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Inhibition of Ostwald ripening in local anesthetic emulsions by using hydrophobic excipients in the disperse phase

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Abstract

The stability of submicron emulsions of different local anesthetic/analgesic substances was investigated in the presence and absence of different hydrophobic excipients (ripening inhibitors). Ostwald ripening was believed to be the underlying mechanism for the instability of these emulsions. In the absence of ripening inhibitors, the mean droplet size of the emulsions increased from 100 nm to about 4–5 μm within an hour of manufacture. The addition of a small amount of a second component of lower solubility to the disperse phase decreased the rate of Ostwald ripening, producing good stability of the emulsions. The efficiency of the ripening inhibitors was directly proportional to their solubility in the disperse phase, i.e. the water. The lower the solubility, the more effective the stabilization of the emulsions. The experimentally observed rates of increase in droplet size in the emulsions were closely correlated with those predicted according to the Liftshitz–Slezov–Wagner (LSW) theory.

Keywords: Local anesthetics; Submicron emulsion stability; Ostwald ripening; Ripening inhibitors

1. Introduction

In a lyophobic sol, a foam, or an emulsion, the reservoir of excess free energy in the interfacial region gives rise to an overall free energy for the system that is well above its global minimum. Such a colloid cannot be formed by spontaneous dispersion, and, when formed, it is thermodynamically unstable. Any apparent stability must therefore be regarded as a purely kinetic phenomenon.

An emulsion is a system consisting of two immiscible liquid phases, one of which, in fine droplets, is dispersed throughout the other, the system being stabilized by a third component, the emulsifying agent. Most emulsions have droplets with diameters of 0.1–100 μm. The instability of an emulsion will appear as phase separation due to creaming (density differences), flocculation (aggregation through interparticle collision), and coalescence (fusion of separate droplets). The process of droplet coalescence is the normal way in which an emulsion coarsens with time, i.e. the mean particle size of the droplet increases upon storage.

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There is a fourth mechanism which causes emulsion instability, provided that the droplets are small and the disperse phase has a finite solubility in the continuous phase. This is known as Ostwald ripening (Ostwald, 1900), or molecular diffusion, and arises as a consequence of the Kelvin effect, which describes the effects of curvature on the chemical potential (Thomson, 1871). This may be written in the form

$$\mu_r - \mu_\infty = 2\gamma V/r \quad (1)$$

where μ_r is the chemical potential of a small particle of radius r, μ_∞ is the chemical potential of the bulk of the same substance, V is the molar volume, and γ is the interfacial tension. Thus, for an oil of low water solubility (Henry's law region), the chemical potential can be derived from the concentration according to the following:

$$\mu_r - \mu_\infty = \mathrm{RT} \ln (C_r/C_\infty) \quad (2)$$

where C_r is the solubility of an oil droplet of radius r and C_∞ is the solubility of the bulk oil. This increase in solubility will make the small emulsion droplets thermodynamically unstable with respect to the larger ones. The relevant size for Ostwald ripening falls in the range 0.1–0.5 μm and below. Once the small droplets have been dissolved, the system should stabilize with respect to this phenomenon (Davis and Smith, 1976).

The most complete theory for calculating the rate of Ostwald ripening is that of Lifshitz and Slezov (1959, 1961) and, independently, Wagner (1961), referred to as the Liftshitz–Slezov–Wagner (LSW) theory. This analysis proposes that after a sufficient time the Ostwald ripening process enters a stationary state in which the cube of the mean particle radius increases linearly with time and the shape of the particle size distribution normalized by the mean radius is invariant with time. The process is assumed to be diffusion controlled, i.e. the rate-limiting step of the growth rate is the diffusion of the dissolved droplet phase through the bulk phase and there is no barrier to the passage of the solute across the interface.

During the development of submicron o/w emulsions of isopropyl-methyl-[2-(3-propoxy-phenoxy)-ethyl]-amine (amino diether), a new local anesthetic/analgesic compound (Table 1), instability was observed after an unexpectedly short time. Amino diether is a strong base with a *p*Ka of 9.3 and a water solubility of about 0.19 mg/ml at 25°C in deionized water. The substance has a very low melting point, and thus is an oil at room temperature.

This work shows that Ostwald ripening was the reason for the observed instability of the o/w emulsions investigated. We also show how the rate of the Ostwald ripening process can be reduced using different hydrophobic excipients (also referred to as ripening inhibitors).

The amino diether emulsions were investigated with respect to the growth of droplet size as a function of time in the absence and presence of different additives. The stabilities of these emulsions were also compared with an emulsion having the same composition but containing a eutectic mixture of two well-known local anesthetics, lidocaine and prilocaine (L-P), as the active substance (Table 1). The experimental results were then compared with the theoretical values according to the LSW theory.

2. Experimental

2.1. Materials and methods

2.1.1. Chemicals

Isopropyl-methyl-[2-(3-propoxy-phenoxy)-ethyl]-amine (amino diether), lidocaine, and prilocaine were manufactured at AstraZeneca Bulk Production, Södertälje, Sweden. Galactolipids (GLs), digalactose diacylglycerol, were supplied by Scotia LipidTeknik AB, Stockholm, Sweden. Table 2 lists the different ripening inhibitors used.

2.1.2. Emulsion preparation

All the emulsions were manufactured by adding the homogenous oil phase and the emulsifier to water at room temperature, while prehomogenizing with a laboratory mixer. The emulsion was then homogenized further at 500 bar using a high-pressure homogenizer, Emulsiflex C30, Avestin, Ottawa, Canada. A minimum of six homogenizing cycles was used in order to achieve an optimal droplet size distribution.

2.1.3. Composition

Both the amino diether and L-P emulsions (o/w) were made with the active substance(s) as the oil phase. The concentration of the ripening inhibitors, when used, was kept constant at 25% (w/w) of the active substance(s), i.e. the oil phase. GLs were used as emulsifiers throughout the experiment at the rate of 10% by weight of the total oil phase.

2.1.4. Droplet size determination

The droplet size distribution was determined using a laser diffraction technique, Coulter LS130, Coulter Electronics, UK, covering a range of 40 nm–2 mm. The emulsion container was inverted carefully ten times before samples were taken from the middle of the container. The droplet size was measured at 1, 24 h, and 1 week after the manufacturing date.

Table 1
Active substances

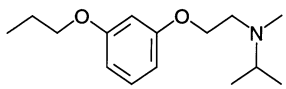
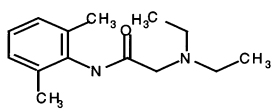
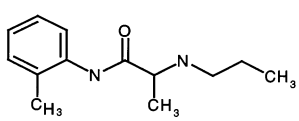
Local anesthetics	Structure	pKa	$S^{25°C}_{water}$ (mg/ml)	Molecular weight (g/mol)
Isopropyl-methyl-[2-(3-propoxy-phenoxy)-ethyl]-amine (Amino diether)		9.3	0.2	251.4
Lidocaine		7.9	4-6	234.3
Prilocaine		7.9	6-8	220.3

Table 2
Different types of ripening inhibitors

Commercial name	Chemical name/group	Manufacturer/supplier	Relative molecular mass	Batch/lot number
Drakeol 7	White mineral oil, C19-24	Penreco, Pennsylvania, USA	346	4407 44 96
Cetiol OE	Dioctyl ether	Henkel-Nopco A/S, Stromso, Drammen	240	40370 1/1
Eutanol G	2-octyldodecanol	Henkel-Nopco A/S, Stromso, Drammen	300	10456152
Eutanol G16	2-Hexyldecanol	Henkel-Nopco A/S, Stromso, Drammen	250	10025031
Miglyol 812	Medium-chain triglyceride, C8-C10 (MCT)	Hüls, Witten, Germany	300	39-534-29

When needed, additional measurements were made by both light microscopy, Ernst Leitz Othoplan, Wetzlar, Germany, and photon correlation spectroscopy (PCS), Malvern Instruments, Malvern, UK, in order to verify the results of the laser diffraction studies.

2.1.5. Kinetic study

In kinetic studies a medium-chain triglyceride, Miglyol 812, was used as ripening inhibitor in different weight ratios, 0–5%.

3. Theoretical

3.1. The rate of Ostwald ripening

The LSW theory provides a means of estimating the rate of Ostwald ripening. The theory is based on the following assumptions: (1) mass transport is due to the molecular diffusion in the continuous phase; (2) the disperse phase particles are spherical and fixed in space; (3) there is no interaction between neighboring particles, i.e. they are separated by distances much greater than their radius; and (4) the concentration of the molecularly dissolved disperse phase in the continuous phase is constant except adjacent to the particle boundaries, i.e. inhomogeneities in the concentration distribution in space caused by diffusion are negligible. According to the LSW theory, the rate of Ostwald ripening is directly proportional to the solubility of the disperse phase in the dispersion medium (Lifshitz and Slezov, 1959, Higuchi and Misra, 1962; Kabalnov et al., 1987a).

$$\mathrm{d}\,(r^3)/\mathrm{d}\,t = w = (8D\gamma_{\mathrm{o/w}}VC_{\infty}/9\ RT) \tag{3}$$

This can be solved as

$$r_t = [r_0^3 + (8\pi tD\gamma_{\mathrm{o/w}}\ VC_{\infty})/RT]^{1/3} \tag{4}$$

where r_t is the radius of the droplet in meters at time t (s), D is the diffusion coefficient of the disperse phase (m^2/s), $\gamma_{o/w}$ is the interfacial tension of the oil-water interface (N/m), and V is the the molar volume of the solute in m^3/mol (Mw/P). The density, P, was set to 1000 kg/m^3 throughout the calculation, C_{∞} is the solubility of the disperse phase in the continuous phase expressed in volume fractions, R is the gas constant (J/mol), and T is the absolute temperature in K.

Eq. (3) demonstrates why not much attention has been paid to Ostward ripening in emulsions. The linearity of the cube of the average radius with time ($t_{r\rightarrow 2r} \propto r^3$) means that in macroemulsions with radii of ≥ 1 μm, the rate of increase in the average radius is very much less than in an emulsion of ≤ 0.5 μm. Consequently, Ostwald ripening is seen as a major problem only in submicron emulsions when the disperse phase has a significant water solubility, and under these conditions the process might be very rapid.

When a second component, a ripening inhibitor, is added to the disperse phase, the nature of the physical parameters of the oils in the disperse phase has to be taken into account in relation to the ratio in which they are used (Kabalnov et al., 1987b):

$$r_t = (r_0^3 + \{8\pi t\gamma_{\mathrm{o/w}}(p_{\mathrm{c1}}/D_{\mathrm{c1}}V_{\mathrm{c1}}C_{\mathrm{c1}} + p_{\mathrm{c2}}/D_{\mathrm{c2}}V_{\mathrm{c2}}C_{\mathrm{c2}})^{-1}\}/RT)^{1/3} \tag{5}$$

where p_c is the volume fraction of the disperse phase components. Higuchi and Misra (1962) were the first to propose the method of Ostwald-ripening retardation in emulsions. These authors theoretically demonstrated that the addition of a small amount of a less soluble substance in a disperse phase may dramatically retard Ostwald ripening due to increasing concentration of the inhibitor in the shrinking droplets, which equalizes the solubility of the major components between the droplets. While this treatment predicts a decrease in the rate of ripening in the presence of the less soluble additive, there is no dependence upon the concentration of the additive.

The most complete study of the effect of adding a second component to the disperse phase on the rate of Ostwald ripening has been given by Kabalnov et al., who investigated the process both theoretically (Kabalnov et al., 1984, 1987b) and experimentally (Kabalnov et al., 1985). Their approach differed from that of Higuchi and Misra in that they considered the bulk phase solubility of the two components as well as the mole (or volume) fractions of the two components within the droplets rather than the emulsion as a whole.

This theory has been verified experimentally in several publications (Buscall et al., 1979; Ugelstad et al., 1980; Davis et al., 1981; Kabalnov et al., 1987a; Trevino et al., 1993). Nevertheless, they have shown that the addition of a second component with a much lower solubility to the disperse phase will increase the stability of the emulsion. The amount needed depends on the droplet size distribution of the emulsion and the disperse phase volume.

3.2. Diffusion coefficient

The diffusion coefficient of the oil phase components in water can be estimated according to the following empirical correlation (Wilke and Chang, 1955):

$$D^{\circ}_{AB} = 10^{-4}[7.4 \times 10^{-8}(f M_B)^{\frac{1}{2}} T]/(\eta_B V_A^{0.6}) \quad \{m^2/s\} \tag{6}$$

where D°_{AB} (m^2/s) is the mutual diffusion coefficient of the solute A at very low concentration in the solvent B and M_B is the molecular weight of solvent B in g/mol. T is the absolute temperature in K (298.15), η_B is the viscosity of the solvent in cP (1.01 cP for water), V_A is the molar volume of solute A at its normal boiling temperature in m^3/mol, and f is the association factor of solvent B, which is dimensionless (2.6 for water).

3.3. Solubility

The solubility of amino diether, lidocaine, and prilocaine was measured experimentally at 25°C in purified water. The solubility of the ripening inhibitors, however, had to be estimated theoretically due to the very low values. The basis of these relations is the so-called group contribution concept. This states that the solubility of a molecule may be estimated from the sum of the contributions of each component group of that molecule to the overall free energy of dissolution (Davis and Smith, 1976).

The free energy resistance of transferring hydrocarbons from the pure liquid to water ($\mu_{HC} - \mu_w$) can be estimated by adding the contribution of the different organic groups of the molecule (Davis and Smith, 1976; Tanford, 1980), and thus can be estimated according to the empirical relation:

$$(\mu_{HC} - \mu_w) = -500 n_{CH_3} - 210 n_{CH_2} \quad (J/mol) \tag{7}$$

where n_{CH_x} is the number of the CH_3 and CH_2 groups, respectively. The chemical potential of the aliphatic alcohols can be calculated according to Eq. (8). The group contribution of an ether oxygen atom is about +833 J/mol.

$$(\mu_{ROH} - \mu_w) = 198 - 195 n_C \quad (J/mol) \tag{8}$$

Thus the chemical potential of transfer of the ripening inhibitors used in this experiment can be estimated. These values can only be used for the infinite dilution state where there is only interaction between the solute and solvent molecules and not between the solute molecules themselves. This condition is, however, met for these excipients due to their low water solubility.

The solubility of the ripening inhibitors can then be estimated by equalizing the free energy of mixing ($\ln X_{HC}$) with the free-energy resistance when the hydrocarbons are transferred to the aqueous environment:

$$\ln X_{HC} = (\mu_{HC} - \mu_w)/RT \tag{9}$$

where X_{HC} is the molar fraction and can be calculated from the weight fraction (C_{disp}):

$$C_{disp} = \{x_{HC}\, n_w/(1 - x_{HC})\}\, M_{w\,(HC)} \tag{10}$$

3.4. Interfacial tension ($\gamma_{o/w}$)

The interfacial tension between the oil and water in the presence of the emulsifier (GL) was set to a constant value of 10 mN/m.

3.5. Aging kinetic study

The droplet size growth was estimated using Eqs. (4) and (5) with different amounts of the medium-chain triglyceride, Miglyol 812, in the emulsion. The amount was varied between 0 and 5% (w/w).

Table 3
Summary of the experimental results of droplet size distribution presented in volume percentage

Active substance (oil phase)	Ripening inhibitor	Time	Mean ± SD (μm)	Median (μm)	90% of droplets (μm)
Amino diether	–	1 h	4.83 ± 0.22	4.08	9.00
		24 h	15.58 ± 0.05	14.74	26.77
		1 w	23.28 ± 0.72	21.29	40.67
Amino diether	Drakeol 7	1 h	0.10 ± 0.03	0.10	0.14
		24 h	0.11 ± 0.02	0.11	0.14
		1 w	0.11 ± 0.02	0.11	0.14
Amino diether	Cetiol OE	1 h	0.12 ± 0.04	0.12	0.18
		24 h	0.28 ± 0.18	0.26	0.55
		1 w	0.52 ± 0.45	0.40	1.30
Amino diether	Eutanol G	1 h	0.10 ± 0.04	0.09	0.20
		24 h	0.13 ± 0.08	0.11	0.25
		1 w	0.15 ± 0.10	0.12	0.30
Amino diether	Eutanol G16	1 h	0.20 ± 0.14	0.15	0.44
		24 h	0.51 ± 0.83	0.17	1.82
		1 w	0.58 ± 1.00	0.17	2.15
Amino diether	Miglyol 812	1 h	0.10 ± 0.04	0.09	0.14
		24 h	0.10 ± 0.04	0.09	0.14
		1 w	0.10 ± 0.04	0.09	0.14
L-P	Miglyol 812	1 h	0.11 ± 0.02	0.11	0.14
		24 h	0.11 ± 0.02	0.11	0.14
		1 w	0.11 ± 0.02	0.11	0.14

4. Results

4.1. Experimental data

The amino diether emulsion was not physically stable when the oil phase consisted only of amino diether. The droplet size distribution of the emulsion was in the submicron region directly after manufacture, although phase separation could be detected after only a short storage time.

Addition of an extra oil phase as ripening inhibitor resulted in improved stability of the emulsion. A medium-chain triglyceride, Miglyol 812, and an alkane, Drakeol 7, produced the best stability profile, with a mean droplet size of 0.1 μm which did not change during the experiment (Table 3).

Other ripening inhibitors improved the stability of the emulsion; however, a droplet size growth at a lower rate could still be detected during the study period (Table 3).

In the L-P emulsion containing no ripening inhibitor, the droplet size could not be measured by the laser diffraction technique due to the high solubility of the oil phase in water. A very high polydispersity could be detected in PCS measurements, which meant that droplets larger than 1 μm existed in the emulsion. Microscopic examination of the emulsion showed that the droplet size increased rapidly after manufacture but the rate of the growth seemed to decline as fast. There was only a small difference between the droplet size distribution at different time points (1, 24 h, 1 week) when inspected microscopically (Fig. 1).

The L-P emulsion containing a medium-chain triglyceride, Miglyol 812, as ripening inhibitor was stable, with a mean droplet size of 0.1 μm throughout the experiment (Table 3).

4.1.1. Aging kinetic study

The experimentally measured droplet size distributions of the amino diether emulsions at different concentrations of the medium-chain triglyceride, Miglyol 812, are listed in Table 6. Emulsions containing 2.5% (w/w) Miglyol 812 or higher were stable throughout the experiment, with a mean droplet size distribution of 0.1 μm.

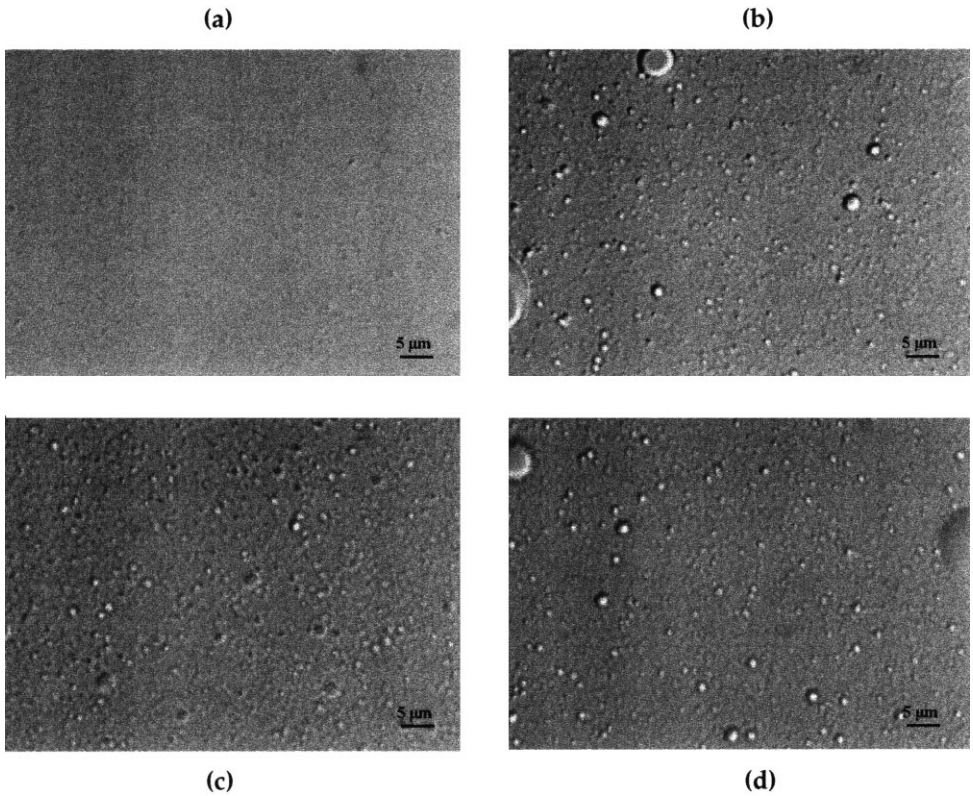


Fig. 1. Photomicrographs of L-P emulsion inspected by light microscope at 1000 × magnification, containing 2.5% w/w. Miglyol 812 (a), and without any ripening inhibitor added to the emulsion after 1 h (b), 24 h (c), and 1 week (d).

A slight increase in droplet size could be detected for emulsions containing 1% (w/w) or less of Miglyol 812 (Fig. 2). A total absence of ripening inhibitor in the formulation resulted in a droplet size growth as a function of time (Fig. 3).

4.2. Theoretical

4.2.1. Model estimation

The chemical potential, solubility ratio, and diffusion coefficient of all the ripening inhibitors were estimated theoretically (Table 4).The droplet size growth of the emulsions was calculated in the presence and absence of the ripening inhibitors, and the results are listed in Table 5.

4.2.2. Aging kinetic study

The theoretically estimated droplet size distribution of the amino diether emulsion at different

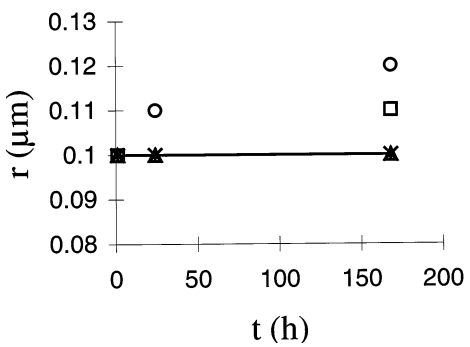


Fig. 2. Droplet size growth at different concentrations (%w/w) of a medium-chain triglyceride (MCT), Miglyol 812, in the amino diether emulsion as a function of time measured experimentally (circles, 0.5% MCT; squares, 1% MCT; triangles, 2.5% MCT; stars, 5% MCT), or estimated theoretically (the line) using Eq. (5).

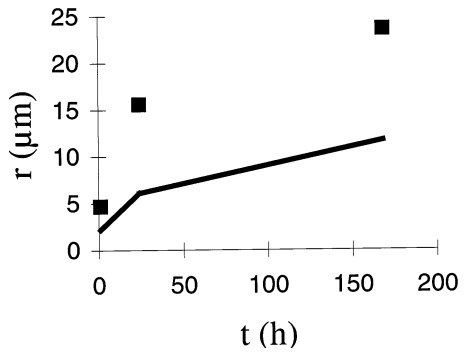


Fig. 3. Droplet size growth as a function of time in the absence of ripening inhibitors in amino diether emulsion, measured experimentally (squares) and estimated theoretically (line) using Eq. (4).

concentrations of medium-chain triglyceride, Miglyol 812, is listed in Table 6.

According to the theoretical estimation, even as little as 0.5% of Miglyol 812 should be enough to keep the mean droplet size at 0.1 μm during the study period (Fig. 2).

A total absence of ripening inhibitor resulted in a droplet size growth in theoretical estimations. The rate of growth measured experimentally was, however, faster than predicted by the theory (Fig. 3).

5. Discussion

Pharmaceutical formulations are designed to release the active substance when administered, i.e. the thermodynamic activity of the substance should be as high as possible. This means that one could always expect Ostwald ripening to occur in a submicron emulsion where the oil phase consists of active substance.

The rate of Ostwald ripening may be reduced in emulsions consisting of single component droplets by the use of a less soluble oil. This was proposed by Higuchi and Misra (1962) and later followed up experimentally by Davis et al. (1981), Kabalnov et al. (1985, 1987b), Taylor and Ottewill (1995). This method is attractive since the rate of ripening can be reduced by several orders of magnitude, using only small concentrations of a suitable additive.

The mechanism by which the addition of a less soluble excipient to an oil droplet reduces the rate of ripening is based on the fact that the two components show different rates of transfer between droplets as a result of their differences in solubility (Pertzov et al., 1984; Kabalnov et al., 1992). Initially, the concentration of the excipient is equal in all droplets; however, as ripening proceeds, the more soluble component (c_1) diffuses from the smaller droplets to the larger ones. The rate of ripening in this stage is close to that in an emulsion of c_1 alone. The less soluble component (c_2) cannot transfer at as high a rate as c_1 and is essentially trapped in the droplets at this stage. The concentrations of both components vary between different drop sizes, with the concentration of c_1 being greater in the larger droplets and smaller in the small droplets, the converse apply-

Table 4
Theoretically estimated physical properities

Material	Chemical potential ($\mu_{droplet}-\mu_{bulk}$) (J/mol) Eqs. (7) or (8)	Solubility ratio (C_∞) (kg solute/kg solvent) Eq. (9)	Diffusion coefficient (D) (m^2/s) Eq. (6)
Drakeol 7	−84165	3.45×10^{-14}	5.44×10^{-10}
Cetiol OE	−54727	3.44×10^{-9}	5.58×10^{-10}
Eutanol G	−65216	6.25×10^{-11}	4.88×10^{-10}
Eutanol G16	−51475	1.33×10^{-8}	5.44×10^{-10}
Miglyol 812	−77948	3.68×10^{-13}	4.88×10^{-10}
Amino diether	–	0.0002*	5.43×10^{-10}
Prilocaine	–	0.007*	5.87×10^{-10}
Lidocaine	–	0.005*	5.66×10^{-10}

* Measured experimentally in deionized water.

Table 5
The droplet size growth as a function of time, estimated theoretically using equation Eq. (4) or Eq. (5)

Active substance	Ripening inhibitor	Time	Mean droplet size (μm)
L-P	–	1 h	6.51
L-P	–	24 h	18.80
L-P	–	1 week	35.94
Amino diether	–	1 h	2.15
Amino diether	–	24 h	6.10
Amino diether	–	1 week	11.67
Amino diether	Cetiol OE	1 h	0.12
Amino diether	Cetiol OE	24 h	0.26
Amino diether	Cetiol OE	1 week	0.48
Amino diether	Eutanol G	1 h	0.10
Amino diether	Eutanol G	24 h	0.11
Amino diether	Eutanol G	1 week	0.16
Amino diether	Eutanol G16	1 h	0.16
Amino diether	Eutanol G16	24 h	0.43
Amino diether	Eutanol G16	1 week	0.82
Amino diether	Drakeol 7	1 h	0.10
Amino diether	Drakeol 7	24 h	0.11
Amino diether	Drakeol 7	1 week	0.16
Amino diether	Miglyol 812	1 h	0.10
Amino diether	Miglyol 812	24 h	0.10
Amino diether	Miglyol 812	1 week	0.10
L-P	Miglyol 812	1 h	0.10
L-P	Miglyol 812	24 h	0.10
L-P	Miglyol 812	1 week	0.10

Table 6
Kinetic studies of the amino diether emulsion at different Miglyol 812 concentrations, experimental data, and theoretical values

Miglyol 812 % (w/w)	Time	Mean ± SD (μm) experimental	Mean droplet size (μm) theoretical
5	1 h	0.10 ± 0.03	0.10
	24 h	0.10 ± 0.03	0.10
	1 week	0.10 ± 0.03	0.10
2.5	1 h	0.10 ± 0.03	0.10
	24 h	0.10 ± 0.03	0.10
	1 week	0.10 ± 0.03	0.10
1	1 h	0.10 ± 0.04	0.10
	24 h	–	0.10
	1 week	0.11 ± 0.04	0.10
0.5	1 h	0.10 ± 0.03	0.10
	24 h	0.11 ± 0.03	0.10
	1 week	0.12 ± 0.02	0.10
0	1 h	4.72 ± 4.15	2.15
	24 h	15.61 ± 9.63	6.10
	1 week	23.63 ± 14.30	11.67

ing to component 2. Consequently, the chemical potential of c_1 is higher in the larger droplets than in the smaller ones (where its concentration is lower). This effect directly counters the chemical potential effect due to the differences in radii of curvature. Eventually a point is reached at which

the chemical potential of c_1 is equal in all droplets as a result of the competition between the two effects. When this point is reached, there is no driving force for further transfer of c_1 and any further ripening can occur only through transfer of the less soluble component, which is at a much reduced rate. This state is referred to as the pseudo-steady state of ripening. Thus, the presence of a less soluble component can significantly reduce the rate of ripening.

There have been relatively few investigations of the effect of insoluble additives upon emulsion stability. As mentioned above, Higuchi and Misra demonstrated that a small addition (1% w/w) of a hydrophobic oil improved the stability of carbon tetrachloride emulsions significantly. The first systematic investigations appear to be those of Smith and Davis (1973), Davis and Smith (1976). They found that very small concentrations of decane, dodecane, or hexadecane significantly stabilized o/w emulsions of hexane, while the same concentrations of octane had little or no effect. Kabalnov et al. (1985) investigated the ripening of hexane in water emulsions in the presence of 1 or 10% w/v additives, using both PCS and rate of creaming to determine the stability of the emulsion droplets. In agreement with Davis and Smith, he found that the rate of ripening of the emulsions decreased markedly with increasing chain length of the additive (i.e. decreasing water solubility) at both concentrations of the additive.

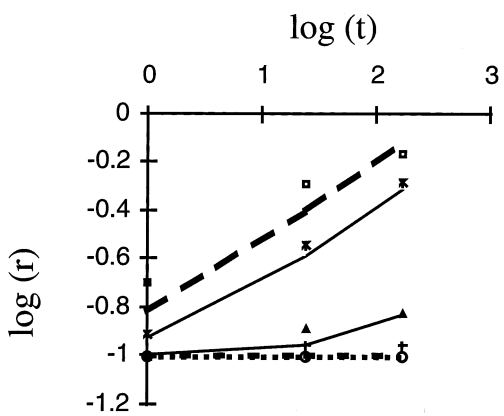


Fig. 4. Droplet size growth as a function of time in the presence of different ripening inhibitors, Miglyol 812 (open circles and thin dotted line), Drakeol 7 (plus sign and thick dotted line), Eutanol G (closed triangles and thick line), Cetiol OE (stars and thin line), Eutanol G16 (open squares and thick, broken line), estimated theoretically (lines), using Eq. (5) and measured experimentally (points)

This paper demonstrates how Ostwald ripening can be controlled in pharmaceutical formulations using hydrophobic excipients. Fig. 4 shows the high correlation between the experimental data and theoretical values.

Secondly, it can be shown that the effectiveness of the ripening inhibitors in stabilizing the emulsion is directly related to their solubility values in the dispersion medium. This is in accordance with the findings of the other investigators in this field (Higuchi and Misra, 1962; Kabalnov et al., 1984, 1985, 1987b; Bremer et al., 1996; Soma et al., 1996, and Taylor, 1998). When the relative growth in droplet size (Table 3) is compared with the solubility (Table 4), it is clear that solubility below 10^{-12} g/ml is needed in order to inhibit the growth.

It was also shown that only a small amount of the ripening inhibitor is needed in order to decrease the rate of Ostwald ripening, which means that the emulsion could be stabilized without significantly affecting the thermodynamic properties, such as the rate of release of the drug from the formulation. According to Henry's law, the activity should decrease proportionally to the ratio of the extra oil phase added to the formulation. However, due to the rapid droplet size growth and phase separation that occurs in the formulations containing no ripening inhibitor, an accurate comparison of the release rate of the drug in the presence and absence of an inhibitor was not possible.

For the emulsions containing no ripening inhibitor, the rate of droplet size growth did not follow the Ostwald ripening theory (Fig. 3). The mean droplet size has already increased to the μm region after 1 h, at which size other instability mechanisms such as creaming and coalescence will affect the emulsion. When creaming occurs in the emulsion, the inter-droplet distance is much less than the radius of the droplets, which gives a higher instability than predicted by the LSW theory. The process of creaming will allow coalescence to occur and, according to coalescence

theory (Van den Tempel, 1960), the cube of the mean particle radius increases exponentially with time (and not linearly, as is the case in Ostwald ripening). Thus, the rate of droplet size growth will not follow the Ostwald ripening theory.

Furthermore, it can be pointed out that depending on the density differences between the oil and water phase, other mechanisms may be more or less important. Amino diether with a density of 0.969 will phase separate much more rapidly than L-P with a density of 1.004 (the densities were measured at 25°C). Creaming, and thus coalescence, occurs more rapidly in the amino diether emulsions, while the oil phase in the L-P emulsion will be more homogeneously distributed throughout the emulsion, resulting in a more stable formulation despite the wide droplet size distribution.

It has to be emphasized that the chemical stability of the ripening inhibitor in the formulation is of crucial importance for predicting the stability of the product.

6. Conclusion

Ostwald ripening is an important factor in the stability of pharmaceutically submicron emulsions and one that has not received as much attention as it deserves. The LSW theory provides a basic understanding for the process despite its limitation of having been derived for ripening in a solid matrix.

The theory of Higuchi and Misra (1962) and the more extended analysis of Kabalnov et al. (1985, 1987a,b)) concerning the effects of low solubility additives in the disperse phase demonstrate an effective method by which Ostwald ripening can be retarded or even effectively halted.

This work showed that addition of small amounts of a hydrophobic excipient, with sufficiently low water solubility, would stabilize the submicron emulsion against Ostwald ripening without significantly affecting the release rate of the drug.

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