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Phase transition water-in-oil microemulsions as ocular drug delivery systems: In vitro and in vivo evaluation

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Abstract

Microemuslion (ME)-based phase transition systems were evaluated for ocular delivery of pilocarpine hydrochloride (model hydrophilic drug). These used two non-ionic surfactants, sorbitan mono laurate and polyoxyethylene sorbitan mono-oleate with ethyl oleate (oil component) and water. These systems undergo phase change from ME to liquid crystalline (LC) and to coarse emulsion (EM) with a change in viscosity depending on water content. This study selected five formulations containing aqueous phase at 5% (w/w) (ME 5%), 10% (w/w) (ME 10%), 26% (w/w) (LC), 85% (w/w) (O/W EM) and 100% (solution) with the model drug at 1% (w/w). Incorporation of pilocarpine hydrochloride did not affect the phase behaviour. The viscosity was increased initially with dilution from ME 5% to ME 10% then LC, indicating structuring of the system, before being reduced in the EM formulation. Drug release depended on the viscosity with lower release rates obtained from formulations with high viscosity. The miotic response and duration of action were greatest in case of ME and LC formulations indicating high ocular bioavailability. Thus, phase transition ME is promising for ocular drug delivery as it provides the fluidity with its viscosity being increased after application increasing ocular retention while retaining the therapeutic efficiency.

Keywords: Microemulsion; Ocular drug delivery; Ophthalmic; Phase transition

1. Introduction

Ocular diseases are mainly treated topically by application of drug solutions administered as eye drops. These conventional dosage forms account for 90% of the available ophthalmic formulations (Le Bourlais et al., 1998). This can be due to the simplicity and convenience of such dosage forms. However, rapid precorneal loss caused by drainage and high tear fluid turnover is amongst the major problems associated with topical ophthalmic drug delivery. Only 5% of the applied drug in eye drops penetrates the cornea and reaches the intraocular tissues with the rest of the dose undergoing transconjunctival absorption or drainage via the nasolacrimal duct before transnasal absorption. This results in loss of drug into the systemic circulation and provides undesirable systemic side effects (Meseguer et al., 1994; Lang, 1995). Accordingly, the challenging objective of pharmaceutical formulators is to develop topical ocular delivery systems with improved ocular retention, increased corneal drug absorption and reduced systemic side effects whilst maintaining the simplicity and convenience of the dosage form as eye drops. Therefore, many strategies have been adopted to partially or fully achieve such target. These included the use of bioadhesive hydrogels (Durrani et al., 1995), formulation of temperature or pH-sensitive in situ gel forming systems (Miller and Donovan, 1982; Gurny et al., 1985), preparation of collagen shields (Unterman et al., 1988; Kaufman et al., 1994), application of particulate and vesicular drug delivery systems such as nanoparticles, liposomes and niosomes (Fitzgerald et al., 1987; Calvo et al., 1997; Vyas et al., 1998; Pignatello et al., 2002; Aggarwal and Kaur, 2005), or employing micellar solutions (Pepić et al., 2004). Microemulsions provided a promising alternative. They are transparent, thermodynamically stable systems that can be prepared easily. Moreover, they can accommodate both hydrophilic and lipophilic drugs (Gasco et al., 1989; HaBe and Keipert, 1997; Vandamme, 2002). To improve ocular retention the viscosity of microemulsion was increased by dispersion in a hydrogel system (Gulsen and Chauhan, 2005).

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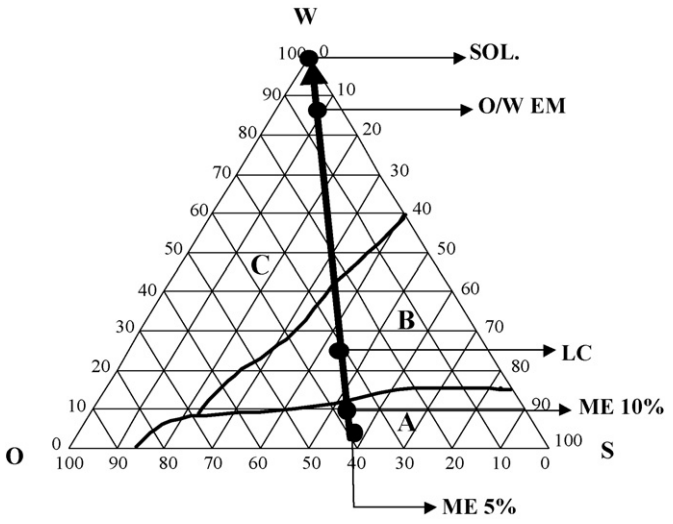

Fig. 1. Pseudo-ternary phase diagram for Crodamol EO, water, Crill 1 and Crillet 4 system. W, 100% water; O, 100% Crodamol EO; S, 100% surfactant blend of Crill 1 and Crillet 4 (ratio of 2:3). (A) Systems forming water-in-oil microemulsions; (B) systems containing liquid crystals; (C) systems forming coarse emulsions; (ME 5%) water-in-oil microemulsion containing 5% (w/w) aqueous phase; (ME 10%) water-in-oil microemulsion containing 10% (w/w) aqueous phase; (LC) lamellar liquid crystalline systems; (EM) oil-in-water coarse emulsion systems; (SOL) aqueous solution. Modified from Alany et al., 2001.

This study evaluated microemuslion-based phase transition systems with different viscosities as ocular delivery systems for pilocarpine hydrochloride (model hydrophilic drug). Phase transition of water-in-oil microemulsion (W/O ME) systems comprising two non-ionic surfactants, sorbitan mono laurate (Crill 1) and polyoxyethylene (20) sorbitan mono-oleate (Crillet 4) with ethyl oleate (Crodamol EO, the oil component) and water has been reported (Alany et al., 2001). The pseudo-ternary phase diagram of this system (Fig. 1) showed three distinctive regions with the W/O ME transforming to lamellar liquid crystalline structure (LC) before subsequent transformation into oil-in-water emulsion (O/W EM) with increasing water content. This phase change is associated with a change in the viscosity. This study selected five different formulations containing the aqueous component at concentrations of 5% (w/w) (ME 5%), 10% (w/w) (ME 10%), 26% (w/w) (LC), 85% (w/w) (O/W EM) and 100% (w/w) (solution). The oil:surfactant blend weight ratios were kept constant with pilocarpine hydrochloride being incorporated at 1% (w/w). These systems were shown to be tolerable by the eye (Alany et al., 2006). These formulations were evaluated as ocular delivery systems with the aim of investigating the influence of phase transition on the release and therapeutic efficacy of the drug after topical application.

2. Materials and methods

2.1. Materials

Ethyl oleate (Crodamol EO), sorbitan mono laurate (Crill1) and polyoxyethylene (20) sorbitan mono-oleate (Crillet 4 super) were obtained form BTB Oleochemicals (Auckland, New Zealand). Pilocarpine hydrochloride (USP grade) was obtained from Sigma Chemical Co. (St. Louis, USA). Deionised water was used as the aqueous component.

2.2. Preparation and characterisation of ocular formulations

Table 1 presents the composition of the tested formulations. The formulations employed two non-ionic surfactants (Crill 1 and Crill 4, blended at 2:3, w/w) with ethyl oleate (Crodamol EO) as the oil component. The formulations were prepared at a constant surfactant blend/oil (w/w) (3:2). These formulations included two W/O ME formulations containing aqueous components at 5% and 10% (w/w), respectively with the later being close to the W/O ME–LC phase boundary. The other formulations were a LC formulation with aqueous component at 26% (w/w), an O/W EM system with 85% (w/w) aqueous component and an aqueous solution of drug. The drug was incorporated by replacing the water content with an aqueous drug solution-containing drug sufficient to produce constant drug concentration (1%, w/w) in all formulations. The oil, surfactant blend and the aqueous phase were vortex mixed for 10 min and the resulting systems were left to equilibrate overnight at ambient temperature before conducting the in vitro and in vivo evaluation. These were examined microscopically using normal and polarised light. The systems were characterized by conductivity measurement (Conductivity Meter, TDScan 3 Tester, Eutech Instruments Pte. Ltd., Singapore). The surface tension of each formulation was also monitored using the torsion balance (Torsion Balance Supplies, Worcs, UK). To ensure maximum drug stability, all formulations were freshly prepared before each study.

2.3. Rheological evaluations

The flow properties and the viscosity of the systems were determined at $32 \pm 1\,^{\circ}C$. Viscosity determinations employed a DV III cone and plate Brookfield viscometer (Brookfield Engineering Laboratories Inc., Stoughton, MA, USA), fitted with CP-40 spindle. The system was calibrated using Brookfield viscosity standard fluids (Brookfield Engineering Laboratories Inc., Stoughton, MA, USA).

Table 1
Details of the tested formulations

Formulation	Composition (w/w)
ME 5%	PHCl, water, Crill1, Crillet 4, Crodamol EO (1:4:22.8:34.2:38)
ME 10%	PHCl, water, Crill1, Crillet 4, Crodamol EO (1:9:21.6:32.4:36)
LC	PHCl, water, Crill1, Crillet 4, Crodamol EO (1:25:17.8:26.6:29.6)
EM	PHCl, water, Crill1, Crillet 4, Crodamol EO (1:84:3.6:5.4:6)
Sol	PHCl, water (1:99)

ME, W/O microemulsion; LC, lamellar liquid crystalline system; EM, O/W emulsion; Sol, solution; PHCl, pilocarpine hydrochloride.

2.4. In vitro drug release

Release experiments employed the FDC-6 Transdermal Diffusion Cell Drive Console (Logan Instrument Corp., NJ, USA). The system is fitted with VTC-200 heater circulator with jacketed vertical glass Franz diffusion cells being the main unit. The artificial membrane (Cellulose tubing, Sigma diagnostics, St. Louis, MO, USA) was mounted between the donor and receptor compartments of the diffusion cells. These cells provided a diffusional area of 1.7 cm^2 and the receptor compartment was 12 ml. Distilled water was employed as receptor. The system was adjusted to ensure that membrane surface was at 32 ± 1 °C to mimic in vivo conditions. The tested formulations (about 2 g) were loaded into the donor compartment before occluding the donor compartments using a parafilm. Receptor samples were taken periodically and replaced with fresh receptor. These were analysed for the drug content by UV spectrophotometric determination at 235 nm (UV/Vis, spectrophotometer, Libra S32PC, Biochrom, England).

2.5. In vivo evaluation

The miotic response obtained after application of the tested formulations to the rabbit eye was taken as an indirect measure of in vivo evaluation. The studies were conducted using six New Zealand Albino rabbits weighing 2–3 kg. The rabbits were fed a normal diet, exposed to alternating 12 h light and dark cycles and restrained by wrapping with a towel during the experiments. All experiments were performed in the same room under standard lighting conditions; light intensities were monitored using a photometer (Lux Meter Q-1400, DSE). The same rabbits were used to evaluate all formulations with 1 week wash out period between each formulation. The pupil diameter was measured from digital images taken using a digital camera (Minolta Dimage 7, 5.2MPixel digital camera) with a ruler with 0.5 mm increments, held under the right eye serving as a calibration scale (Fig. 2). The ruler was placed level to the surface of the eye and the focus of the camera was optically adjusted to both the iris and the ruler. At zero time (before application) basal measurements of the pupil diameter were taken four times in each rabbit. The test system (20 μl) was then instilled into the lower fornix of the conjunctival sac of the right eye using a positive displacement pipette with the left eye serving as a control. Miotic response was monitored and recorded using the digital camera with a static imaging protocol at a10 min intervals for 180 min. The acquired images were analyzed on a computer screen using the ruler as a calibration scale.

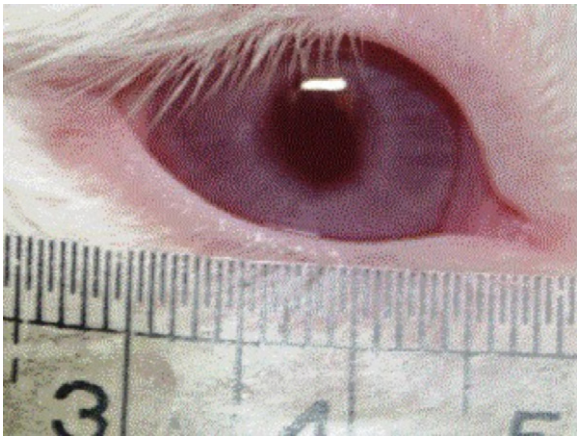

Fig. 2. A digital camera image showing the miotic response being monitored with a ruler serving as a calibration scale.

The change of pupil diameter versus time plots provided the miotic response profiles. These profiles were used to calculate the pharmacokinetic parameters; area under the curve ($AUC_{0–180}$), time required to achieve peak miotic response (T_{max}) and miotic response recorded 130 min post instillation (MR_{130}). The last parameter was selected for comparison, as the miotic response of the drug solution approached zero after 130 min.

All animal manipulations were done in accordance with the guidelines of The University of Auckland animal ethics committee.

The Student's *t*-test was employed for statistical analysis.

3. Results

3.1. Physical appearance, type and surface tension of the prepared systems

The physical appearance of the investigated systems depended on the water content. Thus, the ME 5% and ME 10% formulations were characterised microscopically as microemulsions. Conductivity measurement showed zero values for both formulations, indicating that ME 5% and ME 10% formulations are in the form of W/O microemulsions. Increasing the water content to 25% (w/w) produced a lamellar liquid crystalline formulation (LC), which provided no electrical conductivity. The formulation containing the highest concentration of water was in the form of coarse emulsion (EM). Measuring the conductivity of this EM it was found to be 190 μS, indicating an O/W emulsion system. Monitoring the surface tension of the formulations, equal values (34 ± 1.6 dyn/cm) were recorded for all formulations.

3.2. Rheological properties of the prepared systems

The flow properties and the viscosity of the prepared systems depended on the water content. The microemulsion systems (ME 5% and ME 10%) as well as the coarse emulsion system (EM) exhibited a simple Newtonian flow. On the other hand the lamellar liquid crystalline system (LC) exhibited a pseudoplastic flow. The viscosity was increased with increasing water concentration in the ME systems (112 and 167 mPa s, for ME 5% and ME 10%, respectively) with the apparent viscosity recording very high value for the LC system (5487 mPa s, calculated according to Kabre et al., 1964). For the O/W EM, the viscosity was 4.17 mPa s.

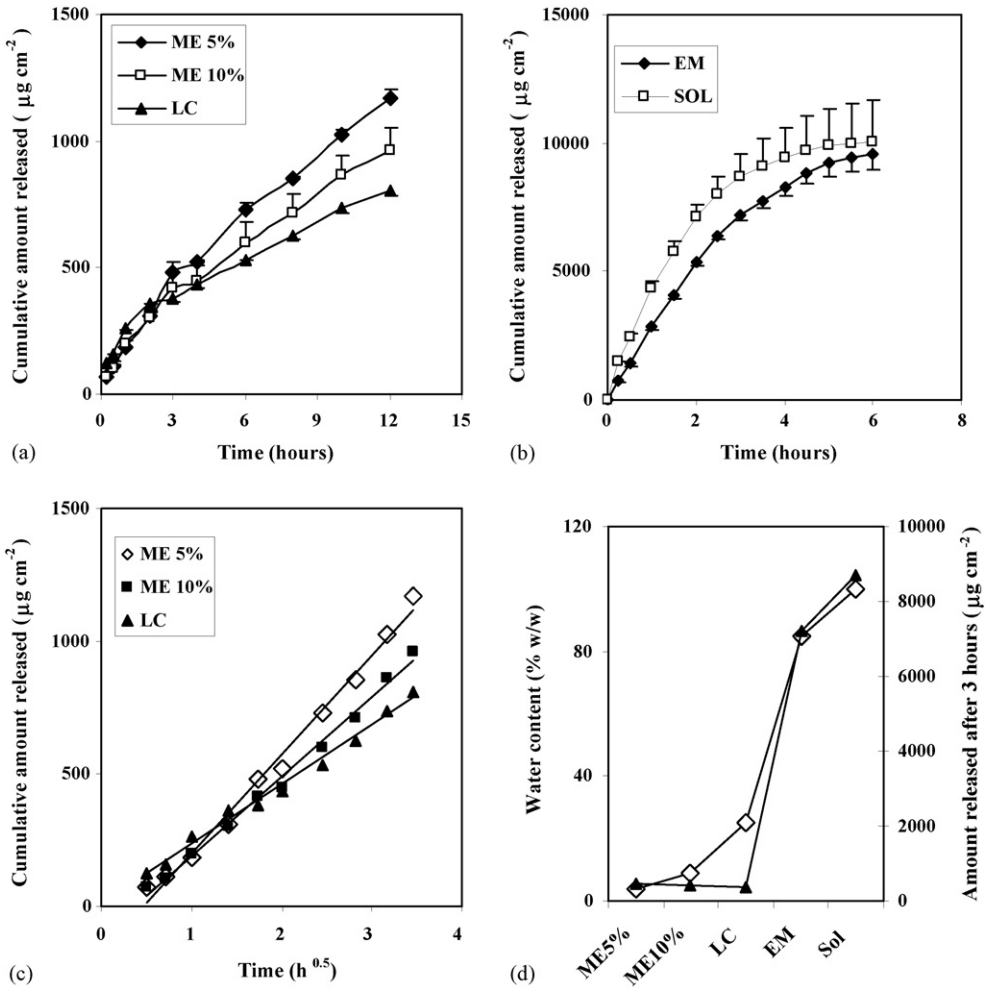

Fig. 3. In vitro release profiles (a–c) of pilocarpine hydrochloride from microemulsion, liquid crystalline and O/W emulsion formulation and (d) a correlation between the water content (open symbol) in each formulation and drug release (closed symbol). Formulation details are in Table 1.

3.3. In vitro drug release

Fig. 3 shows the in vitro release profile of pilocarpine hydrochloride form the tested formulations. As for the viscosity the drug release depended on the water content of the formulations. For ME and LC formulations there was a linear relationship between the cumulative amount of drug released and the square root of time indicating matrix order kinetics. The release rate was in the order of ME 5% > ME 10% > LC (Fig. 3c). For the O/W EM formulation the release profile did not fit the matrix kinetic model. Alternatively, it provided a profile similar to that of the aqueous solution with most of the loaded drug being released in the first 3 h (Fig. 3b). Obtaining different release kinetics from EM and Sol compared to other formulations, the amount released after 3 h was selected for comparison and correlation of drug release with the water content. This selection was based on the fact that the in vivo study was conducted for 3 h. Fig. 3d correlates the water content in each formulation with the total amount of drug released after 3 h. Increasing water content in the formulation provided initial reduction in the drug release before releasing significantly higher amounts in case of EM and Sol. It should be noted that the total amount of drug released were very low in cases of ME 5%, ME 10% and LC compared with the EM and solution systems Fig. 3a and b.

3.4. In vivo evaluation

The miotic response profiles obtained for pilocarpine hydrochloride after application of different formulations are shown in Fig. 4. The calculated pharmacokinetic parameters are presented in Table 2. The miotic response profiles varied depending on the formulation (Fig. 4). Quantitative comparisons used the calculated parameters. There were no significant differences ($P > 0.05$) between all formulations with respect to the time required to achieve peak miotic response (T_{max}). With respect to area under the curve values ($AUC_{0–180}$) the tested formulations were ranked as ME 10% > ME 5% > LC > EM > Sol (Table 2). The $AUC_{0–180}$ value calculated for ME 5% was significantly higher than that of the Sol ($P < 0.05$). For the ME 10% the $AUC_{0–180}$ was significantly higher than that of EM and Sol ($P < 0.001$ in both cases). Regarding the miotic response recorded 130 min post administration (MR_{130}), the formulation were ranked as ME 10% > ME 5% > LC > EM > Sol with ME 10% being significantly different from both EM and Sol

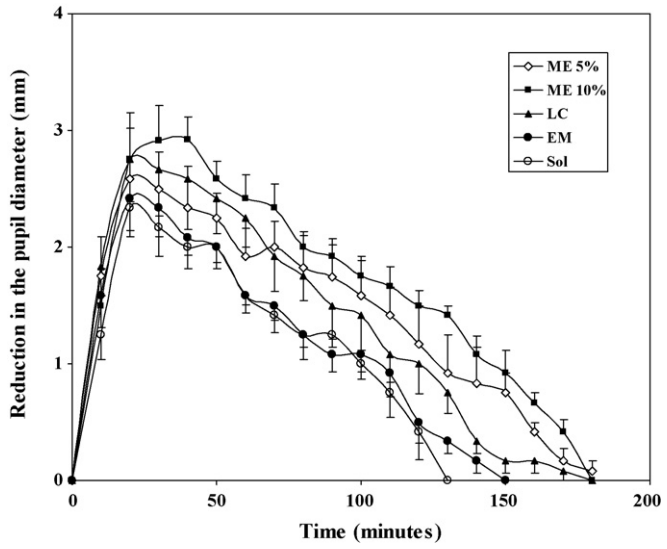

Fig. 4. Miotic response profiles obtained after topical application of microemulsion, lamellar liquid crystalline, coarse emulsion and aqueous solution formulations containing 1% (w/w) pilocarpine hydrochloride.

Table 2
Pharmacokinetic parameters calculated for pilocarpine hydrochloride miotic response obtained after topical application of microemulsion, liquid crystalline, emulsion and aqueous solution formulations

Formulation	T_{max} (min)	AUC_{0-180} (mm min)	MR_{130} (mm)
ME 5%	30.0 (6.32)	261.9 (35.7)*	0.917 (0.326)*
ME 10%	35.0 (7.18)	307.4 (22.9)**	1.42 (0.083)**
LC	26.7 (4.94)	246.7 (35.7)	0.750 (0.171)*
EM	21.7 (3.07)	188.3 (15.2)	0.333 (0.105)*
Sol	23.3 (3.33)	174.2 (13.9)	0

Values between brackets are S.E.M., $n = 6$.
* Significantly different from Sol.
** Significantly different from both Sol and EM. Individual P values are reported throughout the text.

($P < 0.001$ in both cases). All other formulations were significantly different from the Sol only (P values < 0.01 for LC and < 0.05 for ME 5% and EM, compared with Sol).

4. Discussion

The pseudo-ternary phase diagram for the non-ionic surfactants, sorbitan mono laurate (Crill 1) and polyoxyethylene (20) sorbitan mono-oleate (Crillet 4) with ethyl oleate (Crodamol EO, the oil component) and water has been previously reported (Alany et al., 2001). Three distinctive regions have been identified with the W/O ME undergoing phase transition to LC before transformation to O/W EM with increasing water content. This phase transition was associated with a change in the viscosity. This behaviour suggests a possible phase transition for the ME after topical application to the eye due to dilution with the resident tears. This study thus selected five different formulations containing increasing concentrations of water with pilocarpine hydrochloride being incorporated at 1% (w/w) as a model drug. Loading these formulations with pilocarpine hydrochloride did not alter the phase behaviour of the original formulations as has been previously reported by Alany et al., 2001. This indicated that the drug did not affect the original phase behaviour of the system, which is expected from a hydrophilic drug especially with systems containing non-ionic surfactants. Nevertheless, these phase changes were accompanied by a change in the viscosity and flow properties. The flow properties were monitored at 32 °C, which is the temperature of the eye surface. The ME 5% and ME 10% formulations showed a simple Newtonian flow with the latter showing higher viscosity values. The increase in viscosity with increasing water content suggested structuring of the system. For the LC formulation, the flow changed into a pseudo-plastic flow. This suggests that the lamellar LC system is arranged in such away that it can experience long-range due to the interactions between the comprising surfactant molecules with the viscosity decreasing with increasing the rate of shear. Upon increasing the rate of shear the LC structure is likely to be perturbed and as a result the intermolecular forces of attraction weekend. This results in a shear thinning flow behaviour that is favourable for ocular topical formulation with the viscosity reducing upon blinking. Further increase in water content will break the LC structure and the system reverts to the O/W EM as in case of the EM formulation in our case. This formulation showed a sharp decrease in viscosity with the flow becoming Newtonian.

The drug release data (Fig. 3) fitted matrix order kinetics in case of ME 5%, ME 10% and LC systems. This is expected for the W/O ME system whereby the oil acting as the external phase with the water droplets forming a nano-reservoir for the drug. This provides a matrix-like structure. For the LC system the drug will be dissolved in the aqueous domains of the lamellar structure, which again provide a matrix-like system. Once the phase transition takes place and an O/W EM is formed (in case of the EM formulation) the drug became available in the external phase with the release pattern being similar to that obtained from the aqueous solution. Ideally increasing the water content of any system should increase the rate of drug release especially for hydrophilic drugs. Our results revealed a release behaviour, which correlated differently with the water content of the formulations (Fig. 3d). Thus, increasing water content reduced the rate of drug release as we move from ME 5% towards the LC. This reduction in the release is due to structuring of the system and subsequent increase in viscosity. Moving to the EM formulation, which showed a reduction in viscosity, the drug release was significantly increased. The in vitro results, thus, highlighted that phase transition of such ME system may occur after application to the eye due to dilution by tears and sufficient mixing due to blinking. This transition affected the individual formulation's viscosity, the drug release and the retention time of the formulations in the eye. Enhancing the viscosity was reported as a mean of improving eye retention (Greaves et al., 1990; Le Bourlais et al., 1998). Accordingly, the recorded phase transition should affect the overall therapeutic efficacy of formulations in this case.

For evaluating therapeutic efficacy the miotic response was monitored. There were no significant differences between different formulations with respect to the T_{max} indicating the initial availability of the drug from all formulations. With respect to the

AUC_{0-180} and MR_{130} the tested formulations were ranked as ME 10% > ME 5% > LC > EM > Sol. ME and LC systems were significantly superior to SOL with ME 10% being significantly higher than the coarse EM as well. These results indicated the superiority of all colloidal formulations over the SOL. These systems can, thus, provide the required fluidity while retaining the therapeutic efficiency (Fig. 4).

Monitoring the precorneal clearance using gamma scintigraphy revealed that all phase transition formulations provided better retention compared with the solution (Alany et al., 2006). It should be noted though, that the reported preconeal clearance data indicated the superiority of the ME and LC formulations with the retention increasing with increasing viscosity. Subsequently, the formulations were ranked as LC > ME 10% > ME 5% > EM with all of them being retained significantly longer than the SOL (Alany et al., 2006). The LC has been previously shown to be the most viscous amongst the tested formulations with an apparent viscosity that is 10 folds greater than ME 5% and 10% (Alany et al., 2001). Stokes–Einstein's equation (Eq. (1)) states that the diffusion coefficient from a colloidal system is inversely proportional to the viscosity:

$$D = \frac{kT}{6\pi r\eta} \quad (1)$$

where D is the diffusion coefficient; k the Boltzmann constant; T the temperature; r the radius of the diffusing particles; η is the viscosity.

This equation could be used to explain our results. The high apparent viscosity of LC is expected to result in the slower drug diffusion/release when compared to both ME systems. For the in vitro release experiment, the efficient mixing process in the Franz diffusion cells resulted in a complete phase transition of both ME 5% and ME 10% to LC and as such comparable in vitro release profiles were obtained (Fig. 3). The phase transition was confirmed by the visual and light microscope examination that was conducted on these formulations at the end of the in vitro release experiment. On the other hand, the mixing and subsequent phase transition is less likely to happen in vivo due to the minimal blinking and smaller volume of resident tears in the rabbit eye compared to human eye (Worakul and Robinson, 1997).

It follows that both ME formulations were less likely to undergo dilution and phase transition in vivo compared to in vitro and as such the drug was diffusing from an almost intact, less viscous ME (5% or 10%) rather than the more viscous LC system, hence more available for in vivo release. Therefore, it could be suggested that ocular retention is not the only factor affecting the efficacy of ocular formulation, but actually a combination of both processes, namely ocular retention and drug release.

To further explain the difference between the ocular retention results (Alany et al., 2006) and the therapeutic response obtained here, the affinity and mixing with the pre-corneal tear film (PCTF), which is a prerequisite for ocular availability was also considered. The oily nature of the ME system provided greater affinity for the ME to mix with the surface oily layer of the PCTF and thus subsequent mixing with the tear film, relative to the LC system. This highlights the fact that successful ocular formulations should mix with PCTF, release the drug and have good ocular retention. ME 10% provided the best compromise with respect to the three above-mentioned parameters. This accounts for the difference between the ocular retention data (Alany et al., 2006) and the recorded therapeutic response.

Similar to our findings improved ocular availability of dexamethasone was reported after incorporation into a microemulsion system (Fiahlho and Cunha, 2004). In addition, the miotic activity and the AUC of pilocarpine were improved after incorporation into a micellar solution (Pepić et al., 2004). These findings together with our results indicate a possible enhancing effect of the surfactant components of the ME. Furthermore, a microemulsion was dispersed in a hydrogel with the aim of increasing ocular retention. This system was suggested as a potential ophthalmic drug delivery vehicle (Gulsen and Chauhan, 2005).

Although systems with increased viscosity can provide higher ocular retention, the rheological characteristics, are of importance for the ocular application with pseudo-plastic systems being desirable as they show less resistance to blinking (Saettone et al., 1984). The current study reported on microemulsion systems displaying reasonable fluidity to allow ease of administration yet are likely to undergo phase transition provided there is efficient mixing with the resident tears in the eye. This phase change leads to viscosity increase and change in flow properties towards the desirable pseudo-plastic behaviour, thus providing increased ocular retention with improved bioavailability.

These formulations thus combine the conventional advantages of microemulsion systems (e.g. thermodynamic stability, ability to incorporate drugs with different physicochemical properties, ease of application and possible penetration enhancing effect of the surfactant components) along with the ocular retention of normal viscous formulations. Moreover, and upon phase transition due to tear dilution, the resultant LC system will display the desirable high viscosity and pseudo-plasticity, where the formulation is viscous enough to promote ocular retention, yet can thin and display less resistance to blinking. Such formulations clearly offer additional advantages over the traditional viscous formulations such as eye ointments.

5. Conclusion

W/O microemulsion systems can be regarded as potential ocular delivery systems for hydrophilic drugs. Those undergoing phase transition upon dilution with aqueous medium such as tears can be ideal for ophthalmic delivery as they have the required fluidity to allow ease of instillation, yet may undergo viscosity increase after application yielding the desirable pseudo-plastic system and providing longer ocular retention while maintaining the therapeutic efficiency of the parent microemulsion formulation. The ME 10% system, which is close to the W/O ME–LC phase boundary showed a potential as a topical ocular drug delivery formulation as it provided the highest efficiency with a chance of forming the desirable viscous pseudo-plastic system after dilution with resident tears. These findings warrant further investigation in human volunteers.

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