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OPHTHALMIC MICROEMULSION: A COMPREHENSIVE REVIEW

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ABSTRACT

The design and development of new drug delivery systems with the intention of enhancing the efficacy of existing drugs is an ongoing process in pharmaceutical research. It is necessary for a pharmaceutical solution to contain a therapeutic dose of the drug in a volume convenient for administration. In last decade, o/w micro/lipid emulsions have been recognized as an interesting and promising ocular topical delivery vehicle for lipophilic drugs. The aim of present review is to present the potential of o/w and lipidmicroemulsions for ocular delivery of lipophilic drugs. The review covers an update on the state of the art of incorporating the lipophilic drugs, a brief description concerning the components and the classification of lipid/oil in water emulsions. The ocular metabolism after topical instillation and the applications of micro/lipid emulsions are thoroughly discussed.

KEYWORDS : o/w microemulsion, lipophilic drugs, ophthalmic drug delivery

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INTRODUCTION

For the treatment of different extra- and intra-ocular etiological conditions such as glaucoma, uveitis, keratitis, dry eye syndrome, cytomegalovirus retinitis, acute retinal necrosis, proliferative vitreoretinopathy and macular degenerative disease, a lot of lipophilic and poorly water soluble drugs have become available in recent years. However, most of the traditional ophthalmic dosage forms are clearly not only uncomfortable for the patient but also not efficient in combating some of the current virulent ocular diseases. Furthermore, in ophthalmology, the low viscosity topical formulations either in aqueous-based eye drops or in liquid retentive suboptimal forms is generally preferred to provide local drug concentrations in the precorneal or aqueous humor part of the eye.

In the last decade, oil-in-water (o/w) type lipid emulsions, primarily intended for parenteral applications have been investigated and are now exploited commercially as a vehicle to improve the ocular bioavailability of lipophilic drugs (Ding, 1998;Tamilvanan *et al*., 2002; Marti-Mestres*et al*., 2002). The natural biodegradability, nanometer droplet size range, sterilizability and substantial drug solubilization either at the innermost oil phase or at the o/w interface and improved ocular bioavailability are thus making the microemulsion a promising ocular delivery vehicle. For the first time, an anionic lipid emulsion containing Cyclosporine A 0.05% *(Restasis, Allergan, Irvine, USA)* was approved for clinical use by the FDA in December 2002, and is now available in the US for the treatment of chronic dry eye disease (available at *www.restasis.comand www.dryeye.com*). Furthermore, an over-the-counter product that features a non-medicated (blank) anionic emulsion formulation*(Refresh Endura)* has been launched in the US market for eye lubricating purposes in patients suffering from moderate to severe dry-eye syndrome (Sasaki*et al*., 1996;Rieger, 1990).Furthermore, as one of the noninvasive, topical drug delivery vehicles to treat ocular pathologies, the efficacy of o/w microemulsions has also been the focus of recent reviews (Ding, 1998;Marti-Mestres*et al*., 2002; Saettone *et al*., 2000). Thus, keeping in mind the potential of microemulsions, the purpose of this review is to report on the most recent findings on the mode of ocular active lipophilic drug incorporation into lipid emulsions, to classify the microemulsions, to describe briefly the major components needed to formulate ocular compatible o/w microemulsions, to relate the ocular metabolism or concomitant protective mechanism factors faced by lipid emulsions following ocular topical application, to offer a short overview on safety assessment made so far with regard to the ocular topical route and finally to describe the ocular topical delivery of lipophilic drugs through o/w type lipid emulsions. The size and the size distribution of the submicron emulsions obviously depend on the specific formulation. Irrespective of the formulation, most of the lipid emulsions exhibit a narrow size distribution range which may vary from 50 to 700 nm with a mean droplet size of about 200 nm.

Addition of lipophillic drug into oil/lipid:

There are three different approaches to add and dissolve lipophilic drugs into the lipid emulsions.

(A) Extemporaneous drug addition

When looking for a new galenic presentation form for *Amphotericin B* with better ocular tolerance over the commercial *Fungizone* eye drops, incorporated the drug directly to the preformed 20%emulsion, Intralipid(Cohen*et al*.,1996). However, after addition of the solid drug particles or drug solution, several physical changes such as phase separation, nanoprecipitation or creaming may occur within lipid emulsions thus limiting such practices in ocular lipid emulsion preparations. Therefore, ocular active lipophilic agents are not normally incorporated into the lipid emulsions by this extemporaneous addition method.

(B) De novo emulsion preparation

In principle, the drug molecules should be incorporatedby a de novo process. Thus, the drug is initially solubilizedor dispersed together with an emulsifier in suitable single oilor oil mixtures by means of slight heating. The water phase containing the osmotic agent with or without an addition alemulsifier is also heated and mixed with the oil phase bymeans of high speed mixers. Further homogenization takes place to obtain the needed small droplet size range of the emulsion. A terminal sterilization by filtration or steam then follows. The lipid emulsion thus formed contains most of the drug molecules within its oil phase. This is a generally accepted and standard method to prepare lipophilic drugloaded lipid emulsions for ocular use as shown in Fig.1.

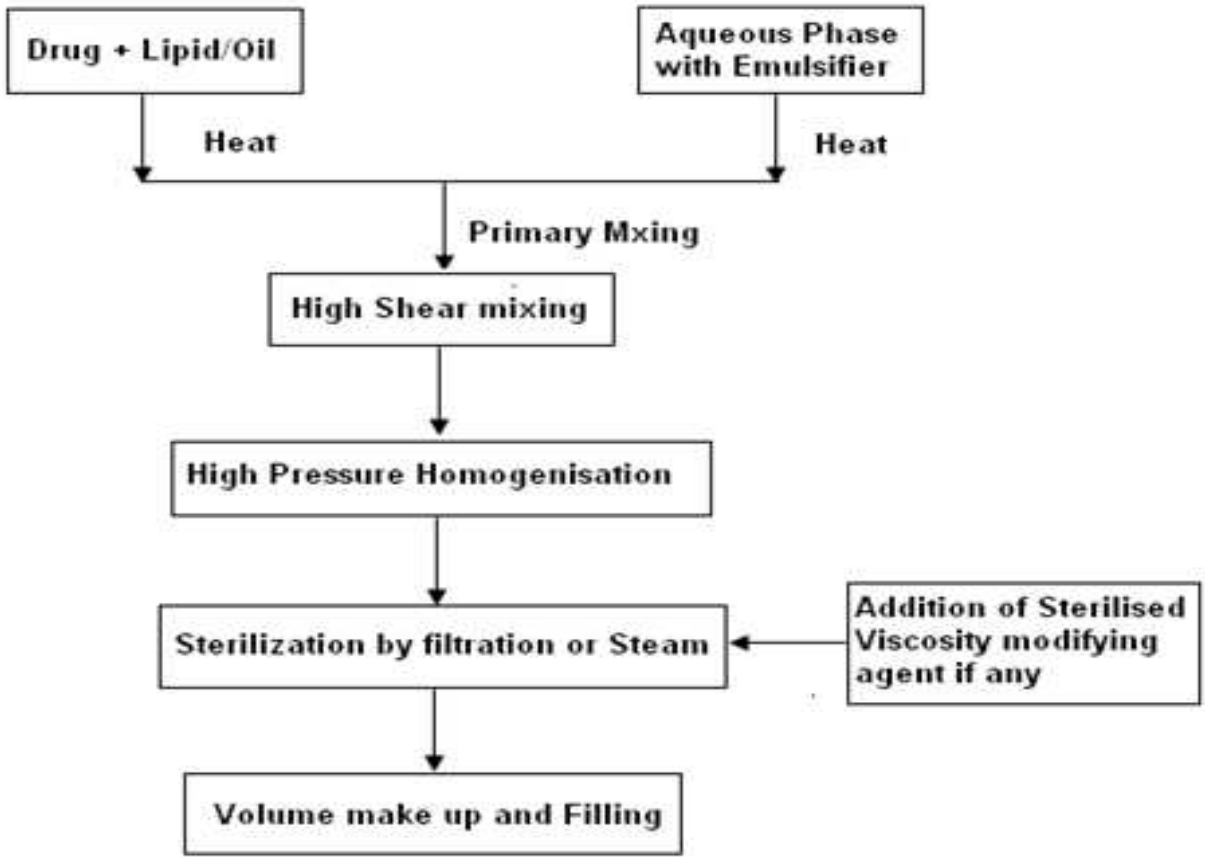

Figure.1
Manufacturing using high pressure homogenization

(C) Interfacial incorporation approach using Phospholipid

Since many drugs of commercial interest including ocular therapeutic agents generally have a solubility that is too low in FDA approved oils, proposed a method to incorporate such drugs into the interfacial o/w layer of the emulsion droplets (Lance *et al*., 1988). This can be achieved by initially dissolving the drug along with the phospholipid in an organic solvent, instead of oil. Following the solvent evaporation, the obtained phospholipids/ drug co-mixture is used in the de novo production of the lipid emulsions (Davis and Washington, 1988). However, this approach suffers from possible drug nanocrystal formation inside the lipid emulsions and from the use of organic solvent during the emulsion preparation process. To overcome such drawbacks, a novel SolEmul technology

has been developed in which an additionalhigh speed homogenization step is included to mix the drug with lipid emulsions. The drug particles are in fact micronized to the nanosize range prior to incorporation into the lipid emulsions. By this technique, adequateamounts of lipophilic drugs can be substantially incorporated into the lipophilic core or intercalated betweenthe selected emulsifier molecular films at the o/w interface of the lipid emulsions. The drugs reported to have been incorporated by this novel approach are *Amphotericin B, Carbamazepine* and*Itraconazole*(Buttle *et al*., 2002;Muller and Schmidt, 2002;Akkar and Muller, 2003; Akkar, *et al*., 2003).

Excipients for the manufacturing of ocular compatible lipid emulsion:

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.

(A) Oils and Lipids

Prior to the formulation design of the lipid emulsions data are needed concerning the drug solubility in the oil vehicle. 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.

Table1
Common emulsion excipients

Lipid/oil	Emulsifier	Cationic lipids and polysaccharides	Others
Sesame oil	Cholesterol	Stearylamine	Glycerol
Castor oil	Phospholipid	Oleyamine	Xylitol
Soya oil	Polysorbate 80	Chitosan	Sorbitol
Paraffin oil	Transcutol P		Thiomersal
Paraffin light	Cremophor RH		EDTA
Lanolin	Ploxamer 407		Methyl Paraben
Vaseline	Polaxamer 188		Propyl Paraben
Corn oil	Miranol C2M		
Glycerin Monostearate	Tyloxapol		
Medium chain Monoglycerides			
Medium chain triglycerides			

Table 1 enlist the common emulsion excipients and the oils suitablefor 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 concentration in ocular lipid emulsions is now widely accepted at or even below 5% (w/w) taking into account that the lipid emulsion must be kept in a low viscosity range, of between 2 and 3 *cp*, which is considered an adequate

viscosity for ocular preparations (Lee and Robinson, 1986). Sometimes, a mixture of oils rather than single oil is employed since drug solubilization in the oil phase is a prerequisite to exploit the lipid emulsion advantages. Jumaa and Muller reported the effect of mixing castor oil with medium chain triglycerides on the viscosity of castor oil(Jumaa and Muller, 1998;Jumaa*et al*., 1999). The oil combination, at the ratio of 1:1 (w/w) led to a decrease in the viscosity of castor oil and simultaneously to a decrease in the interfacial tension of the oil phase. This was related to the free fatty acids contained in castor oil, which can act as a co-emulsifier resulting in lower interfacial tension and, simultaneously in a more stable formulation in comparison with the other oil phases.

(B) Emulsifier

Traditionally, lecithin or phospholipids have been theemulsifiers of choice to produce ocular lipid emulsions. However, emulsifier of this kind is not suitable to produce submicron sized emulsion droplets or to withstand the heat during steam sterilization. Therefore, additional emulsifiers preferably dissolved in the aqueous phase are usually included in the lipid emulsion composition. A typical example of the aqueous soluble emulsifiers is non-ionic surfactants (e.g. Tween 20) after taking into consideration their non-irritant nature when compared to ionic surfactants. The non-ionic block copolymer of Polyoxyethylene-Polyoxypropylene, Pluronics F68 (Poloxamer 188), is included to stabilize the lipid emulsion through strong steric repulsion. However, amphoteric surfactants, Miranol MHT (Lauroamphodiacetate and Sodium tridecethsulfate) and Miranol C2M (Cocoamphodiacetate) were also used in an earlier ophthalmic lipid emulsion(Muchtar and Benita, 1994). It should be added that Restasise contains only polysorbate 80 and carbomer 1342 at alkali pH to stabilize the Cyclosporin-A loaded anionic lipid emulsion.

(C) Preservatives

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 lipid emulsions. The presence of components of natural origin like lecithin or oils with high calorific potential render the lipidemulsion a good medium to promote microbial growth when it is packed in multi-dose containers. Sznitowska et al. studied the physicochemical compatibility between the lecithin-stabilized lipid emulsion and 12 antimicrobial agents over 2 years of storage at room temperature. Preliminary physicochemical screening results indicate that addition of chlorocresol, phenol, benzyl alcohol, thiomersal, chlorhexidine gluconate and bronopol shouldbe avoided due to the occurrence of an unfavourable pH change followed by the coalescence of the lecithinstabilized droplets of the lipid emulsion. Despite a good physicochemicalcompatibility, neither parabens nor benzalkonium chloride showed satisfying antibacterial efficacy in the lipid emulsion against thetested microorganisms and consequently did not pass the test. Therefore, higher concentrations of antimicrobial agents or their combination may be required for efficient preservation of the lecithin-stabilized lipid emulsions probably because of unfavorable phase partitioning of the added antimicrobials within the different internal structures of the lipid emulsions.

Ocular metabolism of lipid emulsions after instillation

Considerations of ocular drug delivery are not detailed in this section. Pertinent information concerning factors affecting drug permeation or retention as well as eyes anatomy and physiology can be found in several reviews (Stjernschantz and Astin, 1993; Lee, 1993; Jarvinen*et al*., 1995; Prausnitz andNoonan, 1998;Washington*et al*., 2001). From a medical point of view, lipid emulsions for ophthalmic use aim to enhance drug bioavailability either by providing prolonged delivery to the eye or by facilitating transcorneal/transconjunctival penetration. Drugs incorporated in o/w type lipid emulsions are lipophilic in nature and,

depending on the extent of lipophilicity, either the corneal or the conjunctival/sclera route of penetration may be favored (Lee, 1993). For the more lipophilic drugs the corneal route was shown to be the predominant pathway for delivering drugs to the iris, whereas the less lipophilic drugs underwent the conjunctival/scleral penetration for delivery into the ciliary body (Chien *et al*., 1990). Thus, transcorneal permeation has traditionally been the mechanism by which topically applied ophthalmic drugs are believed to gain access to the internal ocular structures. Relatively little attention has been given to alternate routes through which drugs may enter the eye.

Ocular delivery of lipophilic drugs by lipid emulsions

For convenience, we have divided this section into two parts based on the charge of the emulsified oil droplets:

Table 2
Non-exhaustive list of oil-in-water (o/w) submicron lipid emulsion for ocular drug delivery

Emulsion type	Drug used
Anionic emulsion	D8-THC (Osborne*et al*., 1995)
Anionic emulsion	Pilocarpine base and Indomethacin (Zurowska-Pryczkowska*et al*., 1999)
Anionic emulsion	Adaprolol maleate (Naveh*et al*., 1994; Zurowska-Pryczkowska*et al*., 1999)
Anionic emulsion	Indomethacin (Calvo*et al*., 1996; Osborne*et al*., 1995; Naveh*et al*., 1994)
Anionic emulsion	Synthetic HU-211 and Pilocarpine base (Muchtar*et al*., 1994; Klang*et al*., 1999; Stevenson*et al*., 2000)
Anionic emulsion	Pilocarpine base (Sznitowska*et al*., 1999; Naveh*et al*., 2000; Naveh*et al*., 1994; Zurowska-Pryczkowska*et al*., 1999; Melamed*et al*., 1994)
Anionic emulsion	Cyclosporin-A (Stevenson, 2000; Ding*et al*., 1995; Ding and Olejnik 1997; Acheampong*et al*., 1999; Sall*et al*., 2000; Turner*et al*., 2000; Kunert*et al*., 2000; Brignole*et al*., 2001; Small*et al*., 2002; Galatoire*et al*., 2003)
Cationic emulsion	Piroxicam(Muchtar*et al*., 1992)
Cationic emulsion	Indomethacin(Klang*et al*., 2000)
Cationic emulsion	Miconazole(Yang and Benita, 2000)
Cationic emulsion	Cyclosporin A(Tamilvanan, 2001; Abdulrazik, 2001)

Anionic lipid emulsions applications

The *in-vivo* data obtained from studies of early formulations confirmed that anionic lipid emulsions can be effective topical ophthalmic drug delivery systems (Muchtar *et al*., 1992)with a potential for sustained drug release Naveh*et al*., 2000. Naveh andco-workers have also noted that the IOP-reducing effectof a single, topically administered dose of pilocarpineloadedanionic lipid emulsions lasted for more than 29 h inalbino rabbits whereas that of the generic pilocarpine lastedonly 5 h (Zurowska-Pryczkowska*et al*., 1999). Zurowska-Pryczkowska et al., studied how lipid emulsions as a vehicle influence chemical stability of pilocarpine, as well as how the drug may affect the physical stability of lipid emulsions. In a subsequent work from the

same group on *in- vivo* evaluation using normotensiverabbits, it was shown that anionic lipid emulsionsformulated with pilocarpine hydrochloride at pH 5.0 couldbe indicated as a preparation offering prolonged pharmacologicalaction (miotic effect) together with satisfactorychemical stability(Sznitowska*et al*., 2001) . However, the ocular bioavailabilityarising from such a formulation did not improve significantlywhen compared to an aqueous solution of the samedrug. On the other hand, Calvo *et al*., observed an improvement in indomethacin ocular bio availability when the drug was incorporated in a lipid emulsioncompared to the commercial aqueous drops followingtopical application into rabbit eye.Beilin *et al*., showed as previously mentionedthat a lipid emulsion increased ocular residence time incomparison to eye drops, correlated the delayed pharmacologicalaction to the delayed residence time. Anselem et al., and Melamed *et al*., prepared an anioniclipid emulsion containing Adaprolol maleate, a novel softb-blocking agent and observed a delayed IOP depressant effect in human volunteers. A similar pharmacologicaleffect was also observed in ailing human volunteers by Aviv*et al*., using pilocarpine base-loaded lipid emulsion.A novel anionic lipid emulsion incorporating theimmunomodulatory agent Cyclosporine-A was developedand its clinical efficacy was investigated for the treatment ofmoderate to severe dry eye disease in animals and humans(Ding*et al*., 1995;Ding and Olejnik, 1997; Acheampong*et al*., 1999). The novel Cyclosporine-A ophthalmic dosage formrepresents a breakthrough in the formulation of a complex,highly lipophilic molecule such as Cyclosporine-A within ananionic lipid emulsion.Ding and Coll, have developed a castor oil in wateremulsion stabilized by Polysorbate 80. The Cyclosporine penetrated into rabbit extraocular tissues (cornea, lachrymalglands and conjunctiva) at concentrations adequate for localimmunosuppression activity while penetration into intraoculartissues was much lower and absorption into bloodwas minimal (Acheampong *et al*., 1999). The oil canthen migrate towards the lower lid where it may residelonger than aqueous fluids and supplement the lipid layer inthe tears. This indicates that lipids containing eye drops suchas lipid emulsions have moved a step closer to natural tearseven in terms of ocular tolerability and therefore should notbe expected to produce any ocular discomfort (Rieger, 1990). Indeed,the lipid substances normally present in tears, such as phospholipids, saturated and unsaturated fatty acids andtriglycerides, are currently used in the preparation of mostlipid emulsions. Therefore, the lipid emulsions closelycorrespond to the natural tear fluid and seem to participate in formation of physiological tear film.

Cationic lipid emulsions applications

The potential of a cationic submicron emulsion suitablefor ocular application of piroxicam was reported (Klang *et al*., 1994). It wasshown that the Piroxicam positively charged emulsion wasthe most effective formulation in lowering the ulcerativecornea score following alkali burn of rabbit corneas. Anincreased uptake of the positive oil droplets by thenegatively charged cornea is a plausible explanation forthe resulting enhancement of the lipophilic drug oculardisposition. Furthermore, the blank emulsions showed a very rapid healing rate over the first three days, with a breakdown on day 14 and then complete re-epithelialization on day 28.Regardless of the preparation instilled, the highest concentrationof Indomethacin was achieved in the cornea,followed by conjunctiva, sclera retina and aqueous humor.However, the cationic emulsion provided significantlyhigher drug levels than the control solution and anionicemulsion only in the aqueous humor and sclera-retina. The stability and oculartolerance following topical instillation into eye ofthese cationic lipid emulsion vehicles were investigated(Klang *et al*., 1994; Klang *et*

al., 1996; Wehrle *et al*., 1996). The promising results obtained with Cyclosporine-A loaded cationic lipid emulsions paved the way for theformulation to recently obtain approval from regulatoryauthorities to undergo Phase-I clinical study for the freedrug cationic lipid emulsion (Etheridge, 2003). Furthermore, it isinteresting to note that the cationic emulsion is promotingthe penetration of Indomethacin and of Cyclosporin-Ato ocular tissues of the posterior segment followingone single topical instillation (Klang *et al*., 2000; Abdulrazik *et al*., 2001). It can be noted thatthe concentration of the respective drugs in the sclera/retinaand in the optic nerve was higher with the cationic emulsionthan with the anionic emulsion. Such relatively highconcentrations in the posterior segment can be reachedonly by diffusion of the drugs through one of the followingpathways: transcorneal, transconjunctival or through theblood circulation secondary to the systemic absorption.Since aqueous humor and blood levels of Cyclosporine werefound to be low, while with Indomethacin the cornealconcentrations of the anionic and cationic emulsions werenot significantly different and the blood levels were alsolow, only the transconjunctival route can represent aplausible approach for the increased concentrations of thedrugs in the posterior segment as previously suggested.However, a direct transscleral access to some ocular tissuesin the back of the eye cannot be excluded. Further studiesare needed to elucidate the mechanism by which drugs canreach the posterior segment of the eye.A cationic lipid emulsion based on an association ofPoloxamer 188 and Chitosan was also prepared andexhibited interesting physicochemical properties regardingstability and charge effects (Jumaa*et al*.,1999;Calvo *et al*., 1997). A remarkable fact fromthe data reported in the present review is that irrespective ofthe drug, the cationic emulsion provided higher drug levelsthan the anionic emulsion formulation. There are evidencesthat colloidal delivery systems can facilitate the penetrationof drugs into ocular surface tissues through an endocyticmechanism (Calvo,1996; Sznitowska, 2000). The endocytic effect is probably morepronounced with the cationic emulsion as suggested (Yang, and Benita, 2000).All these studies stress the effectiveness of cationic lipidemulsions, which promote ocular drug absorption viainternalization possibly through an endocytic process.

CONCLUSION

The o/w type lipid emulsion seems to offer a number of advantages in the treatment of various ocular pathologies by providing an altered ocular pharmacokinetics profile of the lipophilic drug incorporated in lipid emulsion following topical instillation into the eye. The potential role of lipid emulsions in the ocular topical delivery of lipophilic drugs to the posterior segment of the eye is currently under investigation. Attempts were being made to optimize the lipid emulsion formulations to elicit adequate therapeutic concentrations of effective drugs for the treatment of virulent eye pathologies especially in the posterior segment of the eye.

Recent trends in ophthalmic microemulsion

Most of the early investigational ophthalmic emulsions mimicthe formulations of parenteral emulsions, and use phospholipidsand pluronics as emulsifiers. Because phospholipids are sensitiveto oxygen, antioxidants are incorporated into these emulsionformulations to improve their shelf-life. Even with antioxidants,however, the phospholipid-containing emulsions are still limitedin room temperature stability.

The in vivo data obtained from studies of these early formulations confirm that emulsions can be effective topical ophthalmicdrug delivery systems (Garty *et al*., 1994; Muchtar *et al*., 1992), with a potential for sustained drug release (Naveh *et al*., 1994; Barilan*et al*., 1994).Naveh and co-workers noted that the intra ocular pressure-reducing effect of a

single, topically administered doseof Pilocarpine emulsion lasted for more than 29 h in albino rabbits, whereas that of the generic Pilocarpine solution lasted only five hours (Naveh et al., 1994). Oil-in-water emulsions are particularly useful in the delivery of water-insoluble drugs. Previously, ointments and suspensions were the only two available options, but the former suffered from poor patient acceptance because of blurred vision and matted eyelids, and the latter appeared to have problems with particle irritation, poor bioavailability, and changes in polymorphism and particle size upon storage. The newly developed oil-in-water emulsion offers a third option that has the advantages of an ointment without its drawbacks.

In the oil-in-water emulsion, the water-insoluble drug is solubilized in the internal oil phase, thereby remaining in the preferred solution state. By keeping the drug in solution, the issue ofpotential absorption because of slow dissolution of solid drug particles is avoided. In addition, the blurred vision caused by oils is minimized by the water in the external phase. Furthermore, the concentration of the drug in the oil phase can be adjusted to maximize thermodynamic activity, thus enhancing drug penetration.As technologies have advanced, the obstacles preventing the development of ophthalmic emulsions have gradually been removed. The improvements in both machinery and aseptic processing allow for the reproducible manufacture of a sterile product with greater assurance than was previously possible. Moreover, new types of emulsifiers that are safe, non-irritating and chemically unique have become available. Some of these emulsifiers have demonstrated a remarkable ability to stabilize emulsions. Using novel polymeric emulsifiers, a newly formulated Cyclosporine ophthalmic emulsion demonstrates excellent room temperature stability and extremely low ocular irritation (Ding *et al*., 1995; Ding and Olejnik, 1997). This emulsion is in Phase-III clinical studies for the treatment of dry eye disease.

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