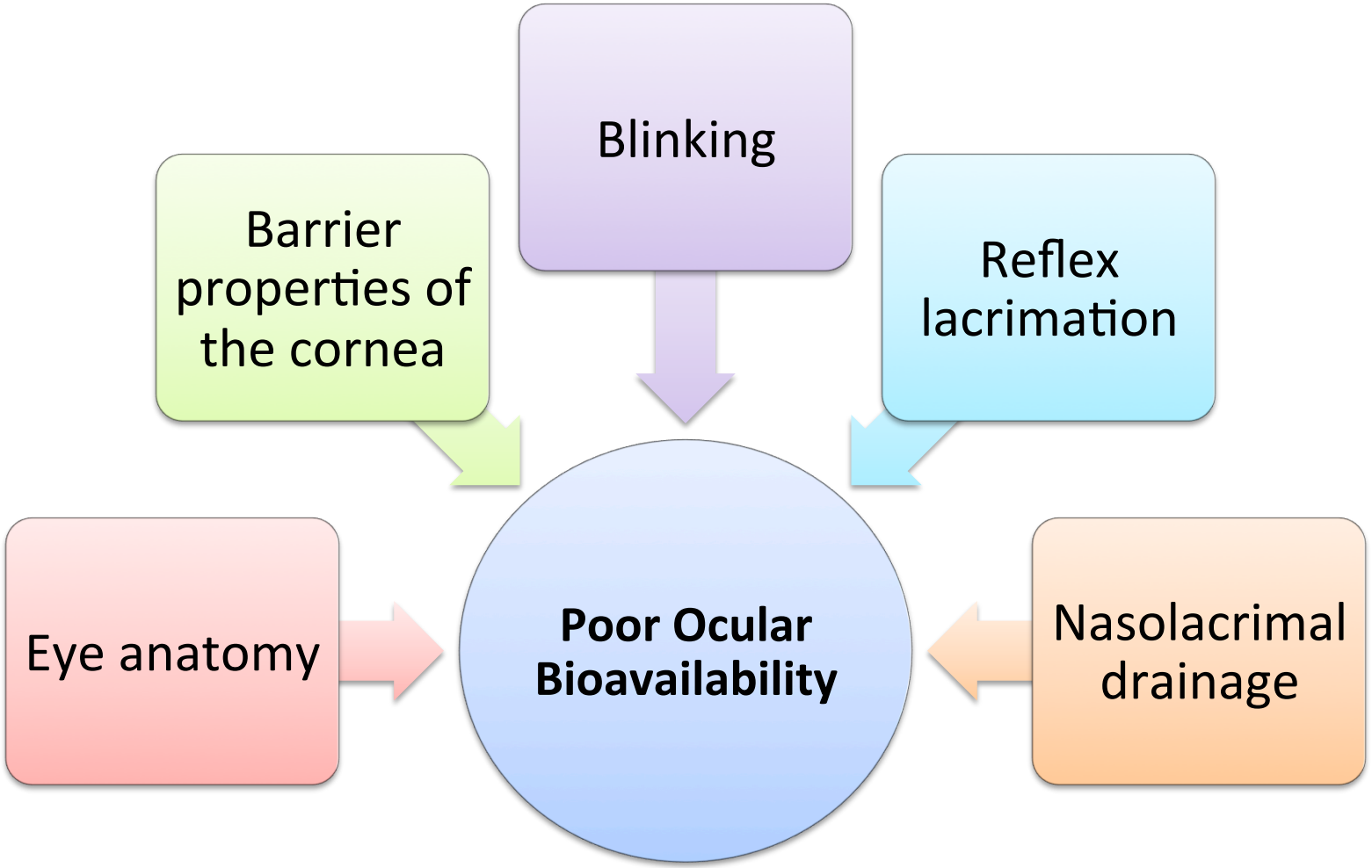
Ophthalmic Preparations 2

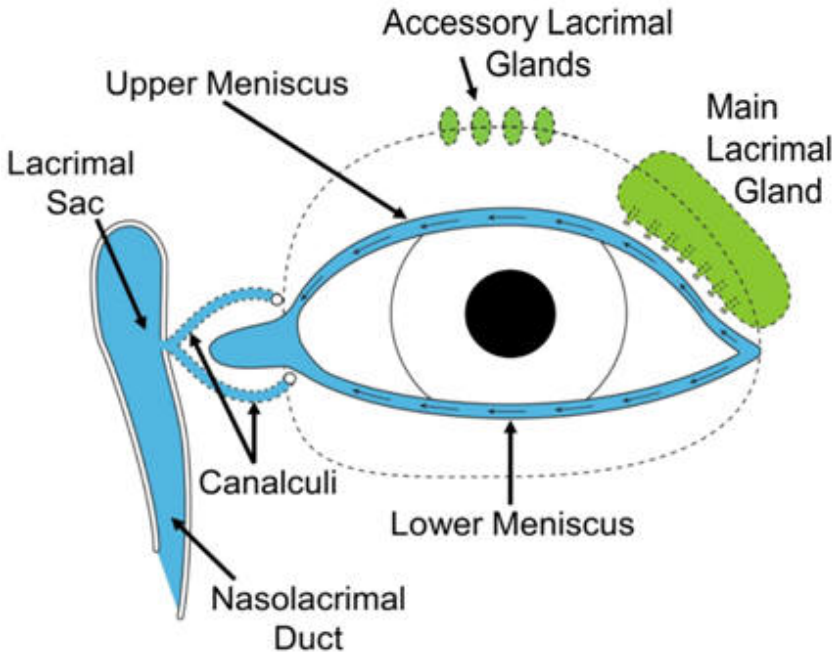
Challenges in Ocular Drug Delivery



Factors Influencing Ocular Bioavailability

Rapid solution drainage by:

- Gravity
- Induced lacrimation
- Blinking reflex
- Normal tear turnover
- Peripheral blood vessels



The normal volume of tears is 7 μl

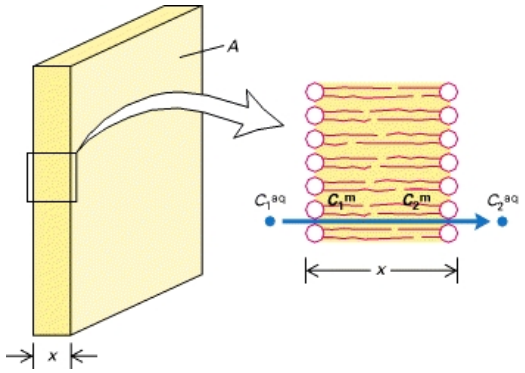
The blinking eye can accommodate a volume of up to 30 μl without spillage

Single eye drop volume is 50 μl

Factors Influencing Ocular Bioavailability

Low corneal permeability (act as lipid barrier)

- Transport of **hydrophilic** and **macromolecular** drugs occurs through scleral route
- **Lipophilic** agents of **low molecular** weight follow transcorneal transport by **passive diffusion**



Fick's first law of passive diffusion

Diffusion coefficient of the drug

Difference in drug concentration

$$J = -D\frac{dC}{dX}$$

Concentration gradient

Rate of transport (Flux density)

Distance between two points

Factors Influencing Ocular Bioavailability

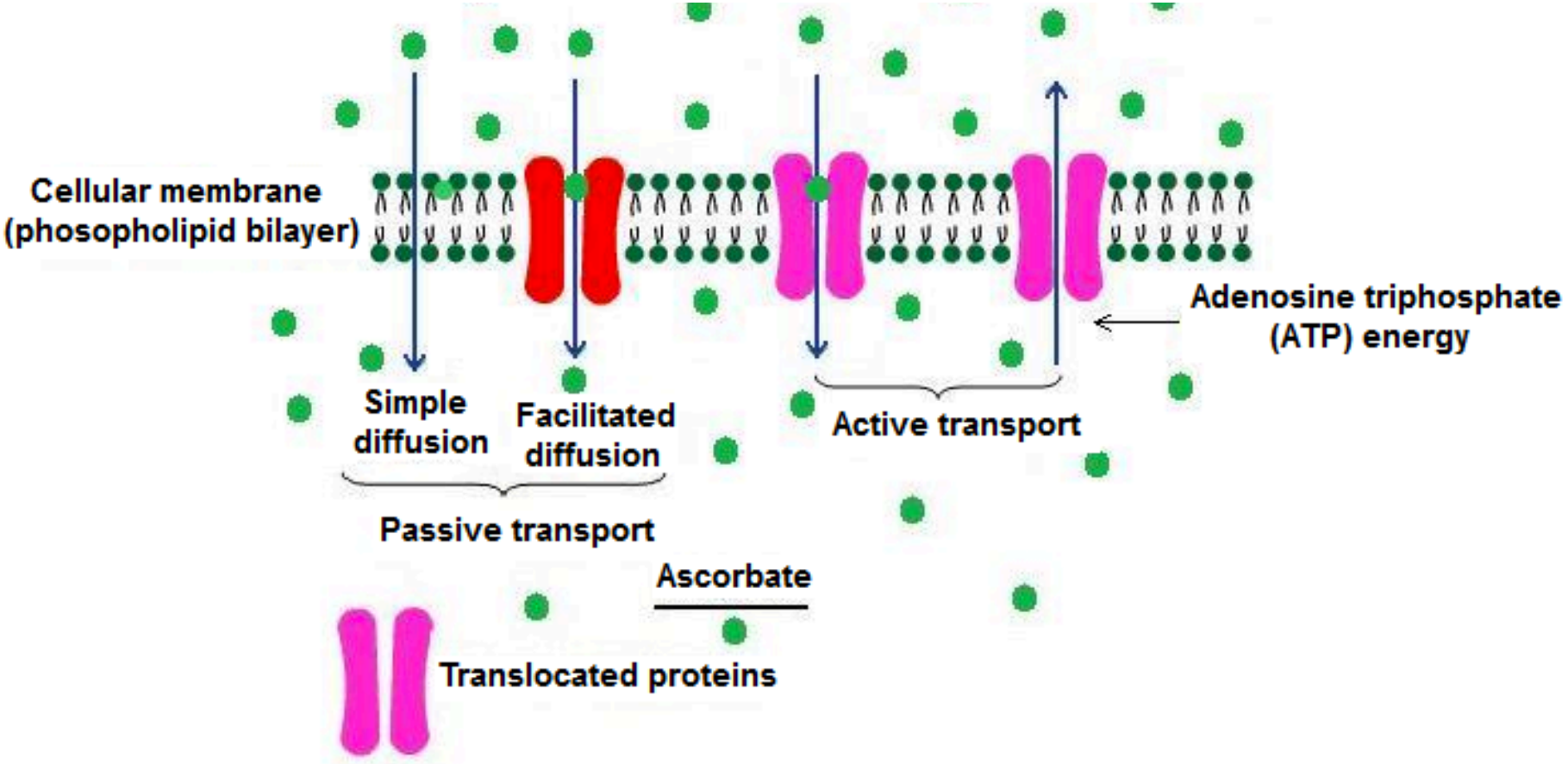
J = The flux rate across the membrane

D = diffusion coefficient

- The diffusion coeffecient ⬆ , as the molecular size of the drug ⬇

dC/dX = concentration gradient

- As the drug solubility ⬆ , the gradient ⬆ , the driving force for drug entry into the aqueous humor ⬆


Cellular membrane
(phosopholipid bilayer)
Simple
diffusion
Facilitated
diffusion
Passive transport
Active transport
Adenosine triphosphate
(ATP) energy
Ascorbate
Translocated proteins

- **Anatomical and physiological factors affecting drug's ocular bioavailability:**

  protein binding, drug metabolism, lacrimal drainage.

- **Other factors affecting ocular bioavailability:**

  physicochemical characteristics of the drug substance and product formulation

  reason: cornea (membrane barrier) contains both lipophilic and hydrophilic layers

  permeated effectively by drug substances with lipophilic and hydrophilic characteristics

Ideal ophthalmic delivery system:

The 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

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:

Adjust concentration and tonicity,

Buffer and adjust pH,

Stabilize the active ingredients against decomposition,

Increase solubility,

Impart viscosity,

and act as solvent or increase solubility.

the use of ingredients to impart a color, odor, or flavor is prohibited.

1- Tonicity and Tonicity-Adjusting Agents:

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

*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 persons.

* The eye seems to tolerate hypertonic solutions better than hypotonic ones.

*Common tonicity adjusting ingredients include: NaCl, KCl, buffer salts, dextrose, glycerin, propylene glycol, and 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

2- pH Adjustment and Buffers:

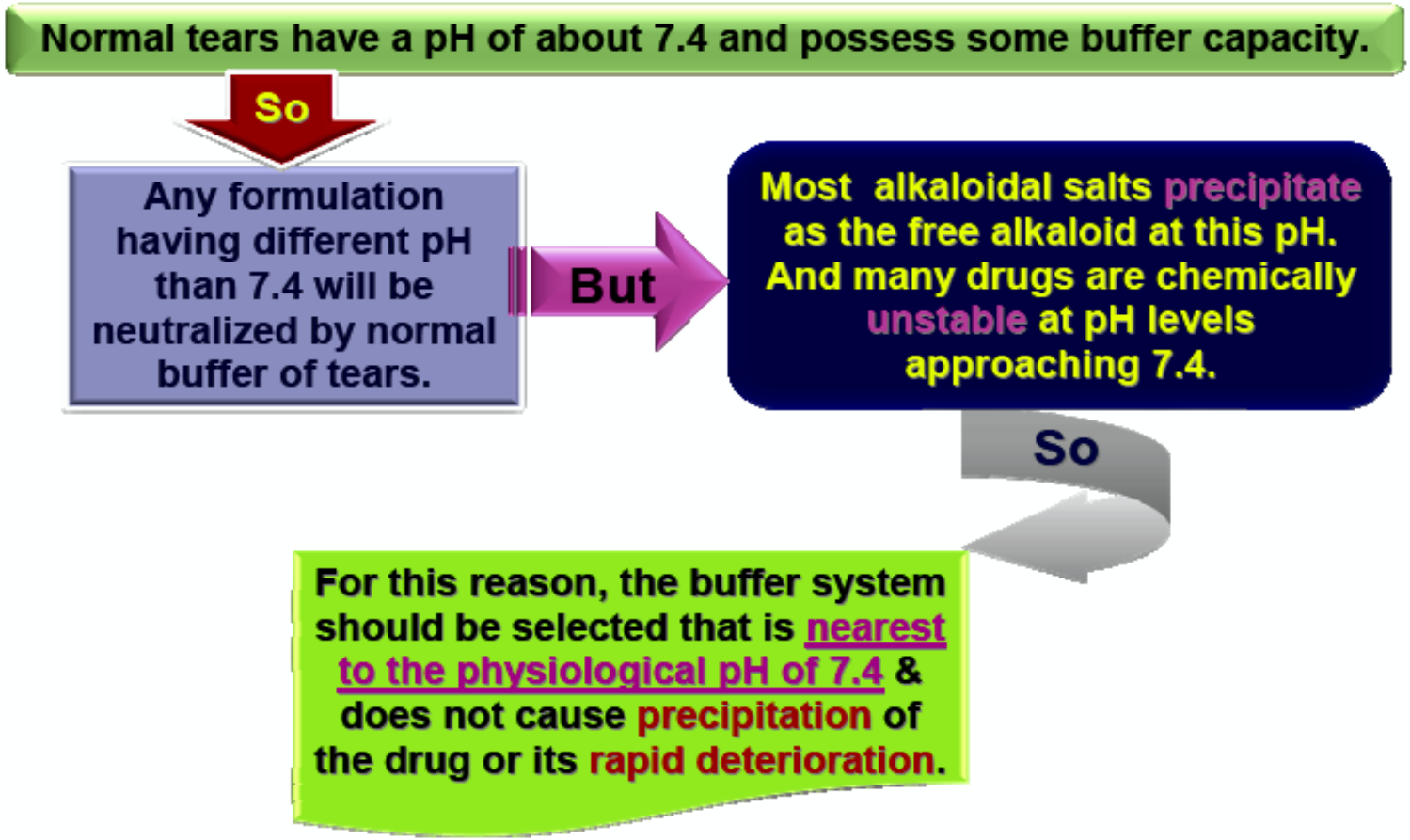
Ideally, every product would be buffered to a pH of 7.4 (the normal physiological pH of tear fluid).

The pH values of ophthalmic solutions are adjusted within a range to provide an acceptable shelf life.

When necessary, they are buffered adequately to maintain stability within this range for at least 2 years.

If buffers are required, their capacity is controlled to be as low as possible (Low buffer capacity) thus enabling the tears to bring the pH of the eye back to the physiological range.

pH & buffer


Normal tears have a pH of about 7.4 and possess some buffer capacity.
So
Any formulation having different pH than 7.4 will be neutralized by normal buffer of tears.
But
Most alkaloidal salts precipitate as the free alkaloid at this pH. And many drugs are chemically unstable at pH levels approaching 7.4.
So
For this reason, the buffer system should be selected that is nearest to the physiological pH of 7.4 & does not cause precipitation of the drug or its rapid deterioration.

2- pH Adjustment and Buffers:

- **Conclusion:**

If buffers are required, their capacity is controlled to be as low as possible ??

1- to enable the tears to bring the pH of the eye back to the physiological range

2- to avoid effect of buffers on tonicity

Examples of buffer vehicles used:

- Boric acid vehicle: pH of slightly below 5
- Isotonic phosphate vehicle: pH ranges from 5.9 - 8

3- *Stabilizers & Antioxidants:*

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

* Antioxidants are the principal 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.

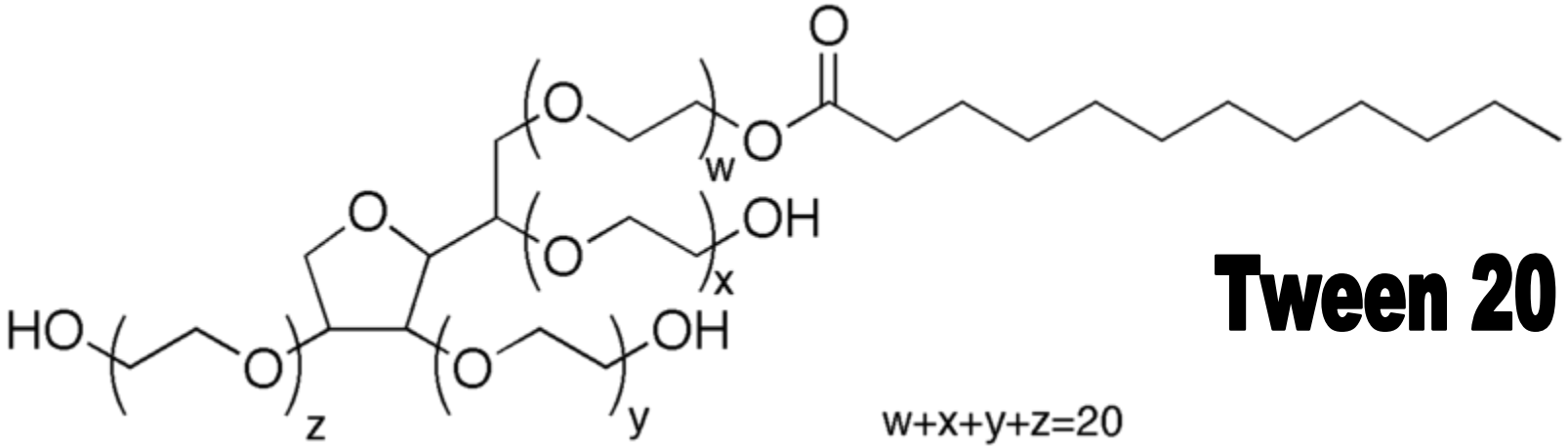
Several antioxidant systems have been developed. These consist of ascorbic acid and acetylcysteine, and and Sodium thiosulfate.

4- **Surfactants:**

The order of surfactant toxicity is:
anionic > cationic >> nonionic.

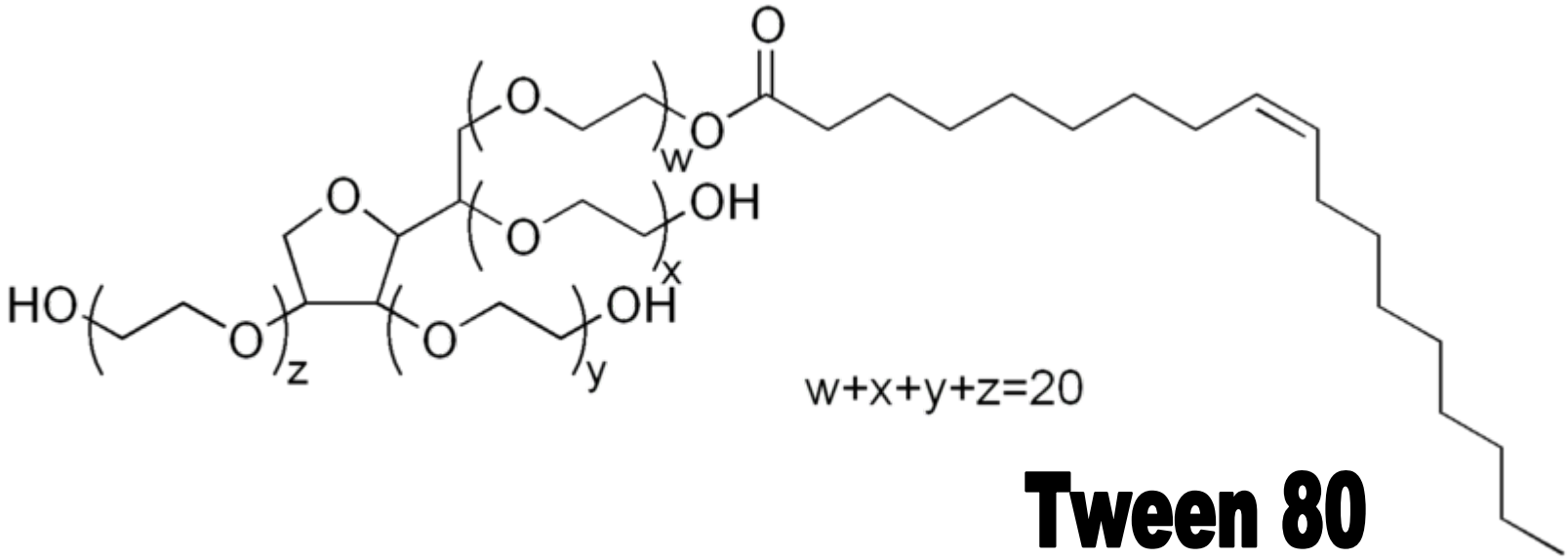
- *Several nonionic surfactants are used in relatively low concentrations to aid in dispersing steroids in suspensions and to achieve or to improve solution clarity.*

Those principally used are the Sorbitan ether esters of oleic acid (Polysorbate or Tween 20 and 80),



Tween 20

w+x+y+z=20



w+x+y+z=20

Tween 80

5- Viscosity-Imparting Agents:

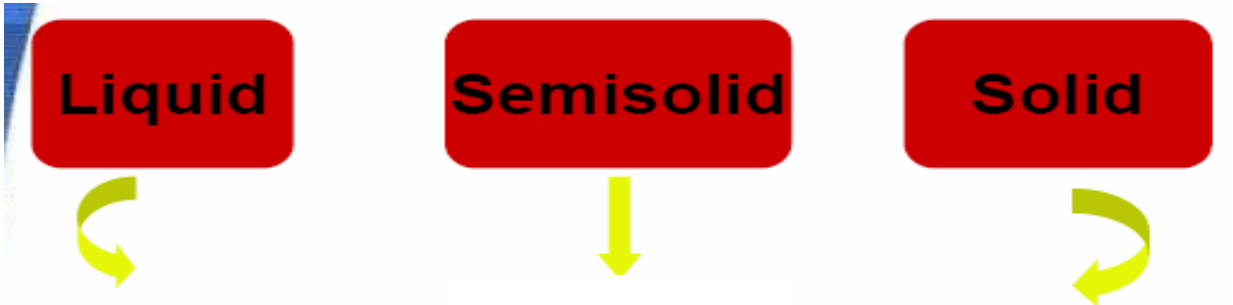
Polyvinyl alcohol, methylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, and Carbomers, ***are commonly used to increase the viscosity of ophthalmic solutions and suspensions.*** **(to retard the rate of setting of particles)**

- ***They increase the ocular contact time, thereby decreasing the drainage rate, increase the mucosdhesiveness and increasing drug bioavailability.***

* ***A secondary benefit of the polymer solutions is a lubricating effect. The major commercial viscous vehicles are hydroxypropyl methylcellulose (Isopto ®) and polyvinyl alcohol (Liquifilm ®).***

Disadvantages: 1- produce blurring vision as when dry form a dry film on the eye lids
2- make filtration more difficult

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