Pull down the eyelid
- Tilting the head backwards
- Look at the ceiling after the tip is pointed close to the lower cul-de-sac
- Apply a slight pressure to the rubber bulb or plastic bottle to allow a drop to fall into the eye.

To prevent contamination:

- Clean hands
- Do not touch the dropper tip to the eye and surrounding tissue
- Try to keep eye open and not blink for at least 30 second

Nasalacrimal occlusion



1- Solutions:

-Nearly all the major ophthalmic therapeutic agents are water soluble salts → solubility عشان ال

The selection of the appropriate salt depend on :

- solubility
- ocular toxicity
- The effect of pH, tonicity, and buffer capacity
- The intensity of any burning sensation
- The most commonly used salts are: hydrochloride, Phosphates, nitrates

B. Manufacturing Techniques:

- ***Aqueous ophthalmic solution:***

* Manufactured by dissolution of the active ingredients and a portion of the excipients into all portion of water.

The sterilization of this solution done by heat or by sterilizing Filtration through sterile depth or membrane filter media into a sterile receptacle.

حسب الدوا إذا يتأثر بالحراره او لا

This sterile solution is then mixed with the additional required sterile components such as viscosity –imparting agents, Preservatives and the solution is brought to final Volume with additional sterile water.

طبعاً بزيد الـ viscosity بعد ما اعمل الـ sterilization

الاشياء اللي رح اضيفها بعد sterilization لازم اضيفها بـ Asptic condition

Disadvantages of eye solutions:

1- The very short time the solution stays at the eye surface.

The retention of a solution in the eye is influenced by viscosity.

2- Its poor bioavailability (a major portion i.e. 75% is lost via naso-lacrimal drainage).

2- suspensions:

بستخدم الـ suspention لما ؟
① بدي احسب الـ stability
② إذا كان الدوا معلق فالنسبة بالـ water
③ عشان احسن الـ bioavailability

* If the drug is not sufficiently soluble, it can be formulated as a suspension.

A suspension may also be desired to improve stability, Bioavailability ,and efficacy.

The major topical ophthalmic suspensions are the steroid anti-inflammatory agents.

An ophthalmic suspension should use the drug in a microfine form; usually 95% or more of the particles have a Diameter of 10µm or less.

لانه الـ Particel إذا كانت كبيرة رح تعمل irrtation

2-Suspensions (Cont.)

المنطقة القريبة من الانف والعين

- The particles retained in the cul-de-sac → contact time and duration theoretically exceed solution يعني ال suspension اطول من ال Contact time ال solution
- Particle size:
  - Affect surface area available for dissolution
  - Affect irritation potential → excessive tearing and rapid drainage

كبر حجم بيكون اقل

- pharmacist should emphasize:
  - Shaking well counsel
  - Do not freeze → agglomerate

B. Manufacturing Techniques:

- ***Aqueous suspensions:***

Are prepared in much the same manner, except that

Before bringing to the final volume with additional

sterile water .

The solid that is to be suspended is previously rendered sterile by – heat ,exposure to ethylene oxide ,ionizing radiation (gamma)

The particle size should be monitored.

3- Gel-Forming Solutions

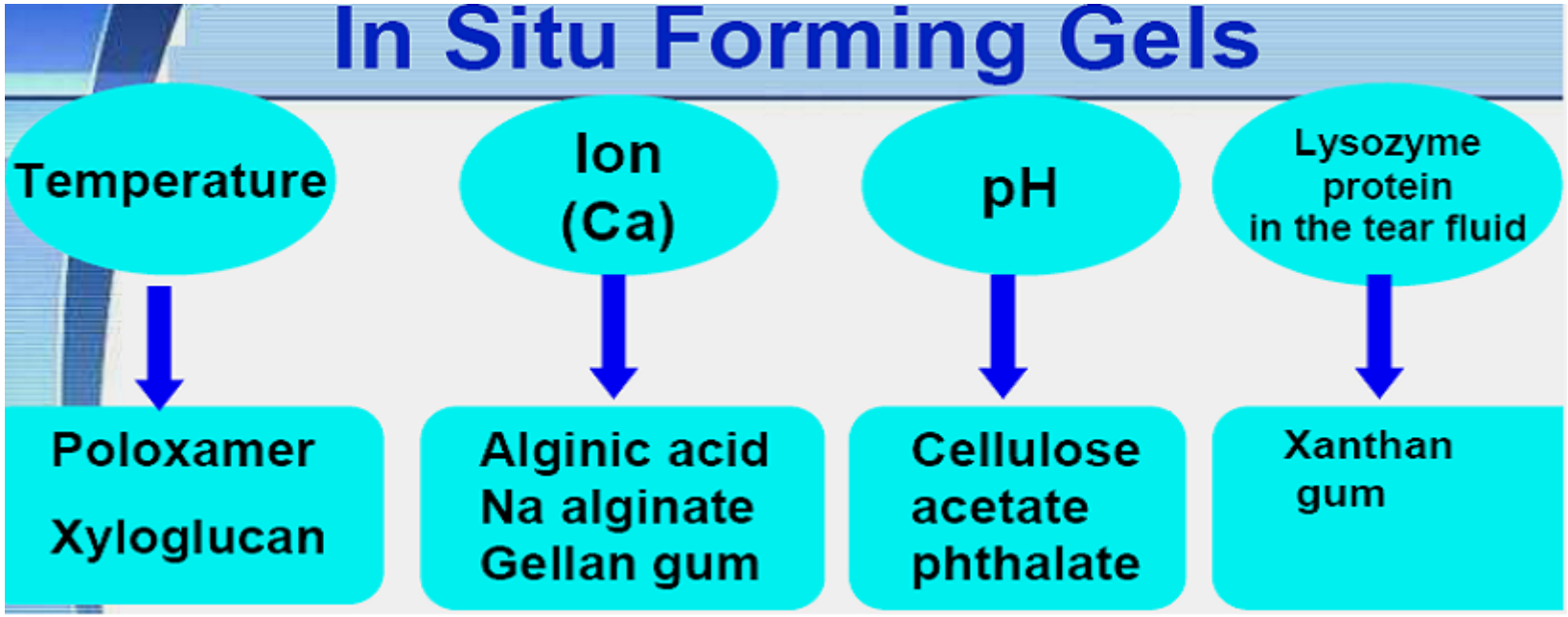
* Solution that are liquid in the container and thus can be instilled as eye drops but forms gel on contact with the tear fluid and provide increased contact time with the possibility of improved drug absorption and Duration of therapeutic effect.

* liquid-gel phase transition-dependent delivery system vary according to the particular polymer(s) employed and their mechanisms for triggering the Transition to a gel phase in the eye.

* Take the advantage of changes in temperature ,pH, ion sensitivity, lysozymes upon contact with tear fluid.

هاي الاشياء
تحفز ال Polymer
انه يتحول لـ gel
(سلق فيروري لكلام)

3- Gel-Forming Solutions



Inactive Ingredients in Topical Drops:

The inactive ingredients in ophthalmic solution and Suspension dosage forms are necessary to perform one or more of the Following functions:

بكون في بالقطره مواد كانت غير active ingredient ، بكون الها وظائف مختلفه مثلاً

1. Adjust tonicity
2. Buffer and adjust pH,
3. Stabilize the active ingredients against decomposition ,
4. Increase solubility,
5. Impart viscosity
6. And act as solvent.

1- Tonicity and Tonicity-Adjusting Agents:

The pharmacist should adjust the tonicity of an ophthalmic Correctly (i.e.., exert an osmotic pressure equal to that of tear fluid , generally agreed to be equal to 0.9% NaCl).

بهمني بالعظم انه يكون
إلها osmotic pressure يساوي
Nacl من ال 0.9

A range of 0.5-2.0% NaCl equivalency does not cause a Marked pain response and a range of about 0.7-1.5% Should be acceptable to most person.

يكونوا مصنعينه
عمدا هيك لعلاج
ال Corneal edema
و هيك المي بتطلع
من ال Cornea

Hypertonic ophthalmic products are used to relieve corneal edema

Commonly tonicity adjusting ingredients include : NaCl, KCL, buffer salts, dextrose, glycerin, propylene glycol, mannitol

Isotonicity

Lacrimal fluid is isotonic with blood having an isotonicity value Corresponding to that of 0.9% Nacl solution

Ideally, an ophthalmic solution should have this isotonicity value

But

The eye can tolerate isotonicity from 0.6% to 2% NaCl without marked discomfort

Some ophthalmic solutions are necessarily hypertonic in order to enhance absorption and provide a concentration of the active ingredient strong enough to exert an effective action.

2- pH Adjustment and Buffers:

pH adjustment is very important as pH affects

1- To render the formulation more stable

2- The comfort, safety and activity of the product.

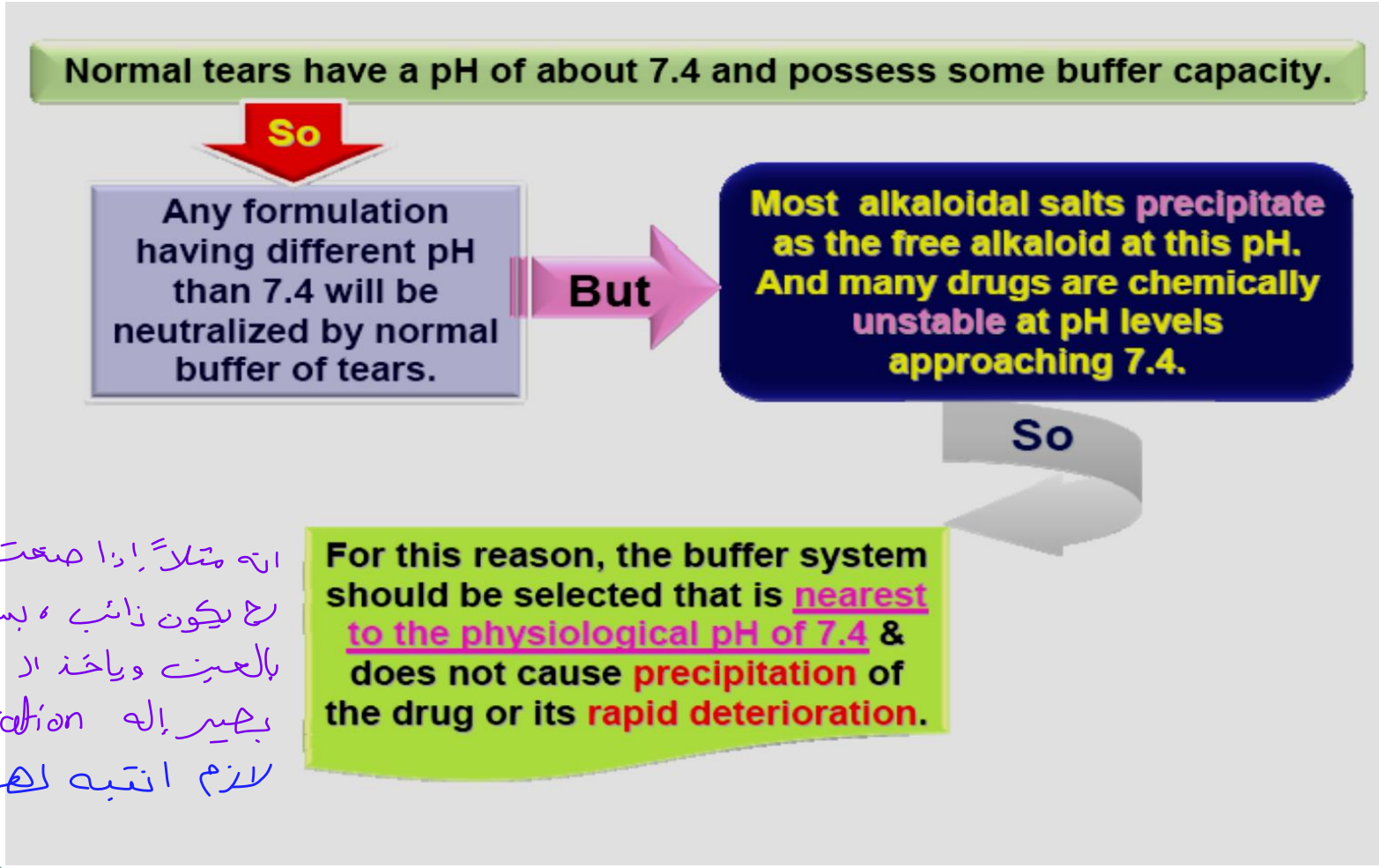
Eye irritation ⟶ increase in tear fluid secretion ⟶ Rapid loss of medication.

3- To enhance aqueous solubility of the drug.

4- To enhance the drug bioavailability

5- To maximize preservative efficacy

pH & buffer



انه مثلاً إذا صنعت دوا اله pH = 5
ح يكون ذائب ، بس مجرد ما احط
بالعين وياخذ ال pH لـ tear ح
يصير اله Precipitation
لازم انتبه لهذا الشي

3- *Stabilizers & Antioxidants:*

* Stabilizers are ingredients added to a formula to decrease the rate of decomposition of the active ingredients.

* Antioxidants are the principle stabilizers added to some ophthalmic solutions , primarily those containing epinephrine and other oxidizable drugs.

* Sodium bisulfite or metabisulfite are used in concentration up to 0.3% in epinephrine hydrochloride and bitartrate solutions.

Several antioxidant system have been developed :-
These consists of ascorbic acid and acetylcysteine and sodium thiosulfate .

4- Surfactants:

The order of surfactant toxicity is :

anionic > cationic >> nonionic .

- several nonionic surfactants are used in relatively low Concentration to aid in dispersing insoluble ingredients in suspensions
 and to achieve or to improve solution clarity (aid in solubilization).

- Those principally used are the sorbitan ether esters of oleic acid (polysorbate or tween 20 and 80).

- Smallest possible conc.


ALLERGAN
Liquifilm
Tears™
(polyvinyl alcohol 1.4%)
ocular
lubricant
sterile
15 mL
ALLERGAN
Liquifilm
Tears™
ocular
lubricant


Alcon®
RELIEVES
DRY
EYES
0.5%
ISOPTO® TEARS
HYDROXYPROPYL
METHYLCELLULOSE
OPHTHALMIC SOLUTION, USP
DIN 00000809
Sterile 15 mL

6- *Vehicles:*

- Ophthalmic drop (using purified water USP) as the solvent.
- For intraocular products→ water for injection, USP

Purified water meeting USP standards may be obtained by : Distillation, deionization, or reverse osmosis.

لما اضيف ال oil لازم اضيف anti oxidant كمان

Oils have been used as vehicles for several topical eye drops products that are extremely sensitive to moisture.

When oils are used as vehicles in ophthalmic fluids, they must be of the highest purity.

Packaging:

- Eye drops have been packaged almost entirely in plastic dropper bottles

The main advantage of the DropTrainer are:

- convenience of use by the patient
- decreased contamination potential
- lower weight
- lower cost

- The plastic bottle and dispensing tip is made of *low-density polyethylene (LDPE) resin*, which provides the necessary flexibility and inertness.
- The cap is made of harder resin than the bottle.

Packaging:

A special plastic ophthalmic package made of polypropylene is introduced. The bottle is filled then sterilized by steam under pressure at 121°C.

Powder for reconstitution use glass containers ,
owing to their heat-transfer characteristics, which are necessary during the freeze-drying processes.

Packaging:

- The glass bottle is made sterile by dry-heat or steam autoclave sterilization.
- Amber glass is used for light-resistance.

Using the code

- Color-coded ophthalmic medications make life easier for doctors and patients.
- When asked to list the medications they take, patients often can't remember, but they easily remember the color of the bottle or the bottle cap.
- The AAO color code system also can improve patient compliance by simplifying and demystifying dosage schedules. Patients who use several eye drops may be overwhelmed by drug names or have trouble remembering when to instill particular drops. To avoid confusion when instructing a patient how to use his medicine, be sure to mention the cap color along with the drug name so the patient makes a mental connection.

الدكتورة حطت بالفيديو انه مش مطلوب نحفظ تراكيز

السلايدات اللي مش مكتوب عليها شرح مطلوبة

لاتنسوا زميلنا ايهم من دعائكم