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A broad overview of Nanoemulsions as a tool for effective ocular drug delivery and an insight to currently developed – A review

Noorul Alam*, Kandhan Kaliyuga Kumar, Rajeswari Pitchaimuthu, Sathish Kumar Paranthaman, Rajalakshmi A.N

Department of Pharmaceutics, College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences, Puducherry, India.

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ABSTRACT:

Globally, the incidence of ocular disorders is increasing, and they have a significant effect on vision, which, in turn, affects the quality of life to a greater extent. Drug deliveries to the ocular diseases are more challenging with the static and dynamic barriers comprising the anterior and posterior parts of the eye. Conventional dosage forms are not competent enough to overcome these barriers. The nanodrug delivery system offers a great opportunity to deliver a drug to the ocular tissue more safely and effectively without invasive procedures. Among the various nanocarriers, nanoemulsions are considered the most promising drug carrier system to improve drug delivery to the eye. Nanoemulsions are dispersions containing liquid-in-liquid with a droplet size in the nano range. In this review, an insight was given about nanoemulsions as the best carrier for ocular drug delivery. In addition, various nanoemulsions designed in the research area and marketed as ocular nanoemulsions for various ocular ailments are portrayed.

Corresponding author
Dr. Noorul Alam
College of Pharmacy,
Mother Theresa Post Graduate and
Research Institute of Health Sciences,
Indira Nagar, Puducherry- 605006.
Tel: +91-8072485437
E. Mail ID: ceuticsalam@gmail.com

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INTRODUCTION:

A survey from 39 countries estimated that 285 million people suffer from visual impairment [1]. Vision loss is one of the most stressful complications of mortal condition. Globally, ocular diseases affect not only the patient's vision but also their quality of life. Optical disease conditions affect both the anterior and posterior parts of the eye. This includes age-related macular degeneration, cataracts, keratitis, glaucoma, diabetic retinopathy, retinoblastoma, allergic conjunctivitis, and ocular trauma [2]. Though various drugs have been identified for treating ocular diseases, the most

challenging and difficult task faced by pharmaceutical scientists is the effective delivery of the drug to the eye [3,4].

The eye is a unique, complex organ that is anatomically divided into two segments: anterior and posterior. The anterior segment includes tissues such as the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens, where the posterior segments of the eye include the sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humor. Drugs are prevented from reaching targeted ocular tissue through static and dynamic barriers [5]. For efficient ocular delivery, the drug must overcome the major barriers offered by the eye in order to protect the eye from toxicants [6]. The static barriers include the static corneal epithelium, corneal stroma, corneal endothelium, and blood-aqueous barrier; the dynamic barriers include tear dilution, the conjunctival barrier, and theretinal-blood barrier [7].

For ocular treatment, though drug administration is common via topical and systemic routes, topical administration is the most preferred by patients with good patient compliance [8]. Topical formulation for the treatment of anterior segment diseases requires frequent administration of highly concentrated drug solutions, which may produce side effects and damage to the ocular surface. So, topical, patient-friendly, and long-acting delivery systems are needed for anterior segment treatments [9]. Topically delivered medication does not reach the target in the posterior segment. Intravitreal delivery is the only option for posterior segment diseases. Intravitreal injections are an enormous burden on the patient and should be given by an ophthalmologist and specialized nurses at a proper interval over a longer period. New drug delivery systems with less invasive and longer acting mechanisms are needed for posterior segment treatments [10]. To overcome these factors, various conventional and novel ocular drug delivery systems have been developed, which are shown in Tables 1 and 2.

Conventional dosage forms, which make up an estimated 90 % of commercially available ophthalmic formulations, include solutions (62.4 %), suspensions (8.7 %), and ointments (17.4 %) [17]. The chronic nature of many ocular disorders requires frequent and prolonged drug treatments. Along with this, the bioavailability of the topically applied therapeutic agents is reduced by ocular barriers to less than 5 percent [18]. Even though conventional topical ocular preparations are being widely used nowadays, some drawbacks are still present, such as low drug bioavailability and low drug permeation through ocular barriers and a short residence time [11]. To overcome these drawbacks, various novel approaches are developed. The novel drug delivery systems provide greater efficacy and bioavailability by producing enhanced retention time and being non-irritant to the eye [19]. Among novel approaches, one of the best approaches is utilising nanotechnology in the ocular drug delivery system.

NANOTECHNOLOGY BASED OCULAR DRUG DELIVERY:

Nanotechnology-based ocular preparations are the best approach for both anterior and posterior treatment of the eye. Nanotechnology-based systems with the appropriate particle size can be developed to ensure increased permeation, reduced irritancy, adequate bioavailability, and compatibility with ocular tissue. Various nanocarriers used in ocular drug delivery include nanomicelles, nanoparticles, liposomes, niosomes, dendrimers, nanosuspensions, nanoemulsions, and nanocrystals [8].These nanocarrier drug delivery system successful delivers drug molecule at predermined rate and interval [20].

NANOEMULSION IN OCULAR DRUG DELIVERY:

For ocular local drug delivery, some of the most researched and applied nano-carriers in drug delivery systems are nanoemulsions. Nanoemulsions (NEs) are well-developed colloidal dispersions for the drug delivery system in nanotechnology, which are widely used as non-invasive, cost-effective nanocarriers to improve the drug's bioavailability [14,21]. Nanoemulsions are novel drug delivery systems, which are nano-sized emulsions consisting of emulsified oil and water systems with mean droplet diameters ranging from 50 to 1000 nm (average: 100 to 500 nm) manufactured for improving the delivery of active pharmaceutical ingredients [22, 23].

Commonly, nanoemulsion is a dispersion of oil and water stabilised by emulsifying agents or suitable co-surfactants that enable the reduction of the interfacial tension at the interphase of two immiscible phases of the nanoemulsion [14]. Also, nanoemulsions can be defined as a clear and stable dispersion of oil and water. NEs are also called miniemulsions, submicron emulsions, and ultrafine emulsions.

Table 1.Various conventional ocular drug delivery systems.

Drug delivery system	Benefits	Drawbacks	Refe-rence
Topical eye drops	Safe, convenient patient compliance. Ease of administration, non-invasive mode of administration.	Elimination in precorneal site, Short residence time, Poor permeability, Low bioavailability, No sustained action. To improve contact time, permeation and ocular bioavailability, various additives are added such as viscosity enhancers,permeation enhancers andcyclodextrins respectively.	[10,13]
Eye emulsion	Improves solubility and bioavailability of drugs. An o/w emulsion type commonly preferred as it is less irritating to the eye. Improves precorneal residence time And drug corneal permeation Sustained drug release	Low stability and prone to various instability such as flocculation, coalescence and creaming.	[10,13]
Eye suspension	Improved drug contact time and duration of action	High viscosity, Needs to be shaken to the required dosage level	[10,13]
Eye ointment	Prolong the contact time. Improved ocular bioavailability Improved sustained action	Vision blurring and eyelids matting	[10]
Eye gels	Comfortable, systemic exposure are decreased, dosing frequency is reduced	Vision blurring and eyelids matting Limited bioavailability.	[13]

Table 2.Various novel ocular drug delivery systems.

Drug delivery system	Benefits	Drawbacks	Reference
Nanomicelles	high drug encapsulation capability, ease of preparation and enhanced bioavailability	Lack of sustained drug release. Expensive.	[15]
Liposomes	Biocompatibility ability to encapsulate hydrophilic and hydrophobic drugs Improves precorneal residence time	Short shelf life, low drug capacity, usage of harsh manufacturing methods, sterilisation issues	[14]
Niosomes	Improved ocular absorption, enhanced bioavailability, and increased drug permeation, biocompatible.	Short shelf-life and eye irritation Aggregation, fusing, leaching, or hydrolyzing	[16]

Dendrimers	Increasing the ocular bioavailability and residence time Improved drug penetration.	Blurred vision and loss ofEyesight.	[17,18]
Nanosuspension	Sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time and enhancement in ocular bioavailability of drugs which are insoluble in tear fluid. Efficient delivery of poorly soluble drugs and hydrophobic drugs.	Stability issues, needs careful handling and time consuming	[14]
Nanoemulsion	Increase drug bioavailability Stable, Non-irritating, Improves drug absorption.	Stability and toxicity issues concern with selection of surfactants and co surfactant	[16]

The difference between emulsion and nanoemulsion is that emulsion is cloudy, while nanoemulsion is very clear in its physical appearance and transparent or translucent in nature because of its characteristic droplet size [24]. Also, nanoemulsions are distinguished from microemulsions in their composition, particle size, particle shape, and stability characteristics. The major difference is that microemulsion is thermodynamically more stable than nanoemulsion [14].

Dilutable nanoemulsions are efficient vehicles for ophthalmic drug delivery due to their sustained effect and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor, as well as ease of sterilisation [23, 25]. Nanoemulsion is considered to have low surface tension and greater drug spreading on the cornea, which can mix properly with the precorneal constituents. This enhances the drug contact time in the corneal epithelium [26]. The prolonged precorneal retention time and high penetration capacity of nanoemulsions result in enhanced ocular bioavailability [14].

Advantages of nanoemulsion in ocular drug delivery system:

- Reduce frequent administration.
- Provide a sustained and controlled release of drugs.
- Prolonged precorneal retention time.
- High drug permeation across ocular tissues.
- Enhanced ocular bioavailability.
- Ease of sterilisation.
- Improved stability.
- Because of their high surface area and tiny droplet size, nanoemulsions increase drug bioavailability while being physically stable, non-irritating, and non-toxic.
- Good patient compliance.
- Solubilize lipophilic drugs and act as carriers for hydrophobic drugs.
- Use less energy.

Disadvantages of Nanoemulsion [27, 28]:

- For stable nanoemulsion, a high concentration of surfactant and co-surfactant is needed.
- Limited capacity to solubilize high melting point substances.
- Different environmental factors affect their stability.

Classification of Nanoemulsions:

Based on the combination of the oil and water components, there are three different types of nanoemulsions that are Oil in water (O/W) NEs, Water in oil (W/O) NEs, and Bi-continuous NEs.

Oil in water (O/W) NEs in which oil droplets are dispersed in a continuous aqueous phase; Water in oil (W/O) NEs in which water droplets are dispersed in a continuous oil phase. Bi-continuous NEs are those in which the system contains inter-dispersed microdomains of water and oil. The interface of all three types of nanoemulsions is stabilised by an appropriate mixture of surfactants and/or co-surfactants. O/W nanoemulsions are the most commonly used nanoemulsion type for ophthalmic use. Three different types of O/W nanoemulsions can be further classified based on the surfactants used, which are Neutral O/W nanoemulsion, Cationic O/W nanoemulsion, and Anionic O/W nanoemulsion [29].

Preparation of Nanoemulsion:

Various approaches have been used by the researchers to formulate the NEs, which are classified based on the energy requirements [30] that are High-energy and Low-energy methods.

High-energy methods:

Previously, high-energy techniques were the primary method for forming a nanoemulsion. As high energy is transferred in the form of a mechanical source that leads to the breakage of the dispersed phase with the dispersion medium to generate a nano formulation, High-energy methods are High-pressure homogenization, High shear stirring, Ultrasonic emulsification, Microfluidic, and membrane methods [31].The greater control of particle size with a choice of formulation composition can be achieved by using these methods [32].

***Low energy methods*:**

In this method, W/O macroemulsion is formed, which is then converted into an O/W nanoemulsion by changing the composition or temperature. Low-energy methods are the phase inversion temperature method (PIT), the emulsion inversion point (or phase inversion composition) method, and Spontaneous nano-emulsification [31].

Stability of Nanoemulsion:

Although nanoemulsions enhance the physical as well as chemical stability of drugs, the stability of the formulation is one of the major problems associated with the development of nanoemulsions [22]. Nanoemulsions are kinetically stable but thermodynamically unstable, and with sufficient time, they will separate into two phases. As the free energy of the colloidal dispersion (i.e., droplets in water) is greater than the free energy of the separate phases (i.e., oil and water), nanoemulsions are thermodynamically unstable [24].

The instability markers of nanoemulsions are flocculation, coalescence, Ostwald ripening, and creaming or sedimentation. In flocculation, droplets migrate together as a single unit and draw closer to one another due to attractive interactions. In contrast, during coalescence, the droplets merge into each other to form a bigger droplet. These can be prevented by small droplet size and by the addition of a suitable surfactant. Typically, a non-ionic surfactant is used. Ostwald ripening can be prevented by the addition of a polymeric surfactant, which increases the elasticity and decreases the effect [33].

Stability studies are performed on nanoemulsions by storing them at refrigerator and room temperatures over a specified period. During this period of storage, viscosity, refractive index, and droplet size are determined. Insignificant changes in these parameters indicate for stability of nanoemulsion. The stability of nanoemulsions may be enhanced by controlling factors such as type and concentration of surfactant and co surfactant, type of oil phase, method of preparation, process variables, and addition of additives.

Applications of nanoemulsion in ocular drug delivery system:

For treating several ophthalmic disorders, drugs are formulated in the form of nanoemulsions for effective treatment. Various studies employed in the development of nanoemulsion as a dosage form for ocular drug delivery are summarised in Table 3, and some of the marketed ophthalmic nanoemulsions are depicted in Table 4.

CONCLUSION:

Nanoemulsions seem to be the most promising carriers for effective drug delivery to the anterior and posterior parts of the eye. This is capable of overcoming both static and dynamic barriers. In recent years, many nanoemulsions have been developed and found effective for ocular drug delivery. Promising marketed nanoemulsions for ocular disorders also substantiate that nanoemulsions seem to be an effective tool for ocular drug delivery.

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Table 3.Various nanoemulsion formulations developed for ocular drug delivery.

Drug	Composition	Method of preparation	Reason	Inference	Ref
Dorzolamide Hydrochloride	Isopropyl myristate, Triacetin -oil phase; Tween 80 - surfactant; Propylene glycol-cosurfactant.	Water Titration method	Low pH high viscosity and frequent administration causes eye irritation.	Non-irritant, high penetration, enhanced drug bioavailability with sustained drug release.	[34]
Timolol	Isopropyl myristate, soya oil -oil phase; Tween80, PluronicF68-surfactant; chitosan-polymer.	Homogenization	Poor bioavailability, decrease contact time, reduce systemic absorption, side effects arise on ocular administration of timolol	Stable, non-irritant isotonic biocompatible nanoemulsion formulated with prolonged residence time and increase in drug permeation	[35]
Acetazolamide	Peanut oil, Oleic acid-oil phase; Tween80, cremophor EL-surfactant Transcutol p-Co surfactant	Water Titration method	Poor patient compliance, poor aqueous solubility, low permeability,	Higher drug release rate, with improvement in patient compliance and decreased number of instillation.	[36]
Moxifloxacin	Ethyl oelate-oil phase; Tween80-surfactant; soluphor p- co-surfactant ;	Titration technique	short residence time	Prolonged moxifloxacin level in aqueous humour	[37]
Celecoxib	Transcutol p, oleic acid - oil phase; tween80,span20-surfactant;propylene glycol-co surfactant	Titration method	Poor bioavailability, corneal impermeability	Increase barrier permeability, improve corneal drug delivery, and improve residence time.	[38]

Table 4.Various marketed ophthalmic nanoemulsions.

Product/ Brand name	Drug	Uses	Reference
Restasis	Cyclosporine A (0.05%)	Immunosuppressant, Treatment of dry eye	[27]
Cyclokat	Cyclosporine A (0.1%)	Treatment of dry eye	[26]
Ikevis	Cyclosporine	Treatment of severe keratitis with DED	[26]
Xelpros	Latanoprost	Prostoglandin analogues	[32]
Systane complete	Propylene glycol	Treatment of dry eye	[26]
OCO 300	Brimonidine	Intraocular pressure reducing drug	[32]
Refresh Endura	Glycerin , polysorbate 80	Artificial Tear	[39]
Durezol	Difluprednate (0.5%)	Treatment of eye inflammation	[27]

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