Original Article

Efficacy and Safety of Different Types of Surfactants used in Nanostructures for Topical Ocular Drug Delivery

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Abstract

The eyes are the most sensitive organ in the human body with complicated physiology, so that any associated dysfunctions or injuries are the leading causes of total blindness. Dynamic barriers of the eyes allow just 5% of medicines of the eye drops to be reached to the eye's aqueous fluids, that's why eye drops shall be administered frequently to keep a drug concentration at the side of action, therefore research hard work focused on developing novel drug delivery system that can overcome problem associated with conventional drug delivery to ocular surfaces subsequently nano-technology based ophthalmic preparations have been extensively studied in the domain of drug administration to the anterior and posterior portions of the eye over the last few decades. Surface active agents (SAAs) have been broadly used for the design of various of the dosage forms targeting ofthalmic tissues. Novel ocular carriers employing SAAs were mainly classified into particulate, vesicular, and controlled release drug delivery systems. Depending on their physicochemical properties, Yet, their use is limited by their possible harmfulness and possible interactions with other formulation ingredients. This review offers information about the efficacy and safety of various types of surfactants utilized in nanotechnology(nanomicelles, niosomes, nanoemulsions) for topical ocular medication delivery over the last ten years. Nonionic surfactants were the most commonly utilized surfactant among other types of surfactants (anionic and cationic) because of their safity and effectiveness in the range used for ofthalmic drug delivery of novel nanotechnology.

Keywords: Ophthalmic drug delivery, Nanotechnology, Surface active agents (SAAs), Nonionic surfactants, Efficacy, Safety.

INTRODUCTION

The eyes are the most multipart organ in the human body and are separated into two parts: the anterior part and the posterior part (Figure 1), with complicated physiology, so that any associated dysfunctions or injuries are the leading causes of total blindness (1). Furthermore, vision loss is linked to aging as well as other visual conditions such as age associated macular degeneration, glaucoma, diabetic retinopathy, and proliferative vitreoretinopathy, in the other hand infection, inflammation, and dry eye are some of the other illnesses that contribute significantly to ocular morbidity (2-4).

Because of the chronic nature of these disorders, frequent treatment administration is required to maintain visual acuity and slow disease progression (5). Approximately one-third of patients require rapid and effective pharmacological therapeutic action (6). Eye drops are the greatest popular route of drug direction to the exterior of the eye because of patient compliance and affordability, wherefore most medications are available as ophthalmic eye drops and ointments(7).

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however, a significant portion of the medicine given topically gets washed away by tear turnover, nasolacrimal drainage, reflex blinking, and ocular static. Dynamic barriers such as corneal and conjunctival barriers like the (epithelial, aqueous–vitreous, Blood-aqueous barrier, and blood-retinal barrier) which allow just 5% of medicines of the eye drops to be reached to the eye's aqueous fluids, that's why eye drops shall be administered frequently to maintain a drug's therapeutic concentration (8, 9) (10).

In ocular therapies, the achievement of an appropriate medication concentration at the site of action is a fundamental challenge, hence, newer delivery techniques are being researched worldwide for improving the ocular bioavailability of medication, as well as to solve conventional ocular therapy issues, such as limited residence period, drug drainage, and recurrent installation (11).

For the reasons stated above, nano-technology based ophthalmic preparations have been extensively studied in the domain of drug administration to the anterior and posterior portions of the eye over the last few decades, These technology with appropriate nano-sized carriers can be created to reduce irritation and inflammation, as well as improve drug absorption and interaction with ocular tissue (12).

Nanoparticles, nanoemulsions, nanomicelles, nanosuspensions, liposomes, niosomes, nanocrystals, and dendrimers were developed as a result of the nanocarrier-based method, These methods have substantial advantages over traditional systems, especially when it comes to drug administration to the posterior eye (8).

In this review, there will be a focus on surfactant nanomicelles, nanoemulsions, and niosomes nanotechnologies in which surfactant is commonly utilized.

The main purpose of the current article is to determine the efficacy and safety of various types of surfactants utilized in nanotechnology for topical ocular medication delivery over the last ten years.

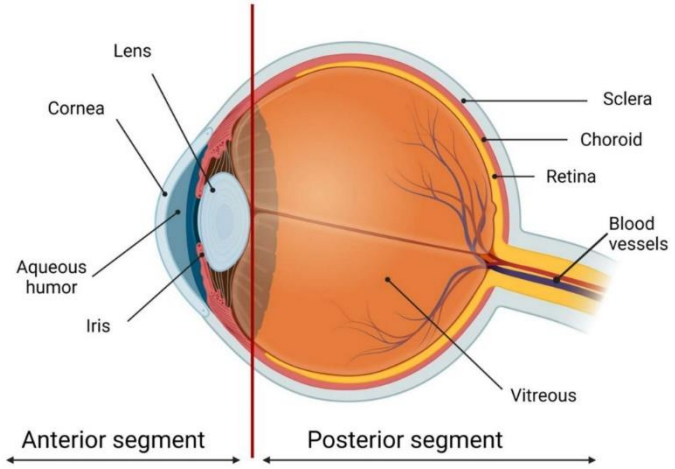

Figure 1. The structure of the eye: the anterior segment and the posterior segment (1)

Nanomicelles

Nanomicelles are colloidal structures made up of amphiphilic monomers that are divided into two parts: a long hydrophilic tail and a small hydrophobic head (13). These particles when exposed to an appropriate solvent, depending on the nature and degree of orientation, orient to self-aggregation and form normal or reverse nanomicelles. The hydrophobic center interacts with lipophilic drugs/agents, while the hydrophilic tail aids in water absorption and increases solubility so, such clustered assembles are termed as normal nanomicelles (14). Normal nanomicelles which can be used to encapsulate, solubilize and transport hydrophobic medications, Because of their capacity to decrease drug degradation, decrease unwanted side effects, and recover medication bioavailability (15).

Nanomicelles are effective drug delivery devices, because of their nano-size, aqueous clear and transparent drug formulation, ability to encapsulate and solubilize lipophilic medicines, and high penetration through ocular epithelia with low or no irritation, and nanomicelles provide distinct benefits in ocular drug administration(16-18).

Furthermore, nanomicelles ensure a steady therapeutic concentration in the tissues by sustaining drug release at the location of action, and in some cases overcoming ocular barriers (19).

Nanomicelles can be designed with either polymeric or surfactants systems (16). in the past two years, one of the most explored and clinically effective ocular drug delivery strategies are the surfactant nanomicelles (19). Surfactants are amphiphilic molecules comprising a polar head and a nonpolar tail as it's shown in (Figure 2), they are recognized to decrease interfacial surface energy (17) The surfactant molecule's head could be neutral (nonionic), dipolar (zwitterionic), or charged (anionic or cationic). Anionic surfactants include sodium dodecyl sulfate (SDS), cationic surfactant: dodecyl trimethylammonium bromide (DTAB), nonionic surfactants include n-dodecyl tetra (ethylene oxide) (C12E4), Vitamin E TPGS, octoxynol-40 and zwitterionic surfactants including dioctanoyl phosphatidylcholine (C8-lecithin) are commonly used, while the tail of surfactant is generally a long chain hydrocarbon and less frequently a halogenated or oxygenated hydrocarbon or siloxane chain (16). Micelles are designed when surfactants are dissolved in water at a percentage above critical micelle concentration (CMC) (20).

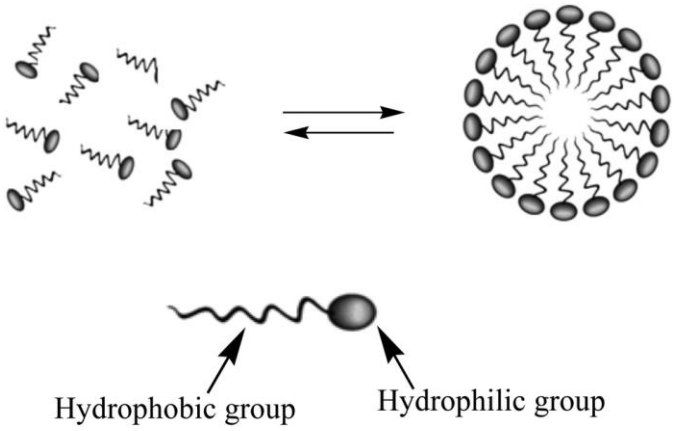

Figure 2. Surfactant micelle structure (21)

In addition to allowing for controlled medication release, surfactants utilized in ocular micelle formulation also help medications become more soluble in water and diffuse into the tissues of the eye (22). By increasing corneal permeability when diffusion is improved, they enable drugs to pass through corneal barriers and enter deeper tissues. As a result, the drug's ocular bioavailability is increased (23).

In this review, we will discuss efforts which were created for the formulations of cyclosporine CsA for ophthalmic drug delivery over the last decade because it is regarded as a good illustration of how trials for the development of an efficient and safe CsA for the treatment of dry eye illnesses were ongoing until the previous two years, by using different types of surfactants. Yet, topical administration of CsA is in no way completed. High lipophilicity of CsA (log P about 3.64, water solubility fewer than ten µg/ml i.e., 0.001% w/v), CsA aqueous preparation development has become infinitely difficult. CsA was dissolved in oil created solvents for topical application to the eye to avoid such issues (24).

In 2003, marketed product Restasis® (Allergan) was accepted by the United S. and Canada for the treatment of (keratoconjunctivitis Sica) KCS. Restasis® is an anionic 0.05% oil in water (o/w) emulsion of CsA in castor oil and water. In 2015, Ikervis® 0.1% stable cationic nanoemulsion (Santen Pharmaceuticals) was accepted in the European Union for KCS. Advanced subdividing of CsA in the topical oil vehicle leads to poor intraocular diffusion and hence created lesser bioavailability in ophthalmic tissues. Therefore, these CsA formulations are often related with ocular contrary effects including instillation site pain, eye burning, stinging, conjunctival hyperemia, and epiphora (24-26).

Additionally, numerous authors stated trainings on nonionic surfactants for micellar solubilisation of CsA by that tend to form collected aggregates (micelles) at/or greater than their critical micelle concentration (CMC). Recently (2018), The awareness in nanomicelles had been raised with the current FDA agreement of Cequa®, a cyclosporine based aqueous nanomicellar formulation specified for the treatment of dry eye condition (24).

Therefore, in the last two years, efforts were made to recover the aqueous solubility and ocular bioavailability of CsA by the adding of surfactants and/or diffusion enhancers technique to the formulations in order to prepare safe and efficient nanomicelle of CsA. In 2020 Eleonora et al, invented a mutual strategy based on nanomicelles and mucoadhesive polymer (Assembling Surfactants-Mucoadhesive Polymer Nanomicelles) (ASMP-Nano), based on a two system of binary surfactants (D-α-Tocopherol polyethylene glycol succinate, VitE-TPGS, and octylphenoxy poly(ethyleneoxy)ethanol, OPEE) in combination with hyaluronic acid (HA) for the ophthalmic delivery of CsA. (27). The combination of surfactants permissible to get nanomicelles able to solubilize an active pharmacological CsA quantity by utilizing the concentration of the surfactant as minimal as probable (28). VitE-TPGS is a famous, harmless water soluble derived of vitamin E, This nonionic surfactant was used in mixture with OPEE that belongs to the sequence of ethoxylated octylphenol, both with similar HLB values (HLB about 13) and with low CMC, Both due to their biocompatibility and negligible toxicity compared with other cationic, anionic or amphoteric polymeric surfactants, are used in many marketable products (27).

Fortunately, they were found that the prepared nanomicelle of CsA contain the double amount of that of Restasis® (0.05%) and the similar as marketed products Ikervis® (0.1%) and Cequa® (0.09 %). Which provides respectable constancy at the physiological temperature. Correspondingly, there was a notable rise in the residence time in tear fluid with a t half-life value 4 times larger than that obtained with Ikervis.

In summary, the combination of the binary nonionic surfactants (Vit E and OPEE) seems to be capable for the production of tiny nanomicelles as a novel system for the topical ophthalmic delivery of CsA to treat dry eye illness because no substantial cytotoxicity and irritation on the bunny rabbit' corneal epithelial cell line was detected with AMSP-Nano formulation, after instillation into the rabbit eyes (27).

Likewise, in 2021 Eleonora et al, developed a mixed system of in situate gelling systems and a loaded drug self-aggregate nanomicellar holder for a poorly water soluble drug Cyclosporine-A (CsA). Dual nonionic surfactants polyoxyl 40 hydrogenated castor oil, RH-40) and (D-alpha-tocopherol polyethylene glycol succinate, VitE-TPGS, were used to yield the nanomicelles, consequently this new combined approach was clear aqueous dispersions that were improving CsA ocular bioavailability. Furthermore, this new (ocular drug delivery system) ODDS showed little cytotoxicity and extended the CsA resident period in the precorneal zone compared to Ikervis® (29). Thus, table (1) include summarization of many types of surfactants used in nanomicelles for ocular drug administration.

Table 1: Surfactants used in the preparations of nanomicelles

Surfactant	Type	Therapeutic agent	Size (nm)	Appearance	Efficacy	Safety	Ref.
(vit-E TPGS) * and OC-40*	Nonionic surfactants	Biotinylated Lipid Prodrug of Acyclovir	10.46 – 10.78 ± 0.05	Highly transparent and homogenous Comparable to water. Spherical in shape.	The prodrug EE* is 90%. With stable micellar composition structure and provide significant effect in extending prodrug release.	No cytotoxic effects and non-inflammatory to corneal epithelial cells.	(28)
(Vit E-*TPGS), and (OPEE)*	Nonionic surfactants	(CsA)	14.41	Clear and stable nanomicelle formulation	EE 77.66 ± 1.77. nanomicelles presented a tendency to extend the drug release.	No significant cytotoxicity, no evident of ocular irritation, and there is no interference with the tear production.	(27)
Vit E-TPGS (RH-40) *	Nonionic surfactants	(CsA)	15.80	Nanomicelles with small size and homogeneous dimensions.	CsA-EE (99.07%). CsA nanomaicelles appear to be an effective substitute in ophthalmic therapy due to their ability to increase drug residence period in the precorneal area.	Good biocompatibility with the ocular tissue. No notable toxic effect, maintained cell viability above 80%.	(29)
(HCO-40*/OC-40)	Nonionic surfactants	Dexamethasone	30.33 ± 0.76	The micelle particles were regularly distributed and had an uneven spherical shape.	The penetrability of drug loaded nanomicelles was significantly high. Very good ocular residence period on the ocular surface.	No significant cytotoxicity. Good biocompatibility and have promising potentials for ocular drug delivery.	(30)
Vitamin E (TPGS) and poloxamer 407	Nonionic surfactants	(CsA)	200	-	Sustain cyclosporine delivery. Combined micelles increased cyclosporine solubility without the need for an oil	All the formulations effectively passed the HET-CAM* assay for the assessment of ocular irritation.	(31)

					phase.		
(HCO-40) and (OC-40).	Nonionic surfactants	Biotin and cidofovir	10-30	Spherical in shape. Clarity was comparable with water with no suspended particulate material.	Excellent medication entrapment, small size and narrow PDI. (poly dispersity index).	Negligible cytotoxicity effect.	(32)
(HCO-40) and (OC-40).	Nonionic surfactants	(CsA)	22.46 ± 0.411	Clear, transparent, and empty from any particulate substances. Similar to water. Smooth surface morphology, with spherical form and no aggregation.	EE of 95%, and, the CsA concentrations in the back of the eye (retina/choroid) were great.	No noticeable toxicity such as cell membrane damage or cytotoxicity to corneal.	(33)
Spans and Tweens (20, 40, 60 & 80)	Nonionic surfactants	Pilocarpine HCL	Size variation according to drug loading amount and type of surfactant used the, range was in (nm)	Multilamellar	EE% is 80%. No remaining problem of low drug entrapment for hydrophilic drugs.	No toxicity at 1 mg/mL drug loading.	(34)
Span 40	Nonionic surfactants	Dorzolamide-Hcl (Dorz).	Size of selected formula was 1007.0 ± 190.9 µm.	Niosomes was well-formed spherical in shape.	According to best selected formula EE% was 70.0 ± 1.4. Increase Dorz bioavailability Eye drops. Sustained drug release about 86.0 ± 3.0 in 8 hours.	No irritation signs were observed.	(35)

*D-α-Tocopherol Polyethylene Glycol Succinate (TPGS), Vit-E (Vitamin E), polyoxyl 40 hydrogenated castor oil (HCO-40), Octoxynol-40 (OC-40), octylphenoxy poly (ethyleneoxy)ethanol (OPEE), hen's egg-chorioallantoic membrane test (HET-CAM), Entrapment Efficiency (EE), Sorbitan Monostearate (Span).

Niosomes

Niosomes are colloidal particles that arise when non-ionic surfactants self-assemble in an aqueous solution to form closed bilayer structures. Hydrophilic molecules are found in the particle core, while hydrophobic molecules are found in the bilayer shell, niosomes can be single-layer or multi-layered (Figure 3) (36).

Cosmetics were the first to use non-ionic surfactant vesicles (Niosomes) (37). With the advancement of nanotechnologies in the field of pharmaceutics, more and

more studies on niosomes as nanocarriers for drug delivery have been conducted in recent years (38). Various studies had shown that niosomes are effective medication delivery vehicles for the eyes as well (39). Among the vesicular system liposomes, Niosomes can be useful in ophthalmic drug delivery (40). Because of its ability to encapsulate various types of drugs for the aim of increasing their stability and efficacy, niosomes may be a workable substitute to liposomes and polymersomes (18). Liposomes, polymersomes, and niosomes are physically comparable to other nanoparticles, and they can all be loaded with both hydrophilic and hydrophobic medications. As a result, they could co-deliver both hydrophilic and hydrophobic drugs in one vesicle (36).

Niosomes have several advantages over liposomes, including high stability, low cost, ease of formulation, and scaling-up (36). Niosomes are substantially more stable than liposomes because their forming components, non-ionic surfactants, are both physically and chemically more stable than lipids (36). The primary component employed in niosome construction is a nonionic surfactant. Most surfactants have hydrocarbon chains in their tails that can be split, linear, or aromatic (38). So, surfactant choice depends on the Critical Micelle Concentration (CMC), Hydrophilic–Lipophilic Balance (HLB) and Critical Packing Parameter (CPP) quantities (41). Similarly, the irritation influence of surfactants declines in the following order: cationic > anionic > ampholytic > non-ionic (38, 41-43).

The greatest frequently used nonionic surfactants during preparation of niosomes are recorded in Table (2).

Niosome sizes range from 20 to 5000 nm, depending on the production process, the kind of vesicles, the type of surfactant, and the ratio of main components of niosomes (surfactant to cholesterol) level. Nano-sized vesicles called small lamellar vesicle (SUV), micron-sized vesicles called large lamellar vesicle (LUV) and multilamellar vesicle (MLV) are niosomal vesicle kinds that take part in various ophthalmic applications(43, 44).

Other factors impacting niosome size include surfactant type and HLB (45). In most cases the HLB value affects on the size of the niosomes produced from spans, thus span 20 has the highest HLB value, followed by span 40. For instance, the size of the derived niosomes for ocular administration from Span 60, Span 40, and Span 20 design with the rising HLB, respectively. On the other hand, the alkyl chain length of the surfactant affects the size of the niosomes made from Tween. The alkyl chain often grows longer as an object's size increases. For instance, in the formulation of niosomes for ocular distribution that use Tween 80, 60, 40 respectively, decreasing size (28).

The capacity of the vesicle to encapsulate drugs is indicated by the niosome's entrapment efficiency (EE), which is also influenced by the type of surfactants used. Longer alkyl chain surfactants have a higher entrapment efficiency than shorter alkyl chain surfactants. Additionally, because Span 60 has the longest alkyl chain between them, niosomes produced with it have a greater EE percent than those produced with Span 40 and Span 20 (46). Correspondingly in their creation of acetazolamide-loaded niosomes for the treatment of glaucoma, Guinedi et al. discovered that niosomes made using Span 60 had a higher EE percent than those made using other methods (38).

In theory, the formation of niosomes necessitates the presence of a specific type of amphiphile as well as an aqueous system. Cholesterol is added to make vesicles that are less prone to leakage. Stabilizers may also be used to prevent vesicle aggregation by a repulsive, steric, or electrostatic effect. The cholesterol% as a formulation parameter is also said to be able to alter the release profile of noisome based complexes. (11). For example, another medication for treating glaucoma, Brimonidine Tartrate, has been demonstrated to release 75% of the drug in 2 hours, compared to a niosomal formulation that released 22% of the medication in eight hours (47).

According to the table (2) most widely used nonionic surfactants are span and tween but also there is another study for niosomes preparation by using another type of surfactants. In subsequence studies, Li et al. created a proniosome by stabilizing it with cholesterol and surfactants (poloxamer 188 and lecithin). These niosome formulations were created for tacrolimus (FK506) topical distribution, and the drug's EE% was 95.32 percent. Studies conducted in vivo revealed good biocompatibility and no irritation. Additionally, the precorneal permeability and drug retention were improved (48).

Similarly, Different surfactants were used by Abdelkader, H et al. such as Solulan C24, Span 60, sodium cholate, and additives like cholesterol and dicetyl phosphate: these surfactants were used to create noisome formulations of NTX(DCP) which have been shown to be tolerable in the cornea and revealed no irritation in vitro (49).

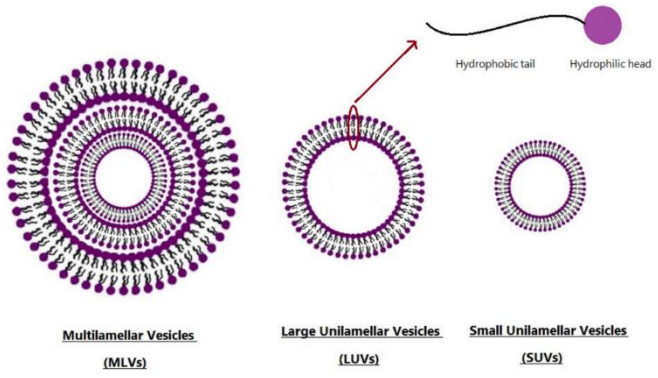

Figure 3. Typical vesicle size of niosomes (38).

Table 2: Types of surfactants used in preparation of nanomicelles.

Surfactants	**Type**	**Therapeutic agent**	**Size**	**Appearance**	**Efficacy**	**Safety**	**Ref.**
(Span 60)	Nonionic surfactant	Naltrexone Hydrochlorid (NTX).	22.41±1.40µm	Shapes were typical spherical to oval giant niosomes. (Unilamellar, and Multilamellar)	EE was up to 61.5% Effectively controlled NTX release. Promoted its transcorneal permeation and improved its corneal permeability.	Nonirritant when tested	(50)
(Span 20, 40, 60) or sorbitan trioleate (Span 85) and (Tween 20,40,80)	Nonionic surfactant	Dorzolamide hydrochloride	25.9±6.4 to 165.5±5.1 (nm).	Small unilamellar	EE % Between 34.81%-97.66%. Significant prolongation of drug release	----	(51)
Span (20, 60, 80) (Tween 60)	Nonionic surfactant	Doxycycline hyclate	117±0.8 - 2478±2.8 (nm).	Perfect spherical-with smooth vesicular surface. Homogenous small unilamellar vesicle	EE% maximum amount 58.5±0.9 Continual release of doxycycline from niosomes period up to 20 hours. Niosomes remained physically stable for 2 months at 4c^{o}.	Draize test shows Non-irritation effect to the eye and very well tolerated.	(52)
Span 60	Nonionic surfactant	Diclofenac potassium	----------	Multi lamellar vesicles. Spherical structure without aggregation.	EE = 82.1% Continuous release over a period of 10 hours.	----------	(53)
Span 20	Nonionic surfactant	Natamycin (NAT) and ketorolac Tromethamine (KT) gels	181.75±0.64 - 498.95±0.64 (nm).	Unilamellar vesicles	(EE%) up to 96.43%. Niosomal dispersion exhibited extended in-vitro drug	No symbols of irritation or damaging properties in the cornea, conjunctiva or iris.	(54)

					release (77.49% over 24 hours).		
(Tween 60, 80 or brij 35).	Nonionic surfactant	Gentamicin	0.76±0.089 - 1.37±0.0659 (µm)	Nearly very well sphere-like shape having a great internal aqueous space.	EE 92.02% ±1.43 Release results (66.29% ±1.33) period of 8 hours.	No irritation effect for all tested niosomal formulations.	(39)
Poloxamer 188 and lecithin	Nonionic surfactant	Tacrolimus	1.33 ± 0.32 µm	Clear solution	EE up to 95.34%. Improved precorneal permeation and retention period.	Niosomes instilled four times/day in rat eyes For 21 consecutive days without any irritation and provide good biocompatibilty with cornea.	(48)
Tween 60 and/ or Span 60	Nonionic surfactant	Ciprofloxacin	50 - 150 nm.	Spherical	EE % is 67.39% to 85.21%, high storage stability up to 30 days	----------	(55)

Nanoemulsions

Nanoemulsions NEs are one of the finest drug delivery systems with kinetic stability and improved solubility when two immiscible liquids are mixed (56). Nano as the name suggests, its droplet size is ranging from (20–200 nm) (57).

Nanoemulsions are nanoscale emulsions made up of the lipid phase, liquid phase and surfactant/ co- surfactant (58). The combination of phases and an emulsifier leads to form a nanoemulsion, they are also known as mini-emulsions, ultrafine emulsions, or submicron emulsions (59). They are categorized as either oil-in-water (O/W) or water-in-oil (W/O) nanoemulsions depending on the type of the surfactant, which establishes the continuous phase (60). NEs which are mature colloidal dispersions for drug delivery in nanotechnology, are frequently used as non-invasive, workable, and cost-effective nanocarriers to increase ophthalmic medication bioavailability through prolonged drug release and due to their ability to penetrate into the ocular structure. Surprisingly, using NEs as topical formulations can dramatically reduce negative effects induced by high and recurrent administration of medication doses using traditional procedures (3, 61, 62).

Both hydrophilic and hydrophobic medicines can be encapsulated in the emulsion droplets, which can serve as a drug reservoir (63). Despite the fact that nanoemulsions have many benefits, they still have significant drawbacks, such as the potential to irritate eyes and impair vision after instillation (3). The crucial elements for safety are the quantity and kind of surfactants and co-surfactants employed to lower the interfacial tension of nanoemulsions (64). The surfactant or co-surfactant must not irritate the ocular tissues and should not be harmful (65). By utilizing Tween 80 3%, Ahmed Alaa et al. created cationic nanoemulsions of Dorzolamide Hydrochloride in 2022. These nanoemulsions were safer and less irritating than commercially available Dorzolamide eye drops and were thermodynamically stable for one month at 25co and 4co (66). At 2020 Jialang Zhang et al. was developed nanoemulstions of Tacrolimus in order to provide prolonged retention time for ophthalmic drug delivery by using two kind of nonionic surfactants; Tween 80 and Poloxamer 188 of 1% (W/V) and 0.1% (W/V) respectively, the data of the study showed that the relative bioavailability of Tacrolimus nanoemulsion is 1.77 fold of the marketed eye drop (Talymus ®), Simultaneously in vitro cytotoxicity data confirmed the safety of the nanoemulsion of Tacrolimus (67). As a result, non-ionic surfactants like Tween 80 have been thought to be safe and are capable of altering the permeability of the ocular surface in a way that is reversible. Due to its safety and lack of eye irritating effects, tween 80 is frequently employed in ocular formulations and has an HLB of 15 (64). Like wise, NEs poloxamer 188 and tween 80 were produced, and after administration, gamma scintigraphy data showed an excellent spreading across the

entire cornea-conjunctiva surface. (3) So most commonly use surfactants in nanoemulsion is summarized in table (3).

Shahla S. et at 2021, proofed that nonionic surfactants are further suitable for ocular preparations, due to their minor ocular toxicity and higher tolerance. Surfactants have the following propensity to irritate the eyes: non-ionic < Zwitterionic < anionic < cationic. when they try to study on different types of surfactants for future use in formulation of Ketorolac Tromethamine KT ophthalmic nanoemulsion because the study shows that Cremophor RH 40 ,Tween 60, and Tween 20 would be the surfactants that would be used in creating nanoemulsions preparation for the delivery of KT to the eye (68).

Table 3: Type of surfactants used in the preparation on nanoemulsions.

Surfactants	**Type**	**Therapeutic agent**	**Size**	**Apearance**	**Efficacy**	**Safety**	**Ref.**
Poloxamer 188, Tween 80	Nonionic surfactants.	Tacrolimus	Mean diameter of droplet sizes 178.8±2.7 Nm	Spherical morphology	EE reached 98%. Lengthen the precorneal residence period and enhancing the bioavailability	*In vitro* cytotoxicity data was safe.	(67)
Poloxamer 188 or Tween 80	Nonionic surfactants.	Rifampicin	Droplet size was 150 nm	Nanoemulsion was (homogenous, clear color and no presence of precipitate)	Average EE% After 24 h were 82.75 ± 0.53 % .	---------	(69)
Tween 80 And Cremophor EL)	Nonionic surfactants.	Dorzolamide Hydrochloride	8.4±0.4 - 12.7±0.9 nm	Transparent systems	Nanoemulsios presented: Fast onset of drug action and extended effect. Improved drug bioavailability. Decrease in the frequencies of directions per day and, a well patient compliance.	Nonirritant and tolerated by the rabbit eye, which is more susceptible to irritant substances than the human eye.	(70)
Tween 80	Nonionic surfactants.	Lutein	10-12 nm with a fine size distribution.	Nanoemulsion was clear. Nanosized spherical particles with fine size distributions.	Release of Lutein was sustained.	----------	(61)

Tween 80	Nonionic surfactants.	Loteprednol etabonate.	41.50± 0.4 nm	Formulations were homogenously clear and transparent.	Drug content was up to 97.12±0.47 Higher infiltration along with controlled drug release. Cooperating the safety and patient compliance.	More than 80% of drug release within 8 hours, with no irritation. Confirmed the efficacy and safety of the nanoemulsion even on multi use.	(71)
Lecithin	Anionic surfactant	Ibuprofen	Droplet size from 251.6-140.1 nm	Highly liquid and consistent, with milky-white appearance.	EE% up to 98.24±0.10 The formulations were found to be stable under all the experimental circumstances tested.	Excellent biocompatibility	(72)

Conclusions

Nanoparticles have received significant consideration in the ocular drug delivery for the transference to the eye's anterior and posterior segments during the last decades. Conventional drug delivery formulation allow just 5% of medicines of the eye drops to be reached to the eye's aqueous fluids, As a result, nanoparticles are potential candidates for ocular usage. , because of their modest size, they do not irritate the eyes, it is also possible to avoid regular drug use as a result of prolonged release of a drug from nanoparticles. Nonionic surfactants were the most commonly utilized surfactant among other types of surfactants (anionic and cationic) because of their safity and effectiveness in the range used for ofthalmic drug delivery of novel nanotechnology such as nanomicelles , niosomes , and nanoemulsions.

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Conflict of interest:

none declared.

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