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Table 1: Anatomical for intraocular drug transport [13]	
Anatomical barriers	Characteristics
Cornea	**Epithelium is a m**ajor barrier to passage of hydro-philic drugs; tight intercellular junctions restrict paracellular diffusion. **Stroma** is a barrier to passage of highly lipophilic drugs
Tear	Drugs bind with mucin, dilution of topical drugs Induced lacrimation and tear film turnover increase drug clearance
Conjunctiva	More permeable than cornea to hydrophilic drugs and macromolecules; has greater surface area **Epithelium** – tight intercellular junctions.
Sclera	**Hydrated stroma** Better absorption of hydrophilic drugs. More permeablity to macromolecules Molecular radius is an important parameter to determine permeation
Choroid	Receives less blood flow, so, less drug permeation from systemic circulation **Choroid Bruch's membrane** limits permeation of lipophilic drugs
Vitreous humour	Hyaluronan- is more permeable to anionic drugs (due to negatively charge) Large, lipophichydrophilic drugs retained more in vitreous humor
Retina	Permeable to small, lipophilic or hydrophilic molecules **Inner limiting membrane** limits entry of drugs from vitreous into retina.
Blood ocular barriers	Blood aqueous barrier- tight junctions limit entry of solutes into aqueous humour and entry of hydrophilic drugs from plasma into aqueous humour Outer blood retinal barrier- Major barrier to hydrophilic drugs Inner blood retinal barrier- Major barrier which limits entry of systemic drugs into retina

Table 2: Advantages, disadvantages and some properties of nanoemulsion		
Advantages	**Disadvantages**	**Other properties**
Carrier of hydrophobic drugs	Requires large amount of surfactant and cosurfactant	Translucent/ translucent system
Improves bioavailability of drugs	Low ability to solubilize high melting point drugs	High surface area/ small droplet size
Good shelf stability	Low stability especially in acidic condition	Liquid morphology
Toxicologically safe	Toxicity of surfactants and cosufractants is likely possible	Has benefit to mask taste

Table 3: Summary of the physicochemical characteristics of a cationic Oil-in-water nanoemulsion[50]	
Parameter	**Description**
Aspect	White opaque to slightly translucent
Ph	5.0-7.0
Osmolality (mOsmol/kg)	270
Droplet size (nm)[a]	<200
Zeta potential (ɔ, Mv)[a]	Positive (+40)
Sterility	Sterile

Table 4: Studies of several ophthalmic nanoemulsion formulations with types of surfactants and cosurfactants and oil used. [68]				
S.No.	**Drug**	**Surfactants and co surfactants**	**Oil**	**Comment**
1	Timolol	Lecithin	Isopropyl myristate	Nanoemulsion bioavialibity in aqueous humour was 3.5 times more than Timolol alone
2	Dexamethasone	Cremophor EL, Propylenegly col,	Isopropyl myristate	Enhanced ocular bioavailability (just about three times compared to conventional dosage form) and sustained effect of drug without ocular

				irritation
3	Indomethacin	Phospholipids Miranol – MHT	MCT	Significant increase in corneal permeability compared to marketed formulation (Indocollyre®) show almost 4 times corneal permeability coefficient without toxicity in *ex vivo* studies
4	Levobunolol	Lecithin, glycerol	Soybean oil	Improved *in vitro* permeability with a reservoir effect
5	Pilocarpine	Macrogol 1500-glyceroltriricinoleate, 6PEG 200, propylene glycol,	Isopropyl myristate	In comparison to aqueous solution, enhanced ocular bioavailability to up to 1.68 times with sustained effect and no ocular toxicity
6	Chloramphenicol	Span20, Span80, Tween20, Tween80	Isopropyl palmitate and isopropyl myristate	Improved stability in nanoemulsion formulation in comparison to conventional system as chloramphenicol is relatively prone to degradation in conventional dosage form

Table 5: Ophthalmic nanoemulsions products.[69]

Nanoemulsions in the market for ophthalmic disease treatment				
Trade name	Drugs	Formulation	Disease	Company
Restasis®	0.05% Cyclosporin A	Nanoemulsion	Dry eye disease	Allergan
Cyclokat®	0.1% Cyclosporin A	Cationic nanoemulsion	Dry eye disease	Santen Pharmaceuticals
Nanoemulsion under clinical trials for ophthalmic disease treatment				
Products	Administration method	Disease	Trial	Phase
Brimonidine Tartrate	Eyedrops	Dry eye disease	NCT03785340	III

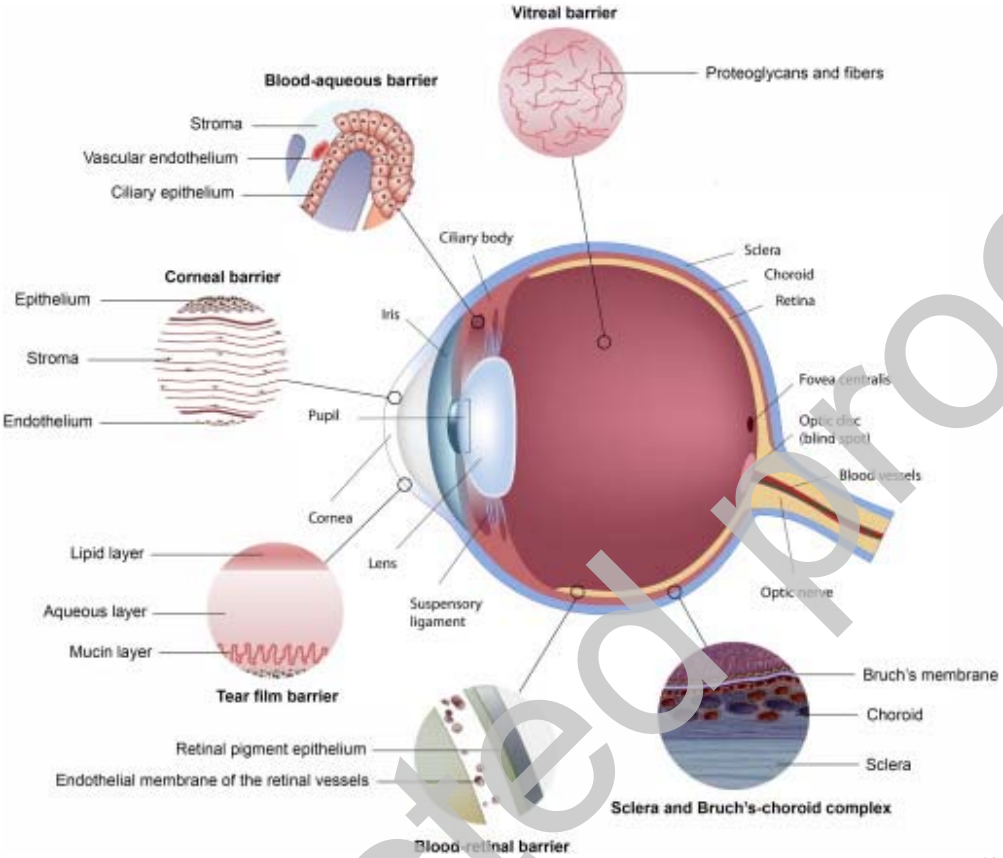


Figure 1: Ocular barriers for drug transport[10]

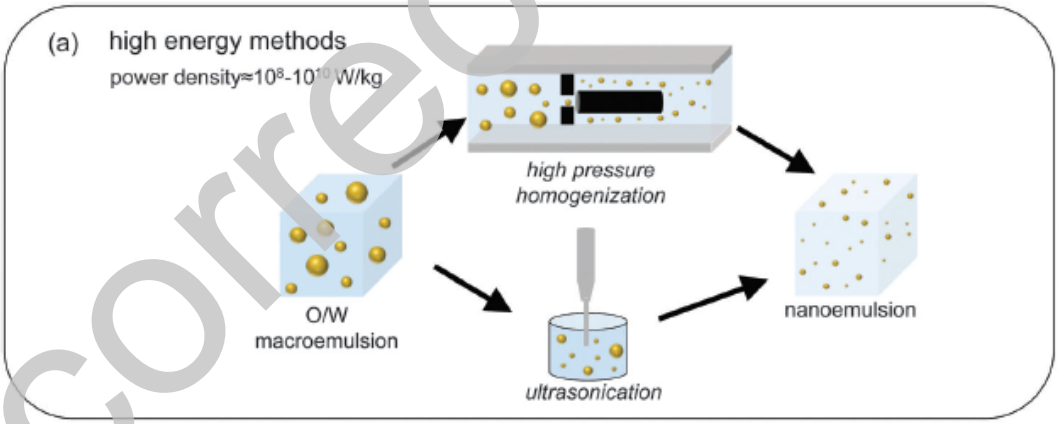


Figure 2 (a): overview of high energy methods for preparing o/w nanoemulsion, such as high pressure homogenization and ultrasonication[31]

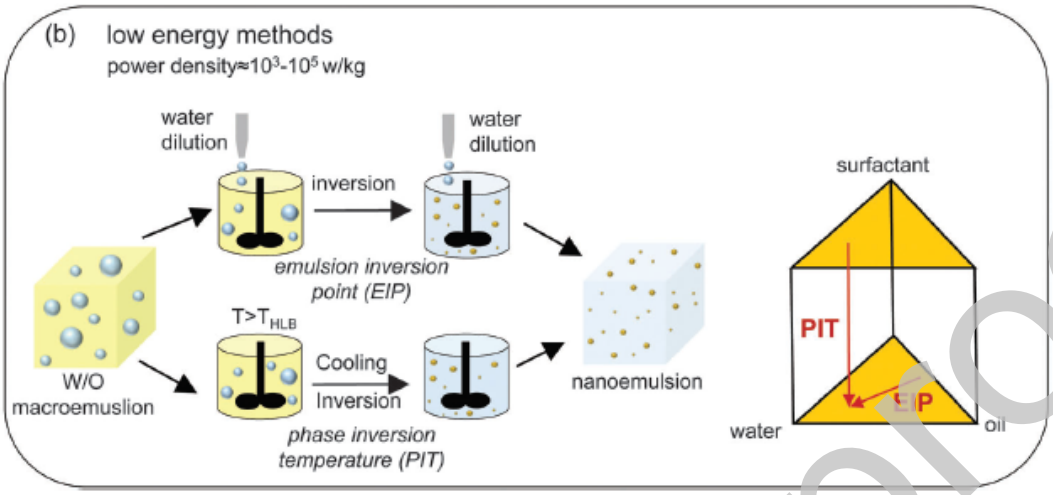


Figure 2(b): Overview of low energy methods for preparing of o/w nanoemulsion Others nanoemulsion preparation methods as bubble bursting, evaporative ripening, and microfluidization are also employed.[31]

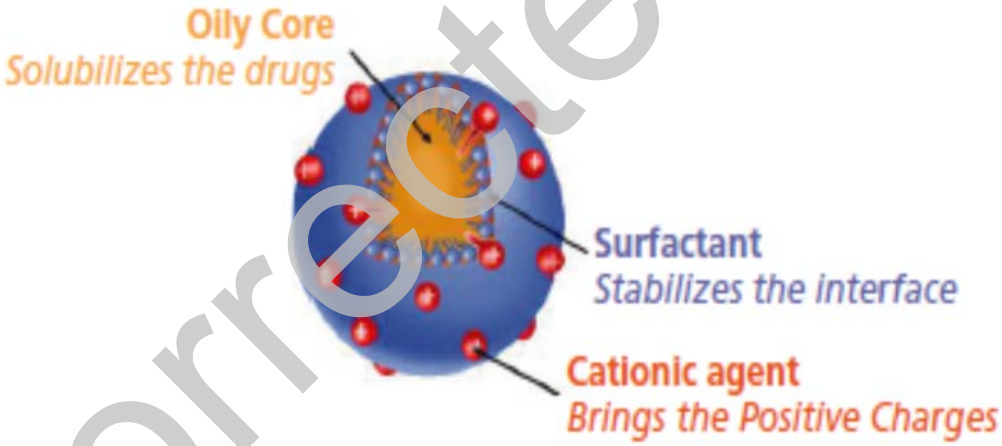
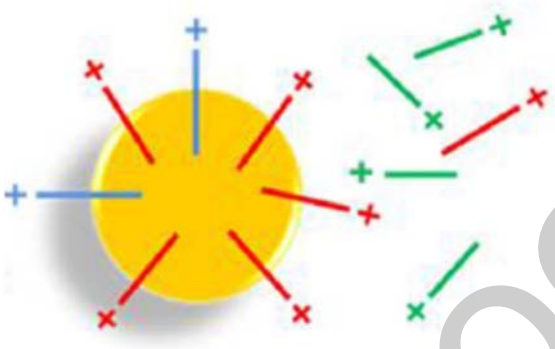
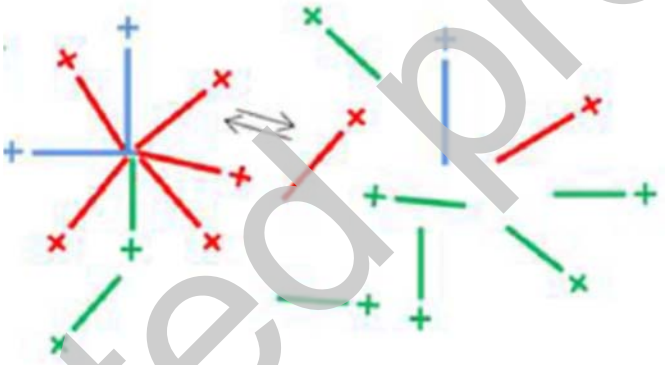


Figure 3: Schematic representation of one of the oil nanodroplets Present in the cationic oil-in-water nanoemulsion [50]



(a) **benzalkonium chloride in emulsion**



(b) **benzalkonium chloride in solution**

Figure 4: Illustration of the phase distribution for the different alkyl derivatives of benzalkonium chloride in (a) emulsion and in (b) aqueous solution[50]