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Nanoemulsion: Safe, Stable and Effective Formulation System for Ophthalmology

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ABSTRACT

Nanoemulsions are only kinetically stable. However, the long term physical stability of nanoemulsions (with no apparent flocculation or coalescence) makes then unique and they are sometimes referred to as 'Approaching thermodynamic stability. The inherently high colloid stability of nanoemulsions can be well understood from a consideration of their stearic stabilization (when using non-ionic surfactants and /or polymers) and how this is affected by the ratio of the adsorbed layer thickness to droplet radius. Successful ocular drug delivery has largely eluded solution due to, the physiological constraints imposed by the protective mechanisms of the eye that lead to poor absorption of drugs with very small fractions (less than 5%) of the instilled dose penetrating the cornea and reaching the intraocular tissues. Low drug contact time and poor ocular bioavailability due to drainage of solution, tear turnover and its dilution or lacrimation are the problems associated with conventional systems. Novel systems offer manifold advantages over conventional systems as they increase the efficiency of drug delivery by improving the release profile and also reduce drug toxicity. Conventional delivery systems get diluted with tear, washed away through the lacrimal gland and usually require administering at regular time intervals whereas novel emulsions are stable, have improved solubility, required reduced dosing frequency and release drug for prolonged periods of time. The aim of this review focuses on micro and nanoemulsions between 1 and 200 nm with a mean droplet size of about 40nm) for ocular drug delivery.

Keywords: Nanoemulsions, surfactant, droplet size, ophthalmic, stability

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INTRODUCTION

Nanoemulsions are transparent or translucent systems mostly covering the size range 50-200nm. Nanoemulsions are only kinetically stable. However, the long term physical stability of nanoemulsions (with no apparent flocculation or coalescence) makes then unique. The inherently high colloid stability of nanoemulsions can be well understood from a consideration of their stearic stabilization (when using non-ionic surfactants and /or polymers) and how this is affected by the ratio of the adsorbed layer thickness to droplet radius.[1] Unless adequately prepared (to control the droplet size distribution) and stabilized against Ostwald ripening (that occur when the oil has some finite solubility in the continuous medium), nanoemulsions may use their transparency with time as a result of increase in droplet size [2-5]. The use of Nanoemulsions as formulations for active delivery and targeting is also an active and interesting application of nanoemulsion. Usually, the average droplet size is between 10 and 100 nm. Due to their characteristics size they are optically transparent. Medically, the oil-in-water (o/w) nanoemulsions are used mainly as delivery carriers for lipophilic drug molecules which show therapeutic activity when administered ocularly. The term nanoemulsion is increasingly used because it gives a clear idea of the nano size range of droplet.[6] There are two major misunderstandings in the literature regarding nanoemulsions. The definition of emulsions by the International Union of Pure and Applied Chemistry (IUPAC) states: "In an emulsion, liquid droplets and/or liquid crystals are dispersed in a liquid". Obviously, microemulsions are excluded from this definition if the word "dispersed" is interpreted as non-equilibrium and opposite to "solubilized", a term that can be applied to microemulsions and micellar systems. Therefore, there is a fundamental difference between microemulsions and nanoemulsions: microemulsions are equilibrium systems (i.e. thermodynamically stable), while nanoemulsions are non-equilibrium systems with a spontaneous tendency to separate into the constituent phases. Therefore energy input from mechanical devices or from the chemical potential of the components is required for their formation Nevertheless, nanoemulsions may possess a relatively high kinetic stability, even for several years. Nanoemulsions is used as ocular drug delivery systems as to provide reservoir for sustained release of drugs and to increase drug bioavailability.[7-8]

Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories:

1. The first is based on use of the drug delivery systems, which provide the sustained and

continuous delivery of ophthalmic drugs.

2. The second involves, minimizing pre-corneal drug loss.

To overcome these problems, various ophthalmic vehicles such as suspensions, ointments, inserts, and aqueous gels have been investigated to extend the ocular residence time of medications for topical application to the eye. These ocular drug delivery systems offer some improvement over conventional liquid dosage forms but, because of blurred vision, lack of patient compliance (e.g., ointments, dendrimers), difficult to insert & remove (e.g., inserts), irritation(e.g., suspension, microparticulates), stability problems, not reproducible, rapid clearance, uptake by conjunctival cells (e.g., liposomes) they have not been universally accepted. As a result, good ocular bioavailability following topical delivery of a drug to the eye remains a challenge yet to be resolved satisfactorily.

Nanoemulsions as have been utilized as ocular eye drops in virtue of their distinct advantages. These include sustained release of the drug applied to the cornea, high penetration in the deeper layers of the ocular structure, and aqueous humor as well as ease of sterilization.[9-11] Thus, these systems can achieve therapeutic action with a smaller dose and a fewer systemic and ocular side effects. The main advantages of novel emulsion for ocular purpose are:

1. Overcome the side effects of pulsed dosing produced by conventional systems.
2. Provide sustained and controlled drug delivery.
3. Increase ocular bioavailability of drug by increasing corneal contact time.
4. Provide targeting within the ocular globes so as to prevent the loss to other ocular sites.
5. Circumvent the protective barriers like drainage, lacrimation and diversion of exogenous chemicals into systemic circulation by conjunctiva.
6. Provide comfort and compliance to the patient and yet improve the therapeutic performance of the drug over conventional systems.
7. Ease of sterilization
8. Improved stability
9. Provide better housing of the delivery system in the eye so that the loss to other tissues besides cornea is prevented.
10. Have a much higher surface area and free energy than micro emulsions.
11. Makes them an effective transport system.
12. Nanoemulsions do not show the problems of inherent creaming, flocculation, coalescence and sedimentation, which are commonly associated with macro emulsion

However the nanoemulsions are also associated with certain limitations that pose serious

concerns and need to be addressed viz., selection of surfactants/co-surfactants and aqueous/organic affects its stability and toxicity issues.

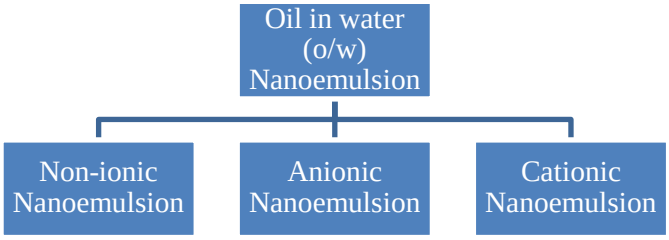

Figure 1. Classification of oil-in-water (o/w) Nanoemulsions based on emulsifier molecules.

ATTRACTION OF NANOEMULSIONS[12-16]

(i) The very small droplet size causes a large reduction in the gravity force and the Brownian motion may be sufficient for overcoming gravity. This means that no creaming or sedimentation occurs on storage.

(ii) The small droplet size also prevents any flocculation of the droplets. weak flocculation is prevented and this enables the system to remain dispersed with no separation.

(iii) The small droplets also prevent their coalescence, since these droplets are non-deformable and hence surface fluctuations are prevented, in addition the significant surfactant film thickness(relative to droplet radius) prevents any thinning are disruption of the liquid film between the droplets.

(iv) Nanoemulsions are suitable for efficient delivery of active ingredients through the eye. The large surface area of the emulsion system allows rapid penetration of actives.

(v) Due to their small size, nanoemulsions can penetrate through cornea and this enhances penetration of activities.

(vi) Unlike micro emulsions (which require a high surfactant concentration, usually in the region of 20% and higher), nanoemulsions can be prepared using reasonable surfactant concentration. For a 20% O/W nanoemulsion, a surfactant concentration in the region of 5-10% may be sufficient.

(vii) The small size of the droplets allows them to deposit uniformly on substrates. Wetting, spreading and penetration may be also enhanced as a result of the low surface tension of the whole system and the low interfacial tension of the O/W droplets.

(viii) Nanoemulsions may be applied as a substitute for liposomes and vesicles (which are much less stable) and it is possible in some cases to build lamellar liquid crystalline phases around the nanoemulsion droplets.

CHARACTERIZATION OF A NANOEMULSION

Droplet size analysis

Droplet size distribution of the Nanoemulsion was determined by photon correlation spectroscopy (PCS), Light scattering was monitored at 25^{o}C at a scattering angle of 90^{o}.[17]

Viscosity determination

The viscosity of the nanoemulsion was determined using Brookfield DV ultra V6.0 cone and plate rheometer at 25+0.3^{o}C.[18]

Refractive index

Refractive index of nanoemulsions formulation was determined using an abbes type refractometer.[19]

Transmission electron microscopy

The morphology and structure of the Nanoemulsion were studied using transmission electron microscopy (TEM). A combination of bright field imaging at increasing magnification and diffraction modes was used, to reveal the form and size of the Nanoemulsions. To perform the TEM observations, the nanoemulsion formulation was diluted with water (1/100). A drop of the diluted nanoemulsions was directly deposited on the holey film grid and observed after drying.[20]

Stability studies

Stability studies on optimized Nanoemulsions were performed by keeping the sample at refrigerator temperature (4^{o}C) and room temperature (25^{o}C). These studies were performed for the specific period of time. The droplet size, viscosity and RI were determined using methods described above during storage. From different batches formulation were taken in glass vials were kept at accelerated temperature of 40^{o}C and 75% relative humidity. The samples were withdrawn at regular intervals of particular time and were analyzed for drug content by stability indicating HPLC method at a particular wave length. Zero time samples were used as controls. In addition, samples of pure oil pure surfactant and core surfactant were run separately to check there was no interference of the excipients used in the formulations.[21-22]

Classification of O/W Nanoemulsion[23-27]

Based on the emulsifier combinations used in the formation of submicron emulsion droplets, the o/w nanoemulsions can be classified into three types (Figure 1). Emulsifiers with the capacity to produce a negative charge at the o/w interface are termed anionic and those able to provide a positive charge at the o/w interface are called cationic. The literature suggests that neither triglycerides nor phospholipidic emulsifier's components of the conventional or anionic emulsions are able to significantly sustain the incorporated lipophilic drug release in simulated or

real physiological environments under sink conditions. Therefore in an attempt to prolong and/or optimize the drug release, cationic lipid or polysaccharide emulsifiers are added to the emulsions to elicit mucoadhesion with anionic ocular tissues by an electrostatic adhesion. Indeed, cationic emulsions prepared using stearyl amine, oleyamine and chitosan can serve this purpose. It was initially believed and now has become clearer from many reports in the literature that an occurrence of electrostatic attraction between the cationic emulsified droplets and anionic cellular moieties of the ocular and topical skin surface tissues enhance the bioavailability of emulsions containing lipophilic drugs. There is another type of emulsion that is neutral in terms of the charge on the dispersed droplets. These are instead stabilized through steric effects exerted by the emulsifier molecule present in the emulsion formulation. According to Capek the stability of the electrostatically- and sterically-stabilized o/w nanoemulsions can be controlled by the charge of the electrical double layer and the thickness of the droplet surface layer formed by non-ionic emulsifier, respectively. In spite of the similarities between electrostatically- and sterically stabilized emulsions, there are large differences in the partitioning of molecules of ionic and non-ionic emulsifiers between the oil and water phases and the thickness of the interfacial layers at the droplet surface. The thin interfacial layer (the electrical double layer) at the surface of electro statically stabilized droplets does not create any steric barrier for mass transfer. This may not necessarily be true for the thick interfacial layer formed by a nonionic emulsifier. $[\delta/(k-1)]= (\delta k)$ The sterically-stabilized oil droplets, however, can favor the transfer of materials within the intermediate agglomerates. Hence, the stability of electrosterically stabilized emulsion (δ k) is controlled by the ratio of the thickness of the non-ionic emulsifier adsorption layer (δ) to the thickness of the electrical double layer (k-1) around the oil droplets.

Excipients for Ocular Nanoemulsion[28-32]

Topical ophthalmic lipid emulsions should be formulated with compatible vehicles and additives. The components of the internal and external phases of the emulsions should be chosen to confer enhanced solubility and/or stability to the incorporated ocular active drug. In addition, it should also be designed to influence ocular biodistribution or therapeutic index. This section is a comprehensive presentation of the general considerations concerning excipient selection and optimum concentrations mainly in relation to the oil phase, the aqueous phase and the emulsifiers. Prior to the formulation design of the nanoemulsions the drug solubility in the oil vehicle must be determined. Additionally, prerequisite information is needed on compatibility of the oil vehicle with other formulation additives and the established ocular tissues-oil vehicle matching before the dosage form can be prepared.

Table1lists the common emulsion excipients and oils suitable for dissolving or dispersing lipophilic drugs of ocular interests. Since fatty oils are triglycerides, care must be taken to minimize or eliminate oxidation. α-Tocopherol is a good example of an antioxidant used to obtain a desired stabilized lipid emulsion under prolonged storage conditions. Therefore, α-tocopherol (0.001–0.002%, w/w) should be included in a typical lipid emulsion formulation for ocular use. The final oil phase conc. in ocular novel emulsions is now widely accepted at or even below 5% (w/w) taking into account that the emulsion must be kept in a low viscosity range, of between 2 & 3 cps, which is considered an adequate viscosity for ocular preparations. Sometimes, a mixture of oils rather than single oil is employed for drug solubilization in the oil phase.

The surfactant concentration is 0.1% in weight in emulsions, it accounts for at least 10% in microemulsions due to the increase of the interface area between the aqueous and oily phases. This high concentration of surfactants can lead to ocular toxicity. Thus, it might be better to decrease the quantity of surfactant and choose a non-spontaneous preparation process. The ionic surfactants are generally too toxic to be used for this application and therefore, non-ionic surfactants are preferred. These surfactants are easily soluble in water due to the presence of ether functional groups. The most used surfactants in the preparation of novel emulsions are the poloxamers, polysorbates, polyethylene glycol and tyloxapol.[2]

Table I: Common excipients used for the formulation of o/w nanoemulsion

Oils	Emulsifiers	Cationic lipids & Polysaccharide	Miscellaneous
Sesame oil	Cholesterol	Stearylamine	α–Tocopherol
Soya oil	Phospholipid	Oleylamine	Glycerol
Castor oil	(Lipoid)	Chitosan	Xylitol
Paraffin oil	Polysorbate 80		Sorbitol
Paraffin light	Transcutol P		Thiomersal
Lanolin	Cremophor RH		EDTA
Vaselin	Poloxamer 407		Methyl
Corn oil	Poloxamer 188		paraben
Glycerin monostearate	Miranol C2M		Propyl
Medium chain monoglyceride	MHT		paraben
Medium chain triglycerides	Tyloxapol		

Traditionally, lecithins or phospholipids have been the emulsifiers of choice to produce ocular emulsions. However additional emulsifiers preferably dissolved in the aqueous phase are usually included in the emulsion composition. A typical example of the aqueous soluble emulsifiers is non-ionic surfactants (e.g. Tween 20) because they are non-irritant than their ionic counterparts. The non-ionic block copolymer of polyoxyethylene–polyoxypropylene, Pluronics F68

(poloxamer 188), is included to stabilize the nano sized emulsion through strong steric repulsion. However, amphoteric surfactants Miranol MHT (lauroamphodiacetate and sodium tridecethsulfate) and Miranol C2M (cocoamphodiacetate) have also been used in an ophthalmic emulsion. Strikingly, if chitosan is a choice of cation producing polysaccharide emulsifier molecules, there is no need to add amphoteric or non-ionic surfactants to the phospholipid or lecithin stabilized emulsions. Conversely, a cationic emulsion based on an association of poloxamer 188 and chitosan without lecithin was prepared and also showed adequate physicochemical properties regarding stability and charge effects.

Additives other than antioxidants such as preservatives like benzalkonium chloride, chlorocresol, parabens, etc. are regularly included in ophthalmic lipid emulsions to prevent microbial spoilage of multi-dose ophthalmic emulsions.

Recently, a report also indicated the stability of oil droplets through the cation conferring chitosan along with poloxamer 188 as a mixed emulsifier. Since the free fatty acid generating phospholipid emulsifier molecule is omitted from the nanosized emulsion system, the stable nanosized emulsion produced from chitosan poloxamer emulsifier combination has the potential to attenuate a microclimate acidic pH in the vicinity of oil phase, oil-water interface and water phase of the emulsion. These non-phospholipid based emulsions should therefore be able to incorporate the acid labile molecules like therapeutic peptides and proteins, and to delineate the scope of applying lyophilization process for the development of a solid or dry emulsion.

Optimization of Nanoemulsion Preparation[33-37]

The properties of nanoemulsions, as non-equilibrium systems, depend not only on composition variables but preparation variables such as emulsifying path, agitation or emulsification time. These variables can have a significant influence on the final properties of the nanoemulsion. Direct application of nanoemulsions requires optimization studies for achieving the best properties for specific applications. The most frequent aim for optimization is to exploit the advantages of nanoemulsions with respect to conventional emulsions (i.e. macroemulsion): small size and low polydispersity. Therefore, in general, optimization is directed to be obtain minimum droplet size and/or minimum polydispersity. Another aim in nanoemulsion optimization is to improve the stability because, as stated above, stability is the main problem to overcome to find practical applications for nanoemulsions. Optimization is also directed to obtain an optimum in the function for which the nanoemulsions are used (e.g. drug delivery). The properties to be optimized, for example droplet size and polydispersity, will depend, of course, on composition variables and could depend on preparation variables, so optimization can be carried out with

respect to these two types of variables. Concerning optimization methods, sometimes the characteristics of emulsification path allow predicting optimum properties of nanoemulsions, so optimizations are carried out by studying the phase behavior of the systems. In other occasions, optimization is experimentally carried out by selective variation of one variable. Finally, given the high number of variables that can influence the final properties of nanoemulsions, optimization is carried out by experimental designs which allow reducing the number of experiments needed. Optimization is presently classified according to the following methods:

1. Phase behavior studies for optimization
2. Optimization by selective variation of parameters
3. Experimental designs for optimization

Phase behavior for optimization of nanoemulsion

Studies on phase behavior for optimization of nanoemulsion properties can be important when the so-called condensation or low-energy emulsification methods are used, because the phases involved during emulsification are determinant in order to obtain nanoemulsions of small droplet size and low polydispersity. In contrast, if shear methods are used, there is not a composition emulsification path and only phases at the final composition are important. The importance of the phase behavior, namely crossing microemulsion (bicontinuous) or lamellar liquid crystalline phase regions during emulsification is described in detail in recent reviews. Some recent original works in which this conclusion was experimentally proved were for nanoemulsions obtained by the phase inversion temperature method; for nanoemulsions obtained by phase inversion composition method, or for nanoemulsions prepared by a self-emulsifying method. Only bi-continuous or O/W microemulsions are considered appropriate for self-emulsifying while lamellar liquid crystal compositions do not self-emulsify by dilution, probably due to viscosity of the lamellar phase. It can be concluded that by slow addition of water to a lamellar liquid crystalline phase nanoemulsions can be obtained, while emulsions with higher droplet size were obtained by rapid dilution (as in self-emulsifying methods).

Optimization by selective variation of parameters

Parameters whose influence on nanoemulsion characteristics can be studied may be classified as composition or preparation variables. For emulsification by low-energy methods composition variables will have a much higher influence than preparation variables, however for shear emulsification, the influence of preparation variables will be determinant. Examples of recent literature about optimization of nanoemulsions obtained by shear include the study of the influence of different variables and the correlation of droplet size with them. Optimization of

nanoemulsion preparation by submitting a coarse emulsion to subcritical water conditions has been reported. The optimization was studied by selective variation of composition parameters (surfactant and oil concentration), and preparation parameter (temperature). For this system small size, 40 nm was obtained. For other condensation methods, variables whose effect is commonly studied are the surfactant oil ratio and the ratio between surfactants when a surfactant mixture is used. For nanoemulsions prepared by the phase inversion temperature method, optimization by selective variation parameters is presented is cited in literature. Variation of droplet size was studied with respect to oil surfactant ratio with the obvious result that the higher the oil surfactant ratio the greater the droplet size and variation of droplet size with surfactant mixing ratio was studied with the remarkable result at droplet size does not depend on surfactant mixing ratio if nanoemulsions are prepared by cooling from the HLB temperature. The optimization with respect to preparation method and variation of droplet size with oil surfactant ratio was presented. The different routes for emulsification was studied and droplet size variation with HLB, water fraction and surfactant concentration was also reported. The effect of variables HLB and oil surfactant ratio was separately studied with the expected result that there was an optimum HLB and that the higher the oil surfactant ratio the greater the droplet size.

Experimental designs for optimization[38-39]

Experimental designs allow to experimentally studying the influence of several variables with a limited number of experiments. Statistical analysis of results allows the identification of variables that have a significant influence, and to correlate desired response with variables by polynomial equations. Not many papers present optimization of nanoemulsion preparation by experimental designs, and most of them deal about pharmaceutical formulations for self-emulsification. Experimental design was used to determine the influence of two qualitative independent variables: type of oil and type of lipophilic emulsifier.

TECHNIQUES FOR PREPARATION OF NANOEMULSION[34-44]

The techniques for the preparation of nanoemulsions (covering the droplet radius size range 10–200 nm) may be classified as:

1. High pressure homogenisers (aided by appropriate choice of surfactants and co-surfactants)
2. Low energy emulsification method at constant temperature

High pressure homogenizers

The production of small droplets (submicron) requires application of high energy. High-pressure homogenizers, generally Niro Soavi Panda PLUS1000 by GEA, Microfluidizer or Manton-Gaulin devices, are designed in order to force macro-emulsions to pass through narrow gaps, by

imposing high pressures.

The fluid accelerates dramatically reaching, in the micro channels of Microfluidizers for instance, a velocity of around 300 ms−1. As a result, shear, impact and cavitation forces are applied on very small volumes and generate nano-scaled nanoemulsion droplets (closely related to the phenomena involved in the use of sonifiers). The primary advantage of high energy nano emulsification methods is that there is a good potential for polymeric nanoparticle generation, since the formulation parameters are directly controllable. Thus the addition of monomers, initiators, or encapsulating molecules may not influence the emulsification process, governed by the high shear processes. If anything, it may be and additional molecules to be encapsulated, monomers, initiators, or stabilizing agents that interfere with the emulsification process, unlike for the low energy methods in which nano emulsification is totally governed by the physicochemical behaviors of the surfactants. One serious concern with high energy methods is the encapsulation of fragile molecules such as peptides, proteins or nucleic acid, which may give rise to drug degradation, denaturation or activity loss during processing.

Low-energy emulsification methods

This method involving only a low quantity of applied energy to generate nanoemulsions. Nanometric scaled emulsion composing the formulation. Two groups of methods are proposed in the literature as discussed below:

droplets may be obtained by diverting the intrinsic physicochemical properties of the surfactants, co-surfactants and excipients

(i) Spontaneous emulsification, uses the rapid diffusion of water-soluble solvent, solubilized first in the organic phase, moving towards the aqueous one when the two phases are mixed. Among the works on spontaneous emulsification, the literature emphasizes the solvent displacement method, also called the Ouzo effect, which consists in nanoemulsion formulation due to the specific and very rapid diffusion of an organic solvent (e.g. acetone, ethanol) from the oily phase to the aqueous one. In theory, the spontaneous nanoemulsification process can provide as much oil-in-water as water-in-oil nanoemulsions, but the majority of the reported studies concern o/w generation.

(ii) Secondly, called phase inversion temperature (PIT) method, which uses the specific properties of polyethoxylated surfactants to modify their partitioning coefficient as a function of the temperature, and leads to the creation of bicontinuous systems when the temperature is close to the PIT, broken-up to generate nanoemulsions. Practically, it leads to o/w nanoemulsions Phase inversion in emulsions can be one of two types:

1. Transitional inversion induced by changing factors which affect the HLB of the system, e.g. temperature and/or electrolyte concentration. Transitional Inversion can also be induced by changing the HLB number of the surfactant at constant temperature using surfactant mixtures,

Table II: Nanoemulsion in ocular delivery

S. No.	Drug	Result
1.	Pilocarpine	(i) Physically stable for 6 months at 4 ºC (ii) Bioavailability is pH dependent
2.	Cyclosporine	(i) On dilution with tear fluid viscosity of formulation is increased (ii) Prolonged pre-corneal residence time
3.	Adaprolol maleate	Safe and effective in human studies
4.	Indomethacin	Improved ocular bioavailability
5.	Piroxicam	positively charged submicron emulsion shows pronounced effect on both the ulceration rate and epithelial defects in the management of corneal alkali-burning
6.	Dorzolamide HCl	(i) More intensive treatment of glaucoma (ii) Higher therapeutic efficacy (iii) Better patient compliance
7.	delta-8-tetra-hydrocannabinol	(i) Intense & long-lasting intraocular pressure depressant effect (ii) No irritation
8.	Dexamethasone	Improved pharmacokinetic parameters
9.	Timolol	Bioavailability of timolol was increased
10.	Levobunolol	Higher apparent lipophilicity
11.	Chloramphenicol	Stability of the chloramphenicol in the microemulsion formulations was increased

2. Catastrophic Inversion which is induced by increasing the volume fraction of the disperse phase. The diameter decreases and the rate constant increases as inversion is approached. For application of the phase inversion principle one uses the transitional inversion method which has been demonstrated by Shinoda and coworkers when using non-ionic surfactants of the ethoxylate type eg. Restasis, Diflucor, Xalatan, Travo. These surfactants are highly dependent on temperature, becoming lipophilic with increasing temperature due to the dehydration of the polyethyleneoxide chain. When an O/W emulsion is prepared using a non-ionic surfactant of the ethoxylate type, it is heated, then at a critical temperature (the PIT), the emulsion inverts to a W/O emulsion. At the PIT the droplet size reaches a minimum and the interfacial tension also reaches a minimum. However, the small droplets are unstable and they coalesce very rapidly. By rapid cooling of the emulsion that is prepared at a temperature near the PIT, very stable and small emulsion droplets could be produced.

CONCLUSION

Effective treatment of ocular diseases is a formidable challenge for scientists in the field especially because of the nature of diseases and presence of the ocular barriers especially in

posterior ocular segments. An ideal therapy should maintain effective levels of drug for the longer duration following a single application. Ocular disorders look intently to be treated and controlled by the use of nano pharmaceutical preparations. Nanoemulsions have the potential to provide sustained release of a drug and higher penetration to the deeper layers of the ocular structure and aqueous humor and hence enhance the therapeutic efficacy and pharmacokinetic parameters of the drug relative to the conventional system. The possibility of nanoemulsion makes this vehicle very attractive for ocular drug delivery.

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