

REVIEW

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## Nanoemulsions as Ophthalmic Drug Delivery Systems

Rasha Khalid Dahir, Amina Mudhafar Al-Nima, Fadia Yassir Al-bazzaz  
Department of Pharmaceutics, University of Mosul, Mosul, Iraq

Amina Mudhafar Al-Nima

[amnah.mudhafar@uomosul.edu.iq](mailto:amnah.mudhafar@uomosul.edu.iq)

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### ABSTRACT

Nanoemulsion is liquid in liquid dispersion with droplet size of about 100 nm, it has transparent appearance, high rate of bioavailability and increased shelf life. It is made up mainly of oil, water, surfactant and cosurfactant and can be prepared by high and low energy methods.

Diluted nanoemulsion is utilized for the delivery of ophthalmic drugs due to their ability to penetrate the deeper layers of the ocular structure, provide sustained release effect, and reduce frequency of administration and side effects. These nanoemulsions are subjected to certain tests such as safety, stability, pH profile, rheological studies and soon. Cationic nanoemulsions are prepared for topical ophthalmic delivery of the active ingredients utilizing from cationic agents for increasing the drug residence time on the ocular surface, reducing their clearance from ocular surface and improving bioavailability of the drug. This article review summarizes the main characteristics of nanoemulsions, ophthalmic nanoemulsions, cationic nanoemulsions as well as their components, methods of preparation and evaluation parameters of ophthalmic nanoemulsions.

**Keywords:** Nanoemulsion, cationic nanoemulsions, ophthalmic drug delivery

### 1. Introduction

Ophthalmic drug delivery system is one of the most important routes of drug administration, which can be regarded as a challenging attempt encounters pharmaceutical scientists.<sup>1</sup> Most of the ophthalmic diseases are treated by topical eye drops instillation, however, there are several problems associated with these formulations like poor bioavailability.<sup>2</sup> As the drug is removed from the precorneal area within few minutes after instillation due to the lacrimal secretion and nasolacrimal drainage.<sup>3,4</sup> There are many problems associated with scale-up of nanoemulsions, for instance, the stability problem, high cost and tedious preparation methods that can be utilized.<sup>5</sup> For the above reasons, pharmaceutical scientists try to formulate ophthalmic preparations that can overcome these problems. Although the incorporation of the drug in different pharmaceutical vehicles likes ointments, suspensions and emulsions can improve bioavailability and provide sustained drug release; they cannot be regarded as the formulation of choice since they are known to cause ocular adverse effects like irritation,

redness of the eye, interference with vision, low stability of the product. In addition to that, chronic administration may increase the systemic availability which may cause severe systemic complications. Formulations containing preservatives also induce adverse reactions upon systemic absorption.<sup>3,6,7</sup>

Nanotechnology is one of the most important promising approaches for ophthalmic drug delivery. It is currently being applied for the delivery of the drug to both anterior as well as the posterior segment of the eye. Nanotechnology-based systems with an appropriate particle size can be formulated to ensure low irritation to the patient eye, adequate bioavailability and compatibility with the ocular tissue. It is an excellent approach to deliver lipophilic drugs which involves the application of cationic nanoemulsion, which benefits from the fact that corneal and conjunctival cells are negatively charged thus can prolong the residence time of the drug on the ocular surface, improve absorption and bioavailability of the drug.<sup>8,9</sup>

### **1.1 Barriers for intraocular drug transport**

Each layer of the ocular tissues has distinct features and poses a diverse barrier following drug administration via a certain route as shown in figure 1.<sup>10</sup>

#### **1.1.1 Tear**

A tear can influence on the administered ophthalmic drug through binding with the administered drug, enhancing clearance and diluting the drug. Tear turnover is one the dynamic barriers which decreases the drug availability significantly leading to inhibiting its therapeutic effect.<sup>1,11</sup>

#### **1.1.2 Cornea**

The cornea which is a non-vascular structure consists of three main layers; the outer one known as the epithelial layer which is a lipophilic layer, the middle one is the stromal layer which is hydrophilic in nature and the inner one is the endothelial layer that separate the aqueous humour and the stroma.<sup>5</sup> The corneal epithelium forms the most important barrier to drug absorption by topical administration, and there is a fact that the corneal cells of glycosyl amino glycans lining the ocular surface are negatively charged at a physiological pH 7.<sup>5,6</sup> When applying a positively charged formulation to the eye it is possible that an electrostatic attraction will occur which will lead to prolonging the residence time of the formulation on the ocular surface.<sup>5,12</sup>

#### **1.1.3 Conjunctiva**

Conjunctiva of the eye is a thin layer that lines the inside of the eyelids and maintains the tear film. The stroma presented in between the outer conjunctival epithelium and inner sclera has abundance of blood and lymphatic vessels throughout the subconjunctiva and it acts as a dynamic barrier to hydrophobic drug absorption. It is rich with capillaries and lymphatic vessels, therefore the drug that administered to the conjunctival sac can be rapidly cleared.<sup>8,12</sup> The conjunctival epithelium is more penetrable to larger molecules and has twenty times larger surface area than that of the cornea because of wider intercellular spaces. The conjunctival pathway favours absorption of large hydrophilic molecules (with molecular weight nearly less than 20-kDa) such as proteins and peptide unlike corneal route which favours lipophilic small molecules (majority of drugs). Though, retardation of passive pathway can occur by the tight junctions present in conjunctival epithelium. Therefore, if drug absorption through conjunctiva is compared to

that through the cornea, the former one is considered as nonproductive leading to low bioavailability of ophthalmic drugs.<sup>11,12</sup>

#### **1.1.4 Sclera**

The sclera is the outer layer of the eyeball that is known as the white of the eye. It can maintain the shape of the eye through its fibrous structure. The hydrophobic nature of the drug affects the permeability of the sclera, when the lipophilicity of the drug increases the permeability across the sclera will decrease and vice versa.<sup>8</sup> Moreover, the permeation of therapeutic molecules like drugs also depends on the hydration degree of sclera as well as to its intraocular pressure. It has been documented that intraocular pressures in the range of (15–20 mmHg) which is normal has very neglected effects on permeability while buttrans-scleral permeability of the solute molecules is affected by high intraocular pressure up to (> 20–60 mmHg) of the solute molecules.<sup>11</sup>

#### **1.1.5 Choroid/Bruch's membrane**

This part of the eye is regarded as the most vascularized part of the body. It has been shown that choroidal thickness decreases with increasing age. In contrast, the thickness of Bruch's membrane increases with age, these changes in the thickness of choroid and Bruch's membrane might affect drug penetration into the retina.<sup>8</sup> Getting older and with age, the choroid becomes thinner and the Bruch's membrane becomes thicker leading to alteration in the barrier property which in turn alters drug permeation of drug molecules over the years.<sup>11</sup>

#### **1.1.6 Retina**

The retina is located at the back of the eye, on which an image is formed from the light that enters the eye from the cornea passing across the anterior part until it reaches the retina in the posterior part of the eye, which then can be interpreted in the brain. It may be subjected to diseases that affect the posterior segment of the eye such as age-related macular degeneration (AMD) and diabetic retinopathy. All of the drugs in the vitreous can be eliminated by anterior and posterior route; the drugs can be eliminated across the retina after passing through the internal limiting membrane that separates the retina and the vitreous.<sup>8,9</sup>

There is over expression of CD44 on the surface of the retina which is important in targeting of a number of drugs and gene-based therapeutics. Retina demonstrates presence of 15-20 nm wide intercellular spaces without tight junctions. As a result, small hydrophilic/ lipophilic drugs can permeate the retina. However, large and cationic molecules face resistant to permeation in retina. Inner and outer plexiform layers present major barriers to diffusion of large molecules in human retina. Retinal exclusion limit (REL) is defined as maximum size of molecule which is able to freely permeate through cornea. In human eyes, REL is suggested to be 76 kDa by Jackson et al. This is supported by observations that hard exudates in hypertensive or diabetic retinopathy persist for months in retina since molecules greater than 76 kDa diffuse through retina very slowly, while macromolecules with molecular weight greater than 150 kDa is arrested by inner limiting membrane.<sup>10-12</sup>

All the above barriers and their characteristics are represented in table 1.<sup>13</sup>

### **1.2 The main challenges and key considerations in ocular drug delivery:**

#### **1.2.1 Challenges:**

The eye is the unique organ, both anatomically and physiologically which contains highly varied structures with independent physiological functions. This complexity of the

eye provides special challenges to ocular drug delivery strategies.<sup>13</sup> One of the challenges is the absorption; as with traditional eye drops, ocular bioavailability after topical administration is only 3-4% due to its impermeable nature and small surface area. Other challenges include poor drug solubility; lipophilic drugs cannot be incorporated in conventional aqueous eye drops, for this reason; they must be formulated as suspensions. Patient compliance; frequent instillations are usually needed with eye drops to reach the desired therapeutic range of the drug. High tolerability or comfort demands limit the formulation options. Excipient choice; limited numbers of excipients are listed in ophthalmology. Finally, the posterior segment drug delivery; it is impossible to deliver conventional eye drops to the posterior segment of the eye<sup>8,9</sup>.

### **1.2.2 Considerations:**

Ocular drugs typically achieve < 10% ocular bioavailability. If a drug applied to the outer surface of the eye, it may pass ocular-blood barriers where it will encounter metabolizing enzymes and cellular transporters before it reaches the site of action. So, it is very important to consider the anatomy and physiology of the eye, including the mucus layer, eyelids, metabolism, blink drainage. Tear composition as enzymes, lipid outer layer, and stability of the tear film. Also the disease state and the occurrence of keratitis or inflammation on absorption as well as clearance of the drug. Ocular comfort and tolerability of the formulation including viscosity, drop size, pH, osmolality. In addition to all above consideration patient anticipation, squeeze ability and type of packaging.<sup>8,9,14</sup>

### **1.3 Efflux transporters – ocular drug bioavailability**

These are the primary barriers that result in poor absorption of the drug and poor bioavailability, especially for anterior segment ocular drug delivery. Several numbers of these barriers have been identified in the epithelial cells of various ocular tissues in human and rabbit, such as P-glycoprotein, also called Multidrug Resistance Protein 1 (MDR1), Multidrug Resistance Associated Proteins (MRP1, MRP2, MRP3, MRP4, MRP5, MRP6, MRP7, MRP8, MRP9), Lung Resistance Protein, and Breast Cancer Resistance Proteins. Researches today are interested in studying their role in ocular drug delivery.<sup>15,16</sup> Efflux transporters for anticancer, antibiotics (ofloxacin and erythromycin) and steroids are recognized and limit bioavailability of these drugs.<sup>14</sup> However; different studies suggest many concepts such as conjugation of drug to dendrimer enables bypassing of the efflux transporter which causes an increase in drug solubility and therefore increasing drug bioavailability. In a study, propranolol (a calcium channel blocker), a well-known substrate of the P-glycoprotein efflux transporter, has been conjugated to lauroyl-G3 dendrimers. This conjugation has shown enhanced solubility.<sup>17</sup> However, the oral application of dendrimers as one of drug delivery is in its beginnings but may come out as a pleasing strategy in the future.<sup>18</sup>

### **1.4.1 Definition of nanoemulsion**

Nanoemulsion can be defined as a clear and stable dispersion of oil and water. It is mainly composed of the internal phase or the dispersed phase and the external phase or the dispersion medium. In addition to that, the surfactant and cosurfactant molecules play an effective role in the formation of nanoemulsion due to their ability to reduce the interfacial tension and create a small particle size, also due to their function in the formation of a stable preparation as a result of the repulsive electrostatic interaction and

steric hindrance. Generally, surfactants are molecules that have a bipolar structure which is composed of hydrophilic and hydrophobic part.<sup>8,19</sup>

Nanoemulsions are colloidal carriers of drug molecules with droplet size in the ranges of 500-1000 nm (preferably from 100 to 500nm). As a drug delivery system, they increase the therapeutic efficacy and minimize the adverse effect and toxic reactions of the administered drug.<sup>20,21</sup>

Nanoemulsions can be distinguished from microemulsions in their droplet size and physical stability characteristics. Microemulsions are isotropic and transparent systems that contain spherical droplets of water phase or oil phase, having a diameter range from 10 -100nm dispersed in an external oil or water phase, respectively. Microemulsions are thermodynamically more stable than nanoemulsions, this can be explained by the necessity of introducing thermal and/or mechanical energy in the preparation of nanoemulsion (i.e. mixing & heating) and phase separation after some time after preparation of nanoemulsions is deterministic. This fact is one of the most distinctive differences between microemulsions and nanoemulsions in terms of stability.<sup>20,22</sup>

Preparation of nanoemulsion can be classified into two main classes, high energy methods such as high pressure homogenization and ultrasonication and low energy methods such as phase inversion.<sup>23</sup>

The translucent appearance of nanoemulsion is due to the droplet size of less than 100nm, as a result of this small droplet size, the nanoemulsion is thermodynamically unstable dispersion. A high concentration of surfactants is required, that causes sticky feel of the formulation. A yellowish appearance and rancid odor which occur after storage as a result of the phospholipids that are generally used to stabilize the nanoemulsion. So to overcome these problems; a formulation was developed and presented (US6335022b1), that utilized from oxyethylenated and nonoxyethylenated sorbitan fatty ester as surfactants.<sup>16</sup> The contrivers believed that the use of the surfactants chosen from oxyethylated or non oxyethylated sorbitan fatty esters with a molecular weight of more than 400 grams per mole, and they are solid at a temperature of less than 45°C can result in a stable formulation. In addition to that, a similar formulation stabilizing effect can result from amphiphilic lipids that are selected from a group of alkaline salts of cholesterol, these formulations can be used as effective delivery vehicles for antiglaucoma, anti-inflammatory, antiviral and anti allergic effects.<sup>23,24</sup>

Bioavailability of the ophthalmic preparations can be improved by enhancing the drug residence time on the cornea through increasing the viscosity of the formulations. This can be achieved by increasing the fraction of the dispersed oil phase and by incorporating water-soluble polymers, which can form a gel with the continuous aqueous phase. Certain studies demonstrated that caution should be recommended in considering the ideal concentration of the water-soluble polymers for getting the required viscosity with a transparency of the preparation.<sup>25</sup>

Prostaglandins which affect a wide range of physiological activities, for instance blood pressure, pain awareness and clotting mechanisms, some of these analogues are utilized in ophthalmic antiglaucoma preparations, such as travoprost, latanoprost and bimatoprost. Unfortunately, they are chemically unstable in aqueous preparation and have a poor water solubility, thus to avoid these challenges, various strategies have been suggested, such as pH adjustment and complexation with cyclodextrin to improve both solubility and stability, solubility can be improved also by the addition of benzalkonium chlorides. The

problem associated with these preparations is ocular intolerability that associated with the resultant positively charged preparation. Carli *et al.*<sup>26</sup> discovered that neutral zeta potential and nontoxic preparation can be obtained from a nanoemulsion formulation that consists of prostaglandin containing oil phase as an internal phase, dispersed in aqueous external phase, utilizing from two or more nonionic surfactants.<sup>27</sup>

Cyclosporin A that was used widely for the treatment of dry eye disease, however, precipitation of the drug occur as a result of its poor solubility in the aqueous medium. In the patent disclosures, US4649047 and US6582718, improved formulation of this drug has been reported.<sup>28</sup>

Positively charged ophthalmic preparation strategy is applied, utilizing from the negative charge of the corneal barriers. United States patent has No. 6007826 which describes an oil/water preparation that made up of surfactants/lipid that has a positively charged polar groups resulted in a cationic preparation that can bound strongly to the corneal surface.<sup>29</sup> Bo Wang and colleagues from Hainan University, China, had developed a Coconut oil-in-water emulsions which were formulated using three polysaccharides. The main effects of the ratio of the compounded polysaccharides on their apparent viscosity and interfacial activity were studied. Many data in addition to the physical stability of the formulated emulsions with different compound-polysaccharides were studied. The results showed that emulsions formulated with compound-polysaccharides manifested smaller average particle sizes, and the stability analysis showed that the emulsion formulated by compounding polysaccharides had preferable physical stability.<sup>30</sup>

#### **1.4.2 Components of nanoemulsion**

The prime components of nanoemulsion are oil, aqueous phase, and emulsifying agents. Different types of oils can be used in ophthalmic nanoemulsion like medium chain triglycerides, mineral oil, vegetal oil like castor oil.<sup>31</sup>

Emulsifying agents are important in maintaining the stability of the product because, without these agents, oil and water phase will separate into two layers. They may be surfactants like polysorbates, cremophors, poloxamers, tyloxapol, vitamin E-TPGS. Emulsifying agents should have certain properties like compatibility with the product, in addition to that, it should be nontoxic.<sup>5,21</sup>

#### **1.4.3 Desirable properties of emulsifying agents**<sup>21,32,33</sup>

1. It should have the ability to reduce the surface tension to less than 10 dyne/cm.
1. It should form a stable and coherent film around the dispersed phase globules to prevent coalescence.
2. It should provide adequate viscosity and zeta potential for optimum stability.
3. It should be effective in low concentration.

### **1.5 Types of films around the dispersed globules in nanoemulsion**<sup>34,35</sup>

#### **1.5.1 Monomolecular film**

The surfactants that stabilize the nanoemulsion, form a monolayer of ions or adsorbed molecules at the interface that reduce the interfacial tension, nowadays a combination of emulsifying agents can be used, which composed of a hydrophilic emulsifying agent at the aqueous layer and lipophilic one at the lipid layer to produce a complex film at the interface.<sup>36</sup>

#### **1.5.2 Multimolecular film**

A multimolecular film around the droplets is formed by hydrated lyophilic colloids, these agents do not lower the surface tension significantly, but can increase emulsion stability through their tendency to enhance the viscosity of the external phase.<sup>34</sup>

### 1.5.3 Solid particulate film

This type of film is produced by emulsifying agents, which are small solid particles; they form a film round the dispersed droplets hence inhibiting their coalescence.<sup>34,35</sup>

## 2. Preparation of nanoemulsion

There are two main methods for nanoemulsion preparation: high energy and low energy methods. Low energy methods involve changing in the composition or temperature, which results in the reversal of the system and formation of small droplets. Most common methods of low energy are emulsion inversion point (EIP) and phase inversion temperature (PIT).<sup>32,37</sup>

The high energy methods, consist of two main steps which result in the formation of nanoemulsion: the first step involve mixing of oil, water, and surfactant for a sufficient period in a simple stirrer system, thus o/w macroemulsion is formed, the second step includes the conversion of macroemulsion into nanoemulsion through mean of homogenizer, that forces the macroemulsion through a narrow gap, this homogenization is repeated several times until constant droplet size is achieved, as shown in figure 2 (a)<sup>22,31,38</sup>. Zhang, Jialiang<sup>39</sup> *et al* prepared tacrolimus-loaded cationic nanoemulsions by using a high-pressure homogenization method. While Dukovski, Bisera Jurisic<sup>40</sup> *et al* used microfluidizer and homogenizer to prepare ibuprofen-loaded cationic nanoemulsion. The low energy method varies from the high energy method in that it starts with w/o emulsion which is converted into o/w emulsion due to change in temperature and composition. Thus emulsion inversion point method involves the conversion of w/o macroemulsion which was formed initially at room temperature into o/w nanoemulsion through a gradual dilution until it passes over the inversion point, where the transformation happens. In this method no need for energy to form the emulsion, owing to the low interfacial tension between oil and water interface which results in small droplets. In phase inversion temperature method, the initial w/o macroemulsion is formed at a higher temperature than the phase inversion temperature, conversion occurs after cooling to produce the required o/w emulsion without needing of energy, see figure 2 (b).<sup>31,41,42</sup> Figure 2 presented with the personal permission from Patrick S Doyle.<sup>31</sup>

### 2.1 Instability of nanoemulsions<sup>9,21</sup>

1. Flocculation: flocculation can be defined as an aggregation of small globules together to form large floccules.
2. Creaming: is settling down or rising up of the floccules, which form a concentrated layer but upon agitation, the emulsion can be reconstituted.
3. Cracking: is a permanent instability of the nanoemulsion, in which the internal phase separates as a layer, that upon agitation, the emulsion cannot be reconstituted, in this case, additional amounts of surfactants may be beneficial.
4. Miscellaneous instability: instability of nanoemulsion may be due to extreme temperature and light, therefore the emulsion should be stored in a tight colored container.
5. Phase inversion: it occurs as a result of a change in the volume ratio of phases or addition of electrolytes, which lead to the change of emulsion type from w/o to o/w and vice versa.

## **2.2 Important factors during the preparation of nanoemulsion** <sup>7-9,34</sup>

One of the most important factor during nanoemulsion preparation is careful choice of surfactants to achieve very low interfacial tension. In order to stabilize the microdroplets to yield nanoemulsion, the concentration of surfactant must be sufficiently high. In addition to above, adequate flexibility and fluidity of surfactants to support the formation of nanoemulsion should also be considered.

## **2.3 Advantages of nanoemulsion** <sup>34,35</sup>

It enhances the bioavailability of the drug, nonirritant and nontoxic, physically stable, improves the absorption of the drug due to its high surface area and small droplets size. It can also be formulated in different formulations, dissolves lipophilic drugs, less amount of energy is required and it helps in taste masking.

## **2.4 Disadvantages of nanoemulsion** <sup>34,36</sup>

It requires the addition of large amounts of surfactants and cosurfactants to maintain the stability of the emulsion, has a limited capacity to solubilize high melting point substances, in addition, toxicity of the surfactants should be taken into account and different environmental parameters can affect nanoemulsion stability. The advantages and disadvantages of nanoemulsion with some of their physical properties are summarized as shown in table 2. <sup>69</sup>

## **2.5 Cationic oil in water nanoemulsion**

Cationic nanoemulsions are those preparations that utilize cationic surfactants which concentrate around the surface of the oil droplets, to make them positively charged. Owing to the negative nature of the ocular surface, cationic nanoemulsions can improve the residence period of the product in the eye through the electrostatic interaction with the opposite charges of eye surface mucus layer. Therefore, cationic nanoemulsions are probably show improved therapeutic efficacy due to an increase in the retention time at the ocular surface.<sup>25,43</sup> Cationic surfactants should have adequate lipophilicity in order to be taken by the oil droplets, with a very small amount present in the aqueous phase. Those preparations show an important role in prolonging residence time of the drug on the ocular tissue which is greater than that observed in anionic oil/water nanoemulsion. In addition to their important biological effects, they can also stabilize the nanoemulsion and prolong their shelf life through preventing coalescence of the oil droplet as shown in figure 3 (Figure 3 presented with the personal permission from Jean-Sébastien Garrigue)<sup>50</sup>, due to their repulsive force.<sup>44,45</sup> Table 3 summarizes some important physicochemical features of a cationic o/w nanoemulsion.<sup>50</sup>

The reason behind discovering these cationic nanoemulsions is that different attempts that had been made to extend drug residence time at the ocular surface, like using of excipients with bioadhesive and viscosity enhancement properties such as cellulose derivatives and propylene glycol, are associated with problems like ocular disturbance and they are only applicable to hydrophilic drugs, in addition to that many lipophilic drugs that are formulated as topical ocular oily or micellar solutions, ointments and creams, are not merely uncomfortable to the patient but as well they are of restricted efficacy.<sup>46</sup>

### **2.5.1 Protective properties of the cationic oil in water nanoemulsion vehicle**

Regarding lipophilic drugs, the application of cationic nanoemulsions to increase ocular bioavailability through prolonging the drug residence time and spreading properties was accompanied with surprising valuable effects on ocular surface.<sup>47</sup>

By mixing the oil phase in the cationic o/w nanoemulsions with the lipid layer of tear film, the water evaporation from the aqueous phase is reduced, this can help in restoring the lacrimal film integrity and maintaining the stability of the product, which is important in those patient suffering from short tear film breakup time due to the lipid deficiency in their tear (meibomian disease). Nanoemulsions are also important in the treatment of keratitis and in the reduction of the dry eye disease symptoms by their ability to mechanically stabilize the tear film and increase the hypoosmolarity of the aqueous film because hyperosmolarity is a proinflammatory factor. In addition to that, these preparations have a beneficial unexpected effect in the wound healing process by reducing the size of the scraped area.<sup>48,49</sup>

### **2.5.2 Choice of the cationic agent**

High zeta potential for the nanoemulsion is one of the most important factors to be considered before choosing the cationic agent. To obtain such high value, the entire cationic agent must be trapped in the oil nanodroplets, with the positive charge positioned at the oil-water interface, and a very small amount of these agents may be existing in the aqueous phase, therefore, high lipophilicity of the cationic agent is required.<sup>49</sup>

The select of the cationic agent most be limited to those previously registered, used in the ophthalmic product, or submissive with the United States or European pharmacopoeia, because there are large numbers of cationic agents, but not all of them can be chosen due to their related toxicity, such as stearylamine, oleylamine, polyethylenimine, polylysine, benzalkonium chloride derivatives.<sup>49,50</sup> Figure 4 (Figure 4 presented with the personal permission from Jean-Sébastien Garrigue)<sup>50</sup> shows a drawing of the phase spreading for the diverse alkyl derivatives of benzalkonium chloride in (a) emulsion and in (b) aqueous solution.<sup>50</sup>

Stearylamine is regarded as one of the most commonly used cationic agents, but this primary amine is very reactive to various excipients, thus it is not described in the pharmacopoeia. Oleylamine is a cationic lipid which has been used for manufacturing ophthalmic nanoemulsions however it has as well a stability problem owing to the existence of the unsaturated site in the aliphatic chain, and the function of its primary amine.<sup>49,51</sup>

Additional cationic molecules that are used for DNA transfection are as well used for cationic drug delivery system, such as polyethylenimine and poly-L-lysine, which are used in various nanoparticles as cationic agents, but some authors regarded them as extremely toxic.<sup>52</sup>

Quaternary ammonium compounds are preservatives, that have also surfactant properties and provide the nanoemulsion with a positive charge, such as benzalkonium chloride, benzododecinium bromide and cetrimide. Their preservative action is due to their capability to bind the negatively charged bacteria and mycoplasma, which destroy their membrane. As a result, their action is not limited to the microorganisms, but also the epithelial cells lining of the ocular surface by the identical mechanism, in addition to that, the preservative action of these agents is neutralized by the emulsion, due to the less

amount of these agents is present freely in the aqueous medium which limits their antimicrobial action and results in toxic effect.<sup>53</sup>

### **3. Evaluation of ophthalmic nanoemulsion**

#### **3.1 Parameters for evaluation**

##### **3.1.1 Zeta potential**

Zeta potential is the measurement of charge repulsion among oil nanodroplets. It is one of the utmost important parameters affecting the dispersed system stability, higher zeta potential results in more stable nanoemulsion. Its value depends on the differences between the electrical potential of the dispersion medium and the stationary layer of fluid close to the dispersed oil nanodroplets.<sup>50,54</sup>

The optimum zeta potential range was established to be in the range between +20 mV and +40 mV.<sup>5</sup>

##### **3.1.2 Refractive index**

It can be determined by the mean of Abbes refractometer, this test is used to determine if there is any probable impairment of vision or distress after administration of the eye drop.<sup>50,55</sup> Tear fluid refractive index is 1.340 to 1.360. It is recommended that eye drops must have refractive index values not upper than 1.476.<sup>56</sup>

##### **3.1.3 Percentage transmittance**

It can be measured by a spectrophotometer<sup>50,54</sup> at a specific wavelength with distilled water as a blank. The formulated nanoemulsion will be considered transparent if the percentage transmittance is more than 99%.<sup>57</sup>

##### **3.1.4 pH**

It can be measured by mean of pH meter; it should be about  $7.2 \pm 0.2$  for maximum comfort. When pH value of the instilled solution is different from tear pH, it results in discomfort and irritant effect, which depends on contact period with the eye surface, the composition of the solution, volume instilled and buffering capacity. But in many cases in which the preparation is not buffered or only slightly buffered, it can be tolerated because the tear can adjust the pH to the physiological level, the accepted pH of the preparation is between 3.5\_8.5.<sup>58,59</sup>

##### **3.1.5 Surface tension**

The tear film is damaged when the surface tension of eye drops is greatly lower than that of the lachrymal fluid which is about 40\_50 mN/m.<sup>60</sup>

##### **4.1.6 Rheological measurement**

The influence of the ophthalmic preparation on normal behavior of tear should be as little as possible, although the less viscous preparation allows little blinking pain and good tolerance, the more viscous one can improve residence time of the drug and ocular bioavailability, the viscosity of the eye drops should not be more than 20 mPa s.<sup>60,61</sup>

##### **3.1.7 Osmolality**

Lacrimal fluid osmolality is between 280\_293 mOsm/kg, but when the eye is opened, the value of osmolality is 231\_446 mOsm/kg due to the evaporation. When the osmolality of the solution is less than 100 or greater than 640 mOsm/kg, the preparation will irritate the eye. However, 1 to 2 minutes subsequent to instillation of a non-isotonic solution, the osmolality is reestablished.<sup>62</sup>

##### **3.1.8 Ocular irritation study**

These studies should ensure that corneal integrity and structure are not affected.<sup>62,63</sup>

##### **3.1.9 Thermodynamic stability studies**

These studies involve subjecting the nanoemulsion formulation to six cycles between 4°C and 45°C, and then the stable formulations were exposed to centrifugation test, at about 3500 rpm; formulations that did not display phase separation will be taken for the freeze-thaw stress test, during this test the formulation was exposed to three freeze-thaw cycles, under standard laboratory conditions.<sup>56,64</sup>

#### **3.1.10 Analysis of droplet size**

It is measured using a diffusion method, using particle size analyzer, light scattering, and LS 230. It can furthermore be measured via correlation spectroscopy, and transmission electron microscopy.<sup>65</sup>

#### **3.1.11 Viscosity measurement**

Viscosity can be determined by using rotary viscometer at different temperature.<sup>54</sup>

#### **3.1.12 Dilution test**

This test is important to ensure that the ophthalmic nanoemulsion does not show any change in its stability after dilution, this test involves that the aqueous phase is added to the nanoemulsion without showing any problem.<sup>54</sup>

#### **3.1.13 Drug content**

A predetermined weight of nanoemulsion is extracted by dissolving it in a appropriate solvent, which is then investigated using a spectrophotometer or HPLC.<sup>54</sup>

#### **3.1.14 Polydispersity**

This test is indicated to determine the droplet size uniformity, using a spectrophotometer, the greater polydispersity mean the lesser uniformity of the droplet size.<sup>54</sup>

#### **3.1.15 Cytotoxicity test**

This test involves the examination of the effects of the preparation on a certain culture of mammalian cells.<sup>66,67</sup>

### **3.2 Examples of ophthalmic nanoemulsion studies and new products**

Nanoemulsions are promising for ophthalmic disease treatment, so diverse studies covering the use of nanoemulsions as ophthalmic drug delivery are summarized in table 4, which include many drugs such as timolol, dexamethasone, indomethacin, levobunolol, pilocarpine and chloramphenicol with their preferred advantages when formulated as nanoemulsion over other traditional formulations and these advantages are shown as comments in table 4. Moreover, recently there are a number of nanoemulsion products available either on the market such as Restasis<sup>®</sup> which is used as nanoemulsion formulation for dry eye disease by Allergan company or in clinical trials such as Brimonidine Tartrate eye drops for dry eye disease under phase III. All these new examples are shown in table 5.<sup>68,69</sup>

## **4. Conclusion**

Owing to the innovation of nanoformulations, there is a significant improvement in ocular disease therapy which is preferred over the systemic route. During the preparation of nanoemulsion, it is necessary to use heat and/or mixing, and after preparation, phase separation may occur. This leads to the fact that nanoemulsion is thermodynamically less stable than microemulsion.

Unlike traditional ocular solutions and suspensions which have considerable bioavailability and require frequent dosing, nanoemulsions have huge potential in

enhancing bioavailability and reducing the frequency of drug administration. The surfactants and cosurfactants are important constituents of nanoemulsion and should be carefully selected. Their concentrations should be high enough to obtain ultra-low interfacial tension, and however, their toxicity should be taken in concern. Also, cationic surfactants can be utilized to increase the product residence time on the eye. Accordingly, the use of the nanoemulsion system for topical ocular therapeutics can overcome the problem of multiple daily doses of the traditional ocular therapy, and improve patient compliance. Nowadays, increasing interest in nanoformulation study and growing literature in this field brings a great shift in the management of eye diseases which create many successful products on the market as well as in clinical trials. The translucent appearance of nanoemulsion is due to the droplet size of less than 100nm, as a result of this small droplet size, the nanoemulsion is thermodynamically unstable dispersion. A high concentration of surfactants is required, that causes sticky feel of the formulation. A yellowish appearance and rancid odor which occur after storage as a result of the phospholipids that are generally used to stabilize the nanoemulsion. and easily manufactured system by methods which may or may not rely on energy. Unlike traditional ocular solutions and suspensions which have considerable bioavailability and require frequent dosing, nanoemulsions have huge potential in enhancing bioavailability and reducing frequency of drug administration. The surfactants and cosurfactants are important constituents of nanoemulsion, and should be carefully selected. Their concentrations should be high enough to obtain ultra-low interfacial tension, and however, their toxicity should be taken in concern. Also cationic surfactants can be utilized to increase the product residence time on the eye. Accordingly, the use of nanoemulsion system for topical ocular therapeutics can overcome the problem of multiple daily dose of the traditional ocular therapy, and improve patient compliance. Nowadays, increasing interest in nanoformulation study and growing literature in this field bring a great shift in the management of eye diseases which create a number of successful products on the market as well as in clinical trials.

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

<b>Advantages</b>	<b>Disadvantages</b>	<b>Other properties</b>
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 cosurfactants is likely possible	Has benefit to mask taste

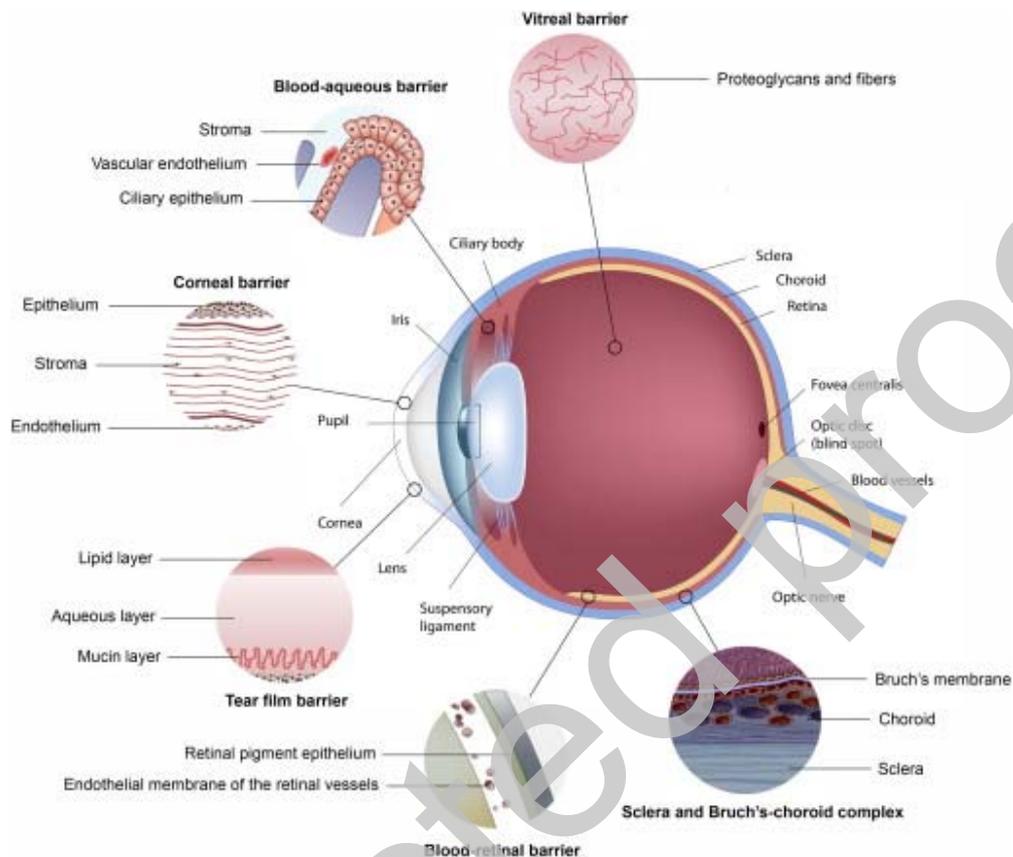
<b>Parameter Aspect</b>	<b>Description</b>
<b>Ph</b>	White opaque to slightly translucent
<b>Osmolality (mOsmol/kg)</b>	5.0-7.0
<b>Droplet size (nm)<sup>a</sup></b>	270
<b>Zeta potential (<math>\zeta</math>, Mv)<sup>a</sup></b>	<200
<b>Sterility</b>	Positive (+40)
	Sterile

<b>S.N o.</b>	<b>Drug</b>	<b>Surfactants and co surfactants</b>	<b>Oil</b>	<b>Comment</b>
1	Timolol	Lecithin	Isopropyl myristate	Nanoemulsion bioavailability in aqueous humour was 3.5 times more than Timolol alone
2	Dexamethasone	Cremophor EL, Propyleneglycol,	Isopropyl myristate	Enhanced ocular bioavailability (just about three times compared to conventional dosage form) and sustained effect of drug without ocular

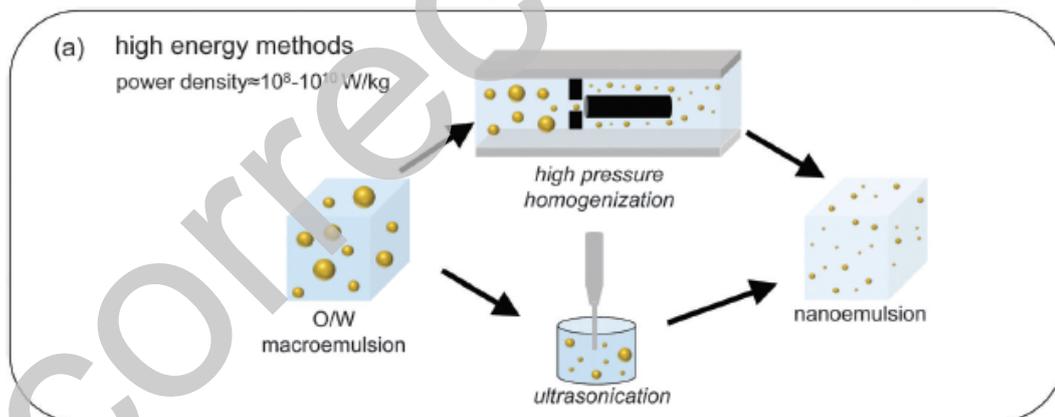
				irritation
3	Indomethacin	Phospholipids Miranol – MHT	MCT	Significant increase in corneal permeability compared to marketed formulation (Indocollyre®) show almost 4 times corneal permeability coefficient without toxicity in <i>ex vivo</i> studies
4	Levobunolol	Lecithin, glycerol	Soybean oil	Improved <i>in vitro</i> permeability with a reservoir effect
5	Pilocarpine	Macrogol 1500-glyceroltriacinoleate, 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.<sup>69</sup>

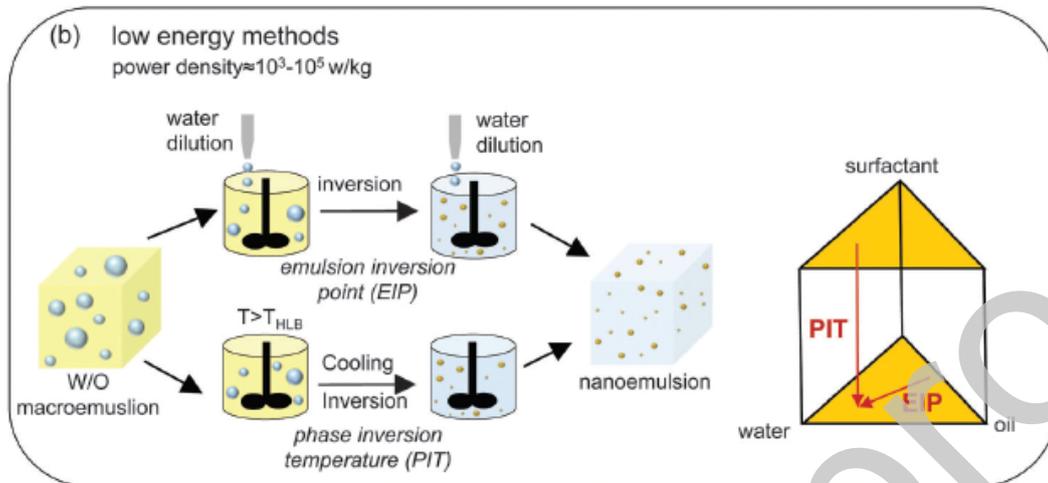
Nanoemulsions in the market for ophthalmic disease treatment					
Trade name	Drugs	Formulation	Disease	Company	
Restasis®	0.05% Cyclosporin A	Nanoemulsion	Dry eye disease	Allergan	
Cyclokat®	0.1% Cyclosporin A	Cationic nanoemulsion	Dry eye disease	Santen Pharmaceuticals	
Nanoemulsion under clinical trials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



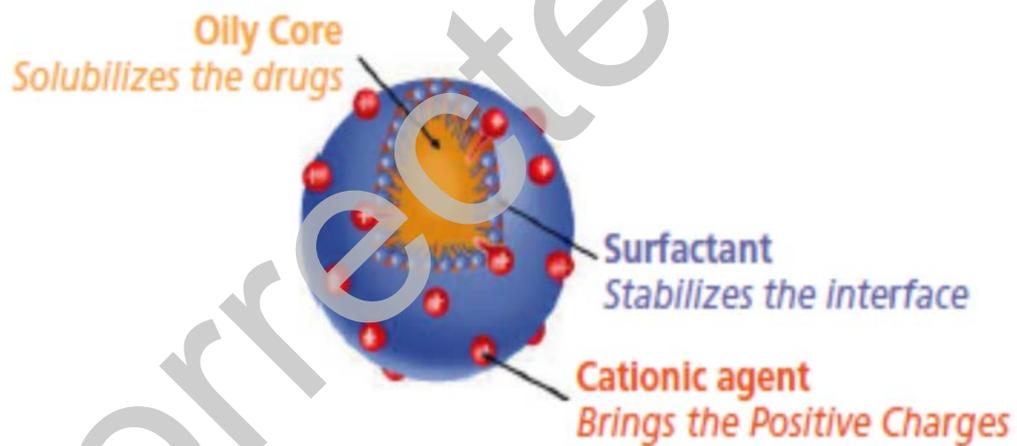
**Figure 1: Ocular barriers for drug transport<sup>10</sup>**



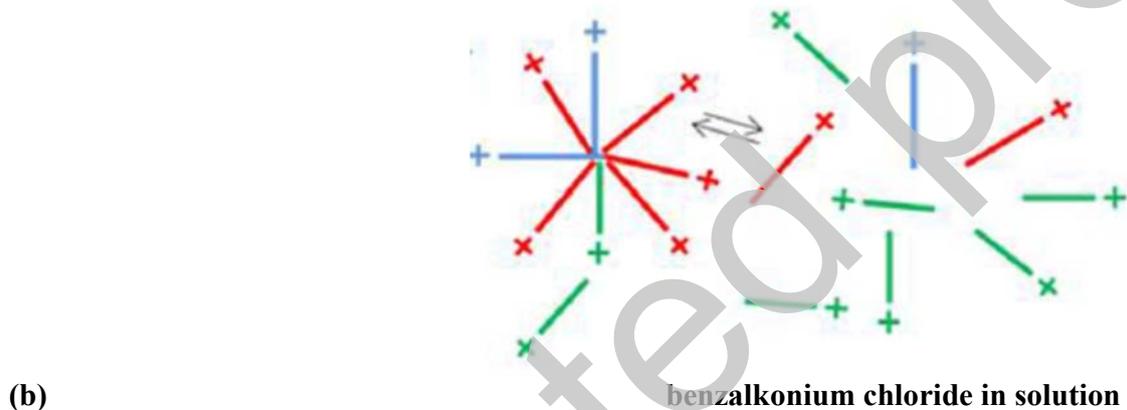
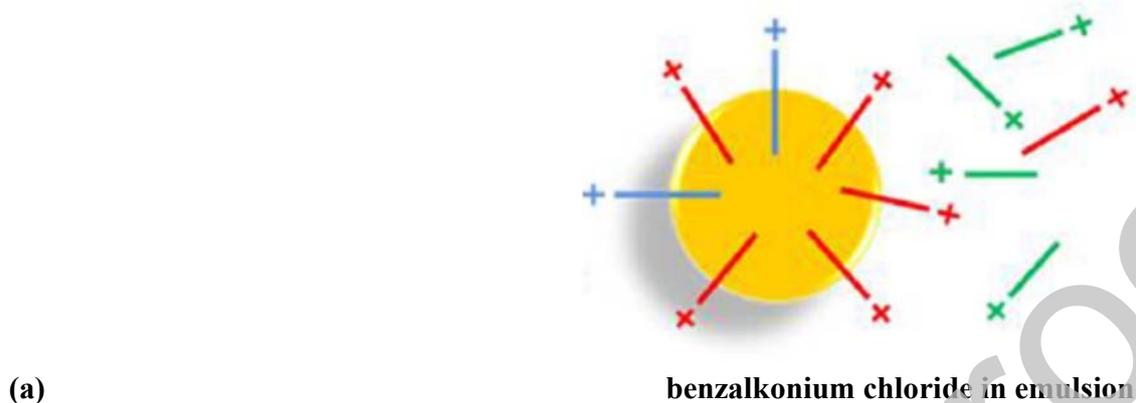
**Figure 2 (a): overview of high energy methods for preparing o/w nanoemulsion, such as high pressure homogenization and ultrasonication<sup>31</sup>**



**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.<sup>31</sup>



**Figure 3: Schematic representation of one of the oil nanodroplets**  
 Present in the cationic oil-in-water nanoemulsion<sup>50</sup>



**Figure 4: Illustration of the phase distribution for the different alkyl derivatives of benzalkonium chloride in (a) emulsion and in (b) aqueous solution<sup>50</sup>**