JPP Journal of Pharmacy and Pharmacology

JPP 2003, 55: 741–748

Received November 19, 2002
Accepted February 28, 2003
DOI 10.1211/0022357021017
ISSN 0022-3573

Microemulsions as colloidal vehicle systems for dermal drug delivery. Part IV: investigation of microemulsion systems based on a eutectic mixture of lidocaine and prilocaine as the colloidal phase by dynamic light scattering *

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Abstract

Stable oil-in-water (o/w) microemulsions used as vehicles for dermal drug delivery have been developed using lidocaine (lignocaine) and prilocaine in oil form (eutectic mixture), a blend of a high (Tween 80, hydrophilic–lipophilic balance (HLB) = 15.0) and a low (Poloxamer 331, HLB = 1.0) HLB surfactant and propylene glycol–water as hydrophilic phase. These microemulsions were able to solubilize up to 20% eutectic mixture of lidocaine and prilocaine without phase separation. The dispersity of the oil phase was investigated by dynamic light scattering. Small colloidal droplets for stable microemulsions of 5∼10 nm were observed. At constant surfactant and hydrophilic phase concentration, increasing the total drug concentration in the microemulsion resulted in an increase in the droplet size of the dispersed, colloidal phase. It was observed that a monolayer of surfactant surrounds the oil (eutectic mixture) core. Colloidal droplets of the microemulsion interact via hard sphere with supplementary attractive interaction. This observed interparticle attractive interaction could explain the observed phase behaviour with respect to change in the basicity of the hydrophilic phase as well as the increase in volume fraction of the dispersed, colloidal phase. It was also observed that the stability and size of this dispersed phase depends on the pH of the composition. Because these microemulsions formed stable, isotropic systems in the range of pH 9.5 to 10.4 with alkali buffer or NaOH solution instead of water as hydrophilic phase, so one can produce microemulsions in this pH area.

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Funding: The Deutsche Forschungsgemeinschaft (GK 134) is gratefully acknowledged for the stipend of A. Shukla.

* Part I: *Pharm. Res*. 2002 **18**: 881–886. Part III: *J. Pharm. Sci*. 2003 **92**: 730–738

Introduction

Microemulsions within the scope of this work can be defined according to Danielson & Lindaman (1981) as systems of water with or without electrolyte, oil and surfactants, which are single isotropic and thermodynamically stable solutions. The formation of microemulsions usually involves a combination of four components, namely oil, water, surfactant and cosurfactant. The tendency towards water-in-oil (w/o) or oil-in-water (o/w) microemulsion is dependent on the properties of the oil and the surfactant, the water-to-oil-ratio and the temperature. In pharmacy, microemulsions have been examined as good vehicles for transdermal application. The advantage of microemulsions as drug delivery vehicles is the improvement of drug delivery of both lipophilic and hydrophilic drugs, compared with conventional vehicles, as well as the potential for enhanced absorption due to surfactant-induced permeability changes, depending on the constituents used for the microemulsion vehicle (Ritschel 1991; Boltri et al 1994; Trotta et al 1994, 1997; Kriwet & Müller-Goymann 1995; Sarciaux et al 1995; Delgado-Charro et al 1997; Dreher et al 1997). In the last few decades, extensive studies have been performed on microemulsions using cosurfactants such as short-chain alcohols. The inclusion of short- or medium-chain alcohols as cosurfactants limits the potential use of the microemulsion due to their high toxicity and irritancy. Therefore, we were particularly interested in the characterization of microemulsions consisting of biologically active substances (lidocaine (lignocaine) and prilocaine) as a dispersed, colloidal phase and pharmaceutically acceptable surfactants as continuous phase.

In this study, o/w microemulsions were formulated using the eutectic mixture of lidocaine and prilocaine as lipophilic colloidal phase, a blend of a high (Tween 80) and a low (Poloxamer 331) hydrophilic–lipophilic balance (HLB) non-ionic surfactant, and a hydrophilic phase (propylene glycol–water) which are of pharmaceutical interest. Lidocaine and prilocaine have been shown to form a eutectic mixture at room temperature (Broberg & Evers 1985), the composition of which is approximately 1:1 w/w (Brodin et al 1994). Hence is derived the name eutectic mixture of local anaesthetics, or EMLA. These microemulsions are significantly better than EMLA cream (Krause 2001). Although eutexia of lidocaine and prilocaine tends to reduce the aqueous solubility of each component, the effect on their combined solubility is small (Danielson & Lindaman 1981). Furthermore, this solid–solid interaction yields a liquid that can be emulsified in water rather than suspended. The liquid state of the diffusible species opens possibilities for increasing percutaneous absorption (Ritschel 1991; Trotta et al 1994, 1997), thus the topical bioavailability of these two local anaesthetics increases.

For selecting a suitable (microemulsion) system for drug delivery, it is important to know something about the physico-chemical properties of microemulsions, such as drug solubility, area of microemulsion in the phase diagram and the resulting size of microemulsion droplets. A particular difficulty concerning their use as a dermal drug delivery system is the direct and unambiguous determination of droplet radius of the colloidal phase, since it is expected to be a strong function of particle–particle interaction. The small size of the colloidal droplets of microemulsions (typically less than 100 nm) necessitates the use of scattering techniques such as neutron and light scattering. In part I (Shukla et al 2002) of our publication series, we characterized the droplet size of o/w microemulsions for dermal administration, that contained different kinds of pharmaceutical oils, using dynamic light scattering (DLS) and small angle neutron scattering (SANS) and we modelled a microemulsion droplet as a layered sphere consisting of an oil core and a penetrable shell of surfactants. In Part II (Shukla et al 2003b), DLS measurements were used to characterize w/o microemulsions containing different kinds of surfactants or dispersed phase, or mixture of them. As discussed in Part I and Part II of this series, a hard-sphere model, which prevents the overlap of different hard-sphere droplets, is used to correct the results for particle–particle interaction. In part III (Shukla et al 2003a), a suitable interparticle interaction model is proposed for o/w microemulsions stabilized by non-ionic surfactant. From the total interparticle interaction energy calculated using our proposed interaction model, parameters describing the stability of our systems are estimated. In this study, dynamic light scattering (DLS) measurements have been used to determine whether or not a microemulsion is indeed produced. Scattering techniques collectively suffer from a disadvantage in that to obtain a reliable estimate of particle size, measurement should be made at a range of low-colloidal-phase volume fractions and should be extrapolated to infinite dilution to avoid the problems encountered as a result of particle–particle interactions. In common with many microemulsions, these systems could not be diluted to a very low-colloidal-phase volume fraction without phase separation. Consequently, to allow meaningful calculation of droplet size, it is necessary to correct scattering measurement in high concentration regions and an appropriate model is then used to correct the results for particle–particle interaction. Therefore, a first series of microemulsions was prepared to investigate the particle–particle interaction. For this purpose, linear interaction theory was used (Corti & Degiorgio 1985). A second series of microemulsions was prepared to investigate the effect of increasing concentration of drug (lidocaine and prilocaine) on droplet size. In a third series of microemulsions, the effect of pH on droplet size was investigated.

Material and Methods

Chemicals

Tween 80 and propylene glycol and were purchased from Caesar & Loretz (Hilden, Germany). Poloxamer 331 was kindly provided by C. H. Erbsloeh (Krefeld, Germany). Lidocaine was purchased from Sigma-Aldrich-Chemistry GmbH (Deisenhofen, Germany) and prilocaine was from Synopharm GmbH (Barsbüttel, Germany). Prilocaine and lidocaine were used as free bases. Water was bi-distilled quality. The chemical structure of components used in the preparation of microemulsions is shown in Figure 1.

Sample preparation

The basic microemulsion was prepared with a eutectic mixture of lidocaine and prilocaine 1:1 w/w (5% w/w), Poloxamer 331–Tween 80 3:2 w/w (20% w/w) and propylene glycol–H_2O 2:1 w/w (75% w/w). Either keeping a fixed surfactant and continuous phase content, or keeping a fixed [eutectic mixture]/[surfactant] molar ratio, defined as μ, the eutectic mixture concentration was increased to prepare a series of o/w microemulsions. To prepare microemulsions with different pH values, NaOH was added to the continuous phase of the basic microemulsion. The composition of the microemulsions is summarized in Table 1.

A complication arose in estimating the volume fraction, ϕ, for the microemulsions because the partition coefficients for surfactants were not known. It was assumed that the surfactant was completely incorporated into the droplet phase. For this assumption, the volume of the dispersed phase was just equal to the sum of the volumes of the surfactants and the added oil. Thus, the volume fraction (ϕ) of the microemulsion droplets could be defined as:

$$\phi = \frac{v_s + v_o}{v_s + v_i + v_o} \quad (1)$$

where v_s, v_i and v_o are the volume of surfactant, hydrophilic phase and oil, respectively.

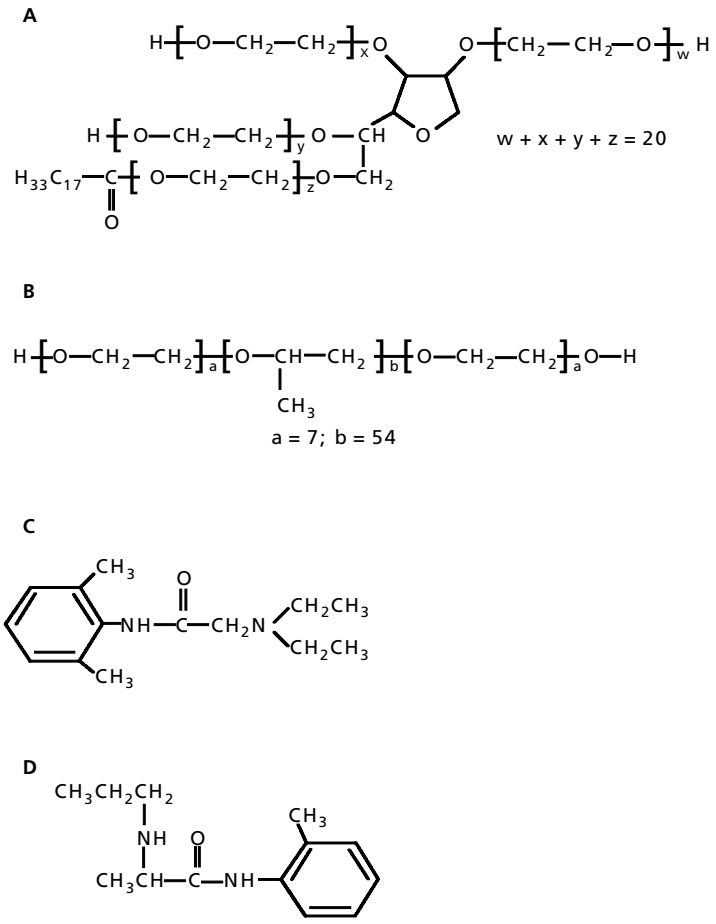

Figure 1 Chemical structure of Tween 80 (polyoxyethylene sorbitan mono-oleate, MW ~ 1309 g mol^{-1}, HLB = 15) (A), Poloxamer 331 (polyoxyethylene–polyoxypropylene–block copolymer, MW ~ 3800 g mol^{-1}, HLB = 1) (B), lidocaine (2-diethylamino-*N*-2,6-dimethylphenyl, MW = 234.3 g mol^{-1}) (C) and prilocaine (*N*-2-methylphenyl-2-propylamino, MW = 220.3 g mol^{-1}) (D).

Data acquisition and statistical analysis

Dynamic light scattering

The light scattering hardware set-up consisted of commercially available equipment for simultaneous static and dynamic experiments from ALV-Laser Vertriebsgesellschaft m.b.H. (Langen, Germany). A green Nd:YAG DPSS-200 laser (532 nm) from Coherent (Auburn, USA) with an output of 200 mW was used. The thermostated sample cell was placed on a motor-driven precision goniometer (±0.01°), which enabled the photomultiplier detector to be moved from 20° to 150° scattering angle. The intensity time-correlation functions (ITCF) $g^{(2)}(\tau)$ were recorded with an

Table 1 The composition of the microemulsions studied.

	Microemulsion A (Constant μ)				**Microemulsion B (Different μ)**					**Microemulsion C (Different pH)**				
Lidocaine–prilocaine (1:1 w/w)	5	10	15	20	2	5	10	15	20	5	5	5	5	5
Poloxamer 331–Tween 80 (3:2 w/w)	5	10	15	20	20	20	20	20	20	20	20	20	20	20
Water–propylene glycol (1:2 w/w)	90	80	70	60	78	75	70	65	60	75	75	75	75	75
NaOH (M)	—				—					0	Buffer	0.01	0.1	1

Content in % w/w except concentration of NaOH, which is given in term of molarity (M).

ALV-5000E multiple tau digital correlator with fast option. The minimal sampling time of this correlator is 12.5 ns. The cylindrical sample cells are made of Suprasil quartz glass by Hellma (Muellheim, Germany) and had a diameter of 10 mm. Before measurements, the samples were filtered through 1.2-μm pore-size filter (Sartorius, Goettingen, Germany) into dust clean sample cells.

The normalized field autocorrelation function $g^{(1)}(\tau)$ is derived from the measured $g^{(2)}(\tau)$ via Siegert relation (Equation 2; Berne & Pecora 1975).

$$g^{(1)}(\tau) = \sqrt{1 - g^{(2)}(\tau)} \tag{2}$$

The normalized field autocorrelation function $g^{(1)}(\tau)$ for a collection of monodisperse hard spheres will decay as a simple exponential (Berne & Pecora 1985). If the system has a distribution of particle sizes, the autocorrelation function can be described by a sum of exponentials:

$$\left|g^{(1)}(\tau)\right| = A_0 + A_1 \sum_{m=1}^{\infty} \exp\left(\frac{(-\tau)^m}{m!}\Gamma_m\right) \tag{3}$$

where m corresponds to the number of different sizes, A_0 is the base line due to background scattering ($A_0 \sim 0$) and A_1 is the 0 delay ($\tau = 0$) intercept ($A \leq 1$). In such a case, the correlation function can be analysed in terms of moments (or cumulants) Γ_m (Koppel 1972). In the analysis, in terms of cumulant, the logarithm of the normalized field autocorrelation function $g^{(1)}(\tau)$ minus A_0 is expanded as a polynomial:

$$\log_e\left[g^{(1)}(\tau) - A_0\right] = \log_e(A_1) - \Gamma_1\tau + \frac{1}{2}\Gamma_2\tau^2 - \frac{1}{6}\Gamma_3\tau^3 + \cdots\cdots \tag{4}$$

In practice, for normal experiments with a limited number of delays, τ, only the first two or three cumulants can be determine with reasonable confidence. In this study, the auto correlation functions, $g^{(1)}(\tau)$, were fitted by a second order cumulant.

The fitting procedure was the first to use a single exponential to fit for a base line because the second cumulant Γ_2 is very sensitive to the correct value of the baseline A_0. Then base line estimate was subtracted from the data, logarithms of these data were plotted as a function of the delay time, τ and fitted by a polynomial equation (4) from which first cumulant Γ_1 and second cumulant Γ_2 were extracted. Last correlation channel included in the fit for cumulant model if $g^{(1)}(\tau) >=$ baseline is valid. Residuals are calculated using equation 5:

$$\Delta \ln\left(g^{(1)}(\tau) - A_0\right) = \ln\left(g^{(1)}(\tau) - A_0\right) - \sum_{n=0}^{j} a_n t_i^n \tag{5}$$

where i is the index of correlation channels, j is the order of the polynomial fit and a_n is the polynomial coefficients. One typical example for the fit of the autocorrelation function $g^{(1)}(\tau)$ is shown in Figure 2.

As shown in Figure 2, residuals are randomally distributed; this shows that there is no schematic error in the fitting.

The apparent diffusion coefficient, D_{app}, can be obtained from the first cumulant as:

$$D_{app} = \frac{\Gamma_1}{q^2} \tag{6}$$

From the second cumulant, the poydispersity index, σ_s, can be obtained as (where R is the droplet size and $\overline{R}$ is the mean droplet size):

$$\sigma_s = \sqrt{\frac{\overline{R^2}}{\overline{R}^2} - 1} = \sqrt{\frac{\Gamma_1}{\Gamma_2^2}} \tag{7}$$

D_{app} has been corrected using a linear interaction (Corti & Degiorgio 1985) theory, in which the diffusion coefficient depends on the volume fraction, ϕ, of the diffusing particles according to equation 8.

$$D_{app} = D_0(1 + \alpha\phi) \tag{8}$$

where α is the virial coefficient of diffusion.

Knowing the value of D_0, the hydrodynamic radius R_h can be calculated by the Stokes–Einstein equation:

$$R_h = \frac{k_B T}{6\pi\eta D_0} \tag{9}$$

where k_B is Boltzmann's constant, T is the absolute temperature and η is the coefficient of viscosity of the solvent (the continuous phase in the case of microemulsion).

Refractive index and dynamic viscosity

The refractive index of all samples was measured using an Abbé Refractometer (ABBEMAT; Dr Kernchen GmbH, Seelze, Germany) at 25.0 ± 0.2 C. The dynamic viscosity, η can be defined as:

$$\eta = \frac{[\text{shear stress}]}{[\text{shear rate}]} \tag{10}$$

The dynamic viscosity of the external phase (propylene glycol–H_2O) was determined at different shear rates (0.2–200 s^{-1}) using a Rotational Viscometer RFS II based on the couette-principle (Rheometrics Scientific, Bensheim, Germany) at 25.0 °C. Data were analysed with the help of computer program RHIOS, version 4.2. It was observed that viscosity increases proportionally as the shearing stress and rate of shear increased, suggesting the Newtonian behaviour of the fluid. Refractive index and dynamic viscosity were necessary to calculate the hydrodynamic radius (R_h) from the diffusion coefficient.

Results and Discussion

Despite of plenty of publications regarding dermal local anaesthetics (McCafferty et al 1988, 1989; McCafferty &

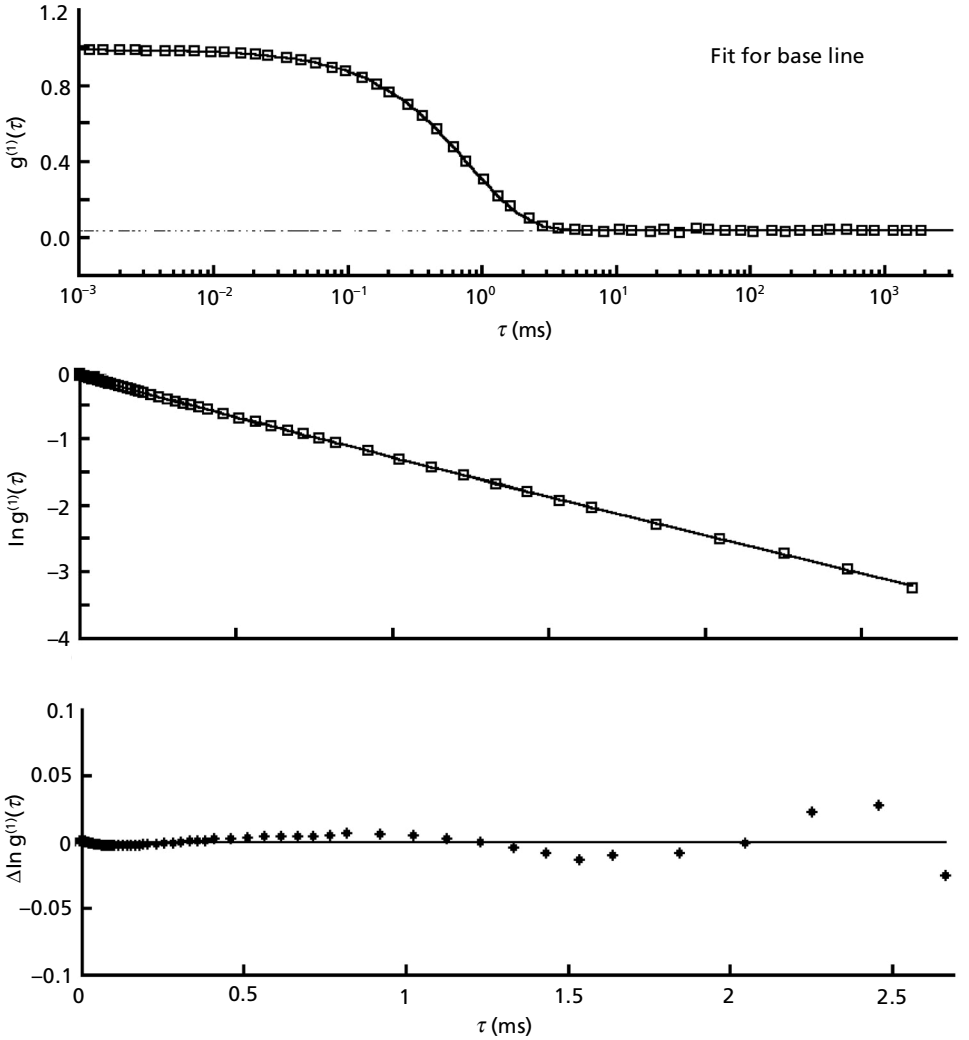

Figure 2 Examples of dynamic light scattering autocorrelation data obtained from an o/w microemulsion (lidocaine–prilocaine 10%, Poloxamer 331–Tween 80 10% and water–propylene glycol 80%) at temperature 25 °C. The autocorrelation data and single exponential fit are plotted in the upper graph. Only the 3rd point of the autocorrelation data is plotted. Data and cumulant fit of order 2 are plotted in middle graph. The residuals (deviations of the experimental points from fitting line) are plotted on the lower graph. This shows no systematic error. The data were taken at scattering angle 90°.

Woolfson 1993), there are only very few investigations of pharmaceutical preparations comprised of local anaesthetics as dispersed, colloidal phase (Zabka & Benkova 1995; Changez & Varshney 2000; Raymond et al 2000). These colloidal vehicle systems offer very good conditions for the fast and deep penetration of biologically active substances into the skin layer (Krause 2001). This study relates the characterization of pharmaceutical microemulsions comprised of a eutectic mixture of local anaesthetics (lidocaine and prilocaine) in oil form. For preparing suitable microemulsions for dermal application, it is important to know the effectiveness of the different concentration of components used in the formulation of microemulsions. Without any oil, lidocaine–prilocaine mixtures as a lipophilic phase and buffer–propylene glycol as a hydrophilic phase formed thermodynamic stable microemulsions. These stable microemulsions can solubilize up to 20% eutectic mixture of local anaesthetics (lidocaine and prilocaine). For practical applications, the effect of pH on microemulsions is also examined. To increase the pH of the microemulsion, water was replaced by Sörensen Clark buffer and different concentrations of NaOH.

To discuss in detail the observed stability of our systems, the particle size distribution of the internal phase using DLS measurements, as well as the pH values of the overall systems, is presented. Particle size distribution is one of the most important characteristics of microemulsions for the evaluation of their stability and penetration mechanism into the skin (Constantin & Yiv 1995; Mueller & Mueller 1984).

All DLS measurements were made at different scattering angles between, 80°, 90° and 100°, at a temperature of 25 °C. The intensity time-correlation functions (ITCF) corresponding to one set of experimental parameters were measured five times and data used for fitting were averaged over these five measurements. Initial studies indicated that the microemulsions were too small to exhibit significant angular dependence, therefore results used for discussion are an average of the results obtained at three different angles.

In first series of microemulsions, systems were diluted with continuous phase (buffer–propylene glycol) keeping a constant molar ratio ($\mu = 9.5$) to preserve a constant droplet radius. The measured diffusion coefficients for this series varied as a function of ϕ (Figure 3). The virial coefficient of diffusion ($\alpha = -0.71 \pm 0.13$) and the free particle diffusion coefficients, D_0 (Table 2), were obtained by linear regression fittings of equation 8 in the range of volume fraction, $0.2 < \phi < 0.4$. The hydrodynamic radius, R_h (which is supposed to consist of the oil core and a strongly bounded surfactant film, including possible solvent molecules which migrate with the droplet), was calculated according to equation 9 (Table 2). To estimate the magnitude of the attraction and repulsion giving rise to α, the measured value is generally compared with the $\alpha^{HS} \sim 2$ for hard-sphere repulsion. If $\delta\alpha = \alpha - \alpha^{HS}$ is positive, the droplets have a net repulsive interaction while if $\delta\alpha$ is negative, the droplets are attractive (Langevin & Rough 1999). We obtained $\delta\alpha \sim -2.71$, which suggests that microemulsion droplets interact via hard-sphere interaction with supplementary attractive interaction. This result shows that attractive dispersion forces are dominant in comparison with the indirect repulsive interactions associated with a given configuration of the microemulsions. A dispersion attractive force arises from the fact that in any material thermal motion and quantum effects produce local charge fluctuations. The resulting transient electric field exerts an attractive force on surrounding material. Such a system undergoes Brownian motion in the usual fashion and the attractive energy gives rise to sticky interactions due to surface adhesion upon collision (D'Angelo et al 1996). Such sticky encounters result in short-lived clusters that may exchange solubilized material before dissociating into separate droplets. Fluctuations in the flexible surface of the surfactant film can produce steric interactions that accomplish the stability of microemulsions (Helfrich force). One other noticeable thing about the results obtained is a definite departure of apparent diffusion from the fitting line at high dilution ($\phi \sim 0.1$). Increase of the apparent diffusion coefficient at high dilution suggests that shape of the microemulsion is unsymmetrical and small because it is strongly strained by interactions with solvent molecules at low volume fraction. For microemulsions of higher volume fraction ($\phi > 0.4$), increase of sticky attractive potential is expected causing coagulation processes. This is consistent with our observed results that microemulsions are not formed at $\phi > 0.4$. So it is found that stable microemulsions interacting via hard-sphere interaction, with supplementary attractive interaction, lie in the range of volume fraction $0.2 < \phi < 0.4$.

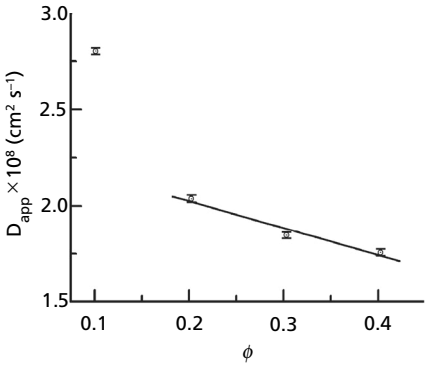

Figure 3 Measured diffusion coefficient, D_{app}, of microemulsions having constant molar ratio of oils and surfactants, μ (microemulsion A), versus volume fraction, ϕ.

Table 2 Dynamic light scattering results for o/w microemulsions studied.

	Microemulsion A				Microemulsion B					Microemulsion C				
ϕ	0.10	0.20	0.30	0.40	0.22	0.25	0.30	0.35	0.40	0.25	0.25	0.25	0.25	0.25
μ	9.50	9.50	9.50	9.50	0.95	2.37	4.75	7.12	9.5	2.37	2.37	2.37	2.37	2.37
pH	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.8	9.9	10.4	12.0
$D_{app} \times 10^8$	2.80	2.04	1.85	1.76	4.57	4.03	3.06	2.34	1.76	3.76	3.63	3.89	1.03	1.54
(cm^2 s^{-1})	±0.02	±0.02	±0.02	±0.02	±0.03	±0.03	±0.02	±0.02	±0.02	±0.04	±0.05	±0.05	±0.04	±0.02
R_{app} (nm)	8.2	11.3	12.4	13.1	5.03	5.72	7.51	9.81	13.1	6.11	6.32	5.91	22.2	14.9
	±0.05	±0.10	±0.10	±0.10	±0.03	±0.03	±0.05	±0.07	±0.10	±0.07	±0.10	±0.08	±0.10	±0.10
$D_0 \times 10^8$ (cm^2 s^{-1})	—	2.31	2.31	2.31	5.42	4.90	3.89	3.13	2.46	—	—	—	—	—
R_h (nm)	—	9.96	9.96	9.96	4.24	4.69	5.91	7.36	9.35	—	—	—	—	—
σ_s	0.25	0.25	0.33	0.42	0.46	0.49	0.49	0.47	0.42	0.41	0.43	0.45	0.42	0.43
	±0.04	±0.04	±0.04	±0.04	±0.03	±0.03	±0.03	±0.04	±0.04	±0.04	±0.04	±0.05	±0.04	±0.10

Errors are smaller than ±2% for the radii and ±10% for the standard deviations σ_s.

In a second series of microemulsions, microemulsions were prepared at different value of μ. Hydrodynamic radius, R_h, calculated from equations 3 and 4 using value of $\alpha = -0.71$ (obtained from first series of stable microemulsions in the range of volume fraction $0.2 < \phi < 0.4$) is listed in Table 2. As shown in Figure 4, incorporation of lidocaine and prilocaine caused an increase in droplet radius. A relationship of R_h and μ can be expressed by empirical formula:

$$R_h[\text{nm}] = (3.98 \pm 0.058) + (0.22412 \pm 0.035)\mu + (0.036 \pm 0.004)\mu^2 \quad (11)$$

It should be noted that the coefficient of the third quadratic term in equation 11 is very small. One can thus easily conclude that there is a reasonable linear relationship between R_h and μ, provided μ is small, which is consistent with results obtained for microemulsions (Visser et al 1988; Charlton & Doherty 2002). The definite departure of R_h from linear relationship at higher μ may be attributed to the shape fluctuations of the droplet. Using the simple geometry of a spherical droplet, one can obtain a relation between μ and R_h as:

$$R_h = 3\frac{V_d}{a_s}\mu + L \quad (12)$$

where V_d is the molecular volume of the dispersed phase, a_s is the cross-sectional area occupied by the hydrophobic group of surfactants at the interface and L is the surfactant shell thickness.

Comparing equations 11 and 12, one can obtain $L = 3.98$ nm. The length of the hydrophilic chain is 3.6 nm and 2.45 nm for Tween 80 and Poloxamer 331, respectively (Shukla et al 2002). This suggests that a monolayer of surfactants surrounds the oil (lidocaine and prilocaine) droplet.

In the third series of microemulsions, the effect of pH on droplet size was investigated. The pH value of the systems rose with increasing basicity of the hydrophilic phase. The diffusion coefficient and droplet size obtained from these systems are listed in Table 2. The droplet size of local anaesthetics in oil form was observed to depend on the pH of the composition, which is consistent with the results obtained from microemulsions having local anaesthetics as dispersed phase (Raymond et al 2000). It was observed that the droplet size was almost the same for microemulsions with water, buffer and 0.01 M NaOH as hydrophilic phase but that with a ten-fold increase in NaOH concentration (0.1 M NaOH), droplets of more than three times the size were formed. A further ten-fold increase in NaOH concentration (1 M) resulted in unstable nanoemulsions. This behaviour can be explained with the help of interactions between the microemulsion droplets. At the high concentration of surfactant (~20% surfactant) that occurred in our systems, at the water side, the hydrated chain of adsorbed non-ionic surfactant molecules repel one another and try to curve the surface around the oil side. This mutual repulsion of hydrated chain can be weakened by adding electrolyte (NaOH) to the aqueous phase and thus an increase in NaOH concentration promotes the attractive part of interaction (Janich et al 1998). Probably, for microemulsions of higher NaOH concentration (> 0.01 M), the attractive potential is strong enough to start a droplet coagulation process, causing an increase in the radius.

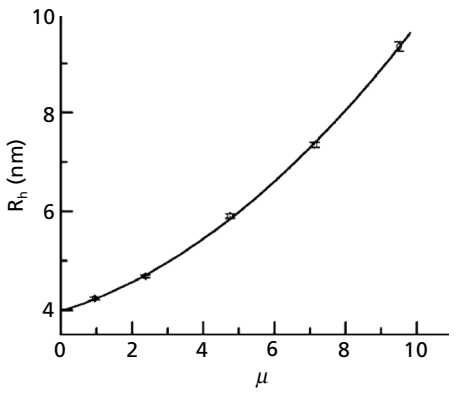

Figure 4 Hydrodynamic radius, R_h, of microemulsions (microemulsion B) versus molar ratio of oils and surfactants, μ.

Another possible explanation for droplet growth at 0.1 M NaOH concentration is that the solubility of lidocaine and prilocaine in the aqueous phase decreases with increase of pH. Lidocaine and prilocaine possess both pK_a value of 7.9. In a microemulsion with a pH value of 10.4, only 0.3% of the local anaesthetics (lidocaine and prilocaine) will be solubilized in the aqueous phase, while 2.5% of the local anaesthetics will be solubilized in aqueous phase of microemulsions with a pH value of 9.5. This may be one of the reasons for the larger droplet radius of the microemulsion droplet at 0.1 M NaOH concentration. Further increase of electrolyte (NaOH) or change in pH have a devastating effect on microemulsion stability by further lowering the repulsive energy barrier and allowing droplets to expel the colloidal phase, so that smaller droplets would be formed at the cost of low stability. For that reason our described interaction potential supports the observed stability for the low NaOH concentration region as well as the droplet growth and stability loss for the high NaOH concentration region.

It has been predicted theoretically for stable microemulsions, using the multiple chemical equilibrium approach (Eriksson & Ljunggren 1995), that the size polydispersities should be in the range of 10–45%. It should be noted that the polydispersities of our system lie in the range 25–50%, which is the upper end of what is expected, both theoretically and experimentally, for the polydispersity of stable microemulsion droplets. A possible explanation for the large polydispersity is that the cumulant analysis (representing only a small correction to the shape of the correlation function) overestimates the polydispersity of microemulsion droplets (Yan & Clarke 1990; Ricka et al 1991; Chirst & Schurtenberger 1994).

Conclusions

In summary, o/w microemulsions, used as vehicles for dermal drug delivery, were formulated using lidocaine and prilocaine in oil form (eutectic mixture) as dispersed,

colloidal phase. These microemulsions were able to solubilize up to 20% local anaesthetics without phase separation. Because these microemulsions formed stable, isotropic systems in the pH range 9.5–10.4 with alkali buffer or NaOH solution, so one can produce microemulsions in this pH area. Existence of colloidal microemulsion droplets and their particle size stability were assessed by dynamic light scattering. In our analysis, linear interaction theory is used in the interpretation of data obtained from concentrated systems.

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