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Application of a new method based on conductivity measurements to determine the creaming stability of o/w emulsions

M. Bury [a,*], J. Gerhards [a], W. Erni [a], A. Stamm [b]

[a] *Pharma Division Preclinical Research, F. Hoffmann-La Roche Ltd, CH-4002 Basel, Switzerland*
[b] *Laboratoire de Pharmacotechnie, UFR Pharmacie - ULP Strasbourg I, BP 24 Illkirch, France*

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Abstract

A kinetic model, based on equations used in biological population dynamics, is proposed to describe the creaming profile of oil-in-water emulsions at the top of a storage cell. The creaming profile itself is determined by conductivity measurements through the emulsion at different heights, and conversion of conductivities into volume fraction values of the dispersed phase in terms of dispersion dielectric theory. The reliability of the proposed model was successfully verified. This methodology (conductivity method and kinetic model) was applied to model emulsions, to analyze the most reliable test scheme for stability assessment (room temperature storage, temperature stress test, and low centrifugational stress test). The conductivity method is sensitive to small changes in the volume fraction of dispersed phase observed at room temperature. The creaming profile can then be analyzed with the kinetic model allowing extrapolations for long-term predictions and shortening the time needed for stability assessments. Additionally, an Arrhenius-type equation relating the creaming rate constants with the corresponding storage temperatures can principally be employed. With regard to centrifugation stress testing, if under centrifugation no creaming can be observed, it is normally correct to assume that the emulsion will be stable at normal gravitational condition. However, the reverse argument does not always apply.

Keywords: o/w emulsion; Creaming; Conductivity measurement; Kinetic model; Testing program

1. Introduction

In a gravitational field, if a density difference exists between the dispersed and the continuous media, dispersed droplets experience a vertical force equating the gravitational force with the opposing frictional drag and buoyant forces. The resulting creaming rate v_0 of a single droplet is given by the well-known Stokes' law:

$$v_0 = \frac{2r^2(\rho - \rho')}{9\eta} g \qquad (1)$$

where r is the hydrodynamic radius of the droplet, ρ the density of the external phase, ρ' the density of the internal phase, η the macroscopic shear

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[*] Corresponding author.

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viscosity of the external phase, and g the gravitation constant. However, Stokes' law is strictly applicable only if the following conditions are obeyed (Higuchi, 1958): spherical and rigid droplets, monodisperse droplet size distribution, non-interacting droplets to ensure independent motion ($< 0.5\%$ disperse phase) and only hydrodynamic factors. For the relatively concentrated emulsions used pharmaceutically, Eq. 1 has no real value from a quantitative standpoint for predicting creaming rates. Two distinct theories emerge to explain the behavior of concentrated dispersions. One set of theories regards this problem as essentially a modification of Stokes law (e.g., Buscall et al., 1982). The alternative theory is to regard the dispersion as a packed bed through which a fluid is allowed to flow (e.g., Higuchi, 1958). Nevertheless, the optimal formulation must be found by a 'trial and error' procedure.

On the other hand, for pharmaceutical applications, where homogeneity is essential for the administration of the correct and uniform drug dose, creaming events may be acceptable as long as the emulsion can be reconstituted by a modest amount of shaking. However, it is undesirable in a pharmaceutical product like semisolid creams. Since pharmaceutical dosage forms have to be stored for a period of years, the formulation scientist must be able to guarantee the long-term stability of an o/w emulsion in the shortest possible time. Stress conditions normally employed to diagnose the instability during preliminary formulation evaluations include elevated temperature and centrifugation (Quack et al., 1975, Cannell, 1985). As a rule, these stress tests rely on visible signs of phase separation being restricted to measurements of the meniscus kinematics. Accordingly, there is a considerable need for more sensitive techniques that reliably monitor the droplet concentration in space and time and provide the desired information for a fast stability prediction.

Recently, a new creaming test method was established which allows such a detailed determination (Bury et al., 1991). This method is based on the measurement of the conductivity through the emulsion at different heights of the storage cell and at different times. The conductivities of the emulsion are interpreted in terms of dispersion dielectric theory (Bruggeman, 1935), providing a data conversion of the qualitative values of conductivity into the quantitative values of volume fraction of the dispersed phase. Likewise this approximation has a large degree of model independency, only requiring a reasonable assumption of the initial volume fraction of dispersed phase. It was proven that this method is capable of detecting creaming processes with good accuracy in a reproducible manner.

In this paper we continue the investigation with the aim of a more general purpose. To interpret in a quantitative way the creaming profiles obtained with this new method, a kinetic model for the description of creaming events was developed. This model was applied to two model systems, to analyse the most reliable test scheme for creaming stability assessment. Under these aspects the following test conditions were applied to the test emulsions: (a) room temperature, (b) temperature stress test and (c) low centrifugational fields.

2. Materials and methods

2.1. Materials

The following materials were all of pharmacopoeial quality and were used as received: polysorbate 60 (Tween 60, ICI), sorbitan stearate (Span 60, ICI), ceteareth-12 (Eumulgin B1, Henkel), ceteareth-30 (Eumulgin B3, Henkel), ceteareth 50 (Volpo CS 50, Croda), PEG-6-32 stearate (Tefose 1500, Gattefossé), hydrogenated palm oil/palm kernel oil PEG-6 complex (Labrafil M 2130 CS, Gattefossé), cetostearyl alcohol (Lanette O, Henkel) stearic acid, caprylic/capric triglyceride (Myritol 318, Henkel), mineral oil highly viscous, isopropyl myristate (Deltyl Extra, Givaudan), carbomer 934 Ph (Carbopol 934 Ph, Goodrich), sodium hydroxide, propylene glycol and benzyl alcohol (Merck). Demineralized water of specific conductance of about 1 μS/cm at 25° C was used throughout the experiments.

2.2. Composition and preparation of the emulsions

Different o/w emulsions were selected whose formulae are given in Table 1. The emulsions in Table 1A are fluid emulsions where the mixing proportion of the surfactants corresponds to HLB 10.0. The total surfactant amount is one-tenth of the oil. Benzyl alcohol was added as preservative, and propylene glycol as co-preservative and humectant. The emulsion given in Table 1B was selected from a receptarium (Gattefossé, 1986) and slightly modified, representing a semifluid lotion as a model system.

For all these emulsions 800 g emulsion were prepared in a 1 l laboratory vessel fitted with a stirrer and a homogenizer, and allowing work under vacuum. In addition, to enable the recording of the conductivity during the whole manufacturing process, the vessel was implemented with a self-made conductivity electrode and a digital conductivity meter (Philips, type PW 9527), a digital thermometer (Waldsee Electronic, type PT 100), and a printer (Wenger). The emulsion was cooled via the double-jacketed laboratory vessel under controlled conditions to room temperature by using a thermostatic water bath (Huber, type variostat).

The oily phase consisting of caprylic/capric triglyceride and sorbitan stearate was mixed and heated to about 70° C. The aqueous phase consisting of polysorbate 60, propylene glycol, benzyl alcohol and water was mixed, heated to about 70° C and added to the oily phase under stirring. After complete addition of the aqueous phase the coarse emulsion that formed was homogenized for the time as given in Table 1A to achieve a mostly identical droplet size distribution. The emulsion was cooled to room temperature under constant stirring (100 rpm), stored in a 25° C chamber for 1 day to allow equilibration and was then slightly manually stirred prior to further use.

2.3. Conductivity cells and measurements

The conductivity cells constructed for the studies under normal gravitational force with six electrode pairs are described in a previous paper (Bury et al., 1991), as are those for studies under

Table 1
Composition of the investigated emulsions (amounts in g): (A) fluid emulsions (droplet size data in μm) and (B) lotion

(A) Ingredients	F 5	F 10	F 20	F 30	F 40	F 50	C 5	C 10	C 20
Polysorbate 60	1.56	1.56	1.56	1.56	1.56	1.56	1.56	1.56	1.56
Sorbitan monostearate	1.44	1.44	1.44	1.44	1.44	1.44	1.44	1.44	1.44
Caprylic/capric triglyceride	5.0	10.0	20.0	30.0	40.0	50.0	10.0	10.0	10.0
Carbomer 934 P	–	–	–	–	–	–	0.05	0.10	0.20
Sodium hydroxide q.s. ad	–	–	–	–	–	–	pH 5.0	pH 5.0	pH 5.0
Propylene glycol	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Benzyl alcohol	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Water demineralized q.s. ad	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Homogenisation time	3 s	5 s	15 s	1 min	1 min	1 min	5 s	5 s	7 s
x_{10} [a]	0.62	0.86	1.11	1.07	1.16	1.06	0.79	0.79	0.79
x_{50} [a]	1.92	1.82	2.00	2.05	2.21	2.08	1.56	1.58	1.60
x_{90} [a]	4.20	3.35	3.72	4.19	4.57	4.31	2.74	2.81	3.11

(B) Ingredients	Amount (g)
PEG-6-32 stearate	7.0
Hydrogenated palm oil/ palm kernel oil PEG-6 complex	3.0
Stearic acid	1.0
Mineral oil highly viscous	7.0
Benzoic acid	0.2
Water demineralized q.s. ad	100.0

[a] x_{50} droplet diameter for the 50th cumulative mass percentile (mean droplet size), x_{10} droplet diameter for the 10th cumulative mass percentile, and x_{90} droplet diameter for the 90th cumulative mass percentile.

centrifugational fields, designed to fit into the tube of a centrifuge (Heraeus Christ, type JJ I KS). The distance between the rotor axis and the midpoint of the top electrode pair was 6.4 cm, and between the rotor axis and the midpoint of the bottom electrode pair 12.1 cm.

Conductivity was measured by using a Philips PW 9527 digital conductivity meter operating at a frequency of 4000 Hz. All measurements were performed with the cell constant set to 1.0 cm^{-1}, and without temperature compensation.

For the purpose of determining the volume

Table 2
Volume fraction of dispersed phase ϕ_o for the investigated emulsions

Emulsion	ϕ_o
F 10	0.1198
F 20	0.2243
F 30	0.3276
F 40	0.4298
F 50	0.5310
C 5	0.1198
C 10	0.1198
C 20	0.1198
Lotion	0.0700

Table 3
Summary of regression analysis according to Eq. 8 (Verhulst equation) respectively Eq. 5 (Malthus equation)

Emulsion	Temp. (°C)	ϕ_o	ϕ_{max} [a]	K	n	R^2
F 10	5	0.1064	0.47 (c)	0.025148	9	0.9851
	25	0.1233	0.4720	0.054553	10	0.9992
	35	0.1228	0.4725	0.080656	8	0.9997
	45	0.1327	0.5050	0.116884	8	0.9980
F20	5	0.2242	0.47 (c)	0.002585	8	0.9999
	25	0.2190	0.4733	0.028367	9	0.9988
	35	0.1981	0.6022	0.134898	9	0.9986
	45	0.2044	0.6485	0.249980	9	0.9985
F 30	5	0.3219	0.55 (c)	0.000972	10	0.9999
	25	0.3244	0.5483	0.029276	11	0.9999
	35	0.3151	0.6689	0.120699	11	0.9996
	45	0.3159	0.6646	0.281568	9	0.9984
F 40	5	0.4152	0.62 (c)	0.000755	10	0.9999
	25	0.4295	0.6250	0.020103	11	0.9999
	35	0.4192	0.6933	0.107942	9	0.9996
	45	0.4203	0.6773	0.243849	9	0.9995
F 50	5	0.5292	0.59 (c)	0.001731	10	0.9999
	25	0.5356	0.5881	0.020484	13	0.9999
	35	0.5264	0.7003	0.057701	11	0.9999
	45	0.5262	0.7138	0.091978	11	0.9998
C 20	5	0.1212	–	0.000112	8	0.9999
	25	0.1184	–	0.000353	12	0.9999
	35	0.1213	–	0.000556	12	0.9999
	45	0.1157	–	0.001276	12	0.9993
Lotion	5	0.0725	–	0.000094	6	0.9996
	25	0.0719	–	0.000699	9	0.9977
	35	0.0747	–	0.001514	9	0.9901
	45	0.0777	0.6959	0.103962	9	0.9947

[a] If a regression coefficient is given, the fit is performed according to Eq. 8 (logistic equation) and otherwise according to Eq. 5 (Malthus equation). (c) Indicates that this value was set as constant for the statistical evaluation.

fractions of sedimenting dispersions Bruggeman's equation (1935) was reformulated (Bury et al., 1991):

$$\phi_{x,t} = 1 - (1 - \phi_o)\left(\kappa^i_{x,t} / < \kappa^i_t > \right)^{2/3} \qquad (2)$$

where $\phi_{x,t}$ is the volume fraction of dispersed phase at some height (x) of the creaming cell and after some time (t), ϕ_o the initial volume fraction of dispersed phase, $\kappa^i_{x,t}$ the internally calibrated conductivities, and $\langle \kappa^i_t \rangle$ the averaged conductivity at each particular measurement time.

2.4. Determination of the volume fraction of the dispersed phase

In preparing the disperse systems, it is most convenient to add quantities of the two phases by weights, although one is ultimately interested in the volume fraction of the dispersed phase in the system. The initial volume fraction of the dispersed phase, ϕ_o, and the weight fraction of the dispersed phase, ϕ_w, are related through:

$$\phi_o = \phi_w(\rho_t/\rho_d) \qquad (3)$$

where ρ_d and ρ_t are the densities of the dispersed phase and of the total dispersion. These densities were measured with a Paar Precision Density Meter (type DMA 50) at 25 ± 0.1° C. The determination was performed with all emulsions of Table 1 as well as with the dispersed oily phases, assuming that the lipophilic surfactant is completely dissolved in the dispersed phase and the hydrophilic surfactant in the aqueous phase. Furthermore, it is assumed that benzyl alcohol and propylene glycol are present in the aqueous phase only. With these approximations the initial volume fraction of dispersed phase was calculated as given in Table 2. In order not to complicate the calculations it was assumed that these initial volume fractions are temperature independent.

2.5. Droplet size analysis

The droplet size analysis was performed using a laser diffraction technique (Malvern MasterSizer). The following procedure was adopted for the dilution step: about 1 ml of the emulsion was diluted with demineralized water to about 50 ml. Then about 0.5–1 ml of this dilution was placed in the receiver of the MasterSizer (50% stirring and pump intensity), until an extinction of about 0.2 ± 0.05 absorbance units was achieved. For emulsion with higher viscosity, 80% stirring and pump intensity were employed, so that the sample became homogenous after dilution. Using a 45 mm lens this diluted dispersion was immediately measured for 10 s. The results are reported as x_{50} being the droplet diameter for the 50th cumulative mass percentile (mean droplet size), x_{10} the droplet diameter for the 10th cumulative mass percentile, and x_{90} the droplet diameter for the 90th cumulative mass percentile.

2.6. Statistical analysis

All statistical evaluations were performed with the software package RS/1 Release 4.3.1 (Bolt Beranek and Newman Inc.).

3. Results and discussion

3.1. Derivation and verification of the kinetic model

Fluid emulsions were chosen as model systems since with these emulsions creaming events are detectable within a short period of time. To cover a range of cases the weight fraction of the dispersed phase was varied between 10 and 50% (Table 1). To exclude droplet size effects in comparing the creaming behavior of these emulsions, different homogenization times were employed during manufacturing. More or less uniform mean droplet size distributions were achieved (Table 1).

Generally, when a local inhomogeneity is created in an initially uniform emulsion by creaming, the thermal motion of the droplets tends to damp this inhomogeneity. This is the phenomenon of diffusion. The general case of dispersed systems both diffusing and moving with a constant drift velocity has been treated mathematically (Mason and Weaver, 1924; McQuarrie, 1976). However, the concentration dependence of the creaming rate $v_{(\phi)}$ and the diffusion coefficient $D_{(\phi)}$ makes the differential equation a system of non-linear partial differential equations. Due to this non-linear character of the rate equation its solution is an extremely difficult task, and a precise functional form is unknown for real emulsions.

To derive empirically a kinetic model it was decided not to consider the whole $\phi_{x,t}$ profile, but to restrict the further analysis to the volume fraction of dispersed phase determined at the top electrode ($x = 6$ in Eq. 2). The volume fraction ratios of dispersed phase of the fluid emulsions are depicted in Fig. 1a–c as determined at the top electrode of the creaming cell ($\phi_{6,t}/\phi_o$) and obtained from samples stored at 5, 25 and 45° C. In Fig. 1a the profiles of the emulsions F 40 and F 50 have been omitted, since they show identical creaming behavior to emulsion F 30. To interpret the creaming events and with view to these creaming profiles, two phenomena are to be identified: (a) an exponential increase in the 5° C samples (Fig. 1a and b); (b) a sigmoidal curvature in the 25 and 45° C samples (Fig. 1b and c) dependent on the initial volume fraction of dispersed phase. Very closely analogous to the physical kinetics to be considered in the present study are those describing the growth, decay and interaction of biological populations (Beier, 1965; Nicolis and Prigogine, 1977; Murray, 1993). To outline a general formulation of the basic equations of populations dynamics, with $N_{(t)}$ being the population of the species at time t, the rate of change has as the simplest model:

$$dN/dt = KN \rightarrow N = N_o \exp(Kt) \qquad (4)$$

where K is a positive constant and the initial population $N_{(o)} = N_o$. For creaming events Eq. 4 is rewritten in the following form:

$$\phi_{(t)} = \phi_o \exp(Kt) \qquad (5)$$

where N (number of individuals) is understood as the number of emulsion droplets and the volume fraction of dispersed phase is denoted by $\phi_{(t)}$. N_o is interpreted as the initial volume fraction of dispersed phase ϕ_o, and the constant K as the creaming rate constant.

If K were unlimited, then Eq. 4 would predict a population explosion through an exponential growth of N, which is usually referred to as

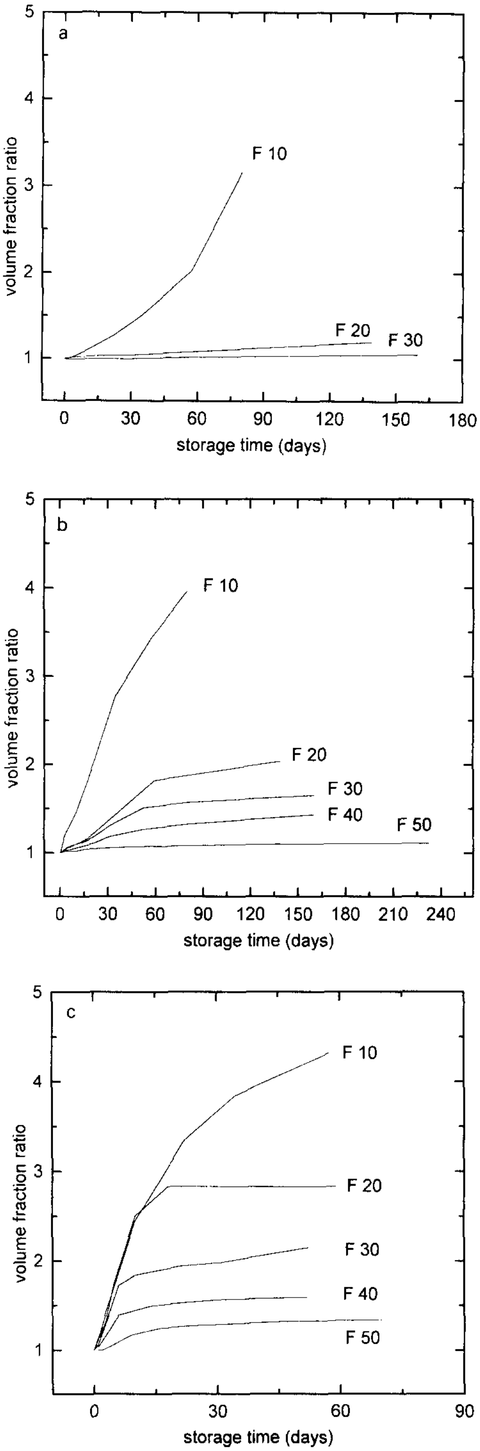

Fig. 1. Volume fraction of dispersed phase of the fluid emulsions at the top electrode of the creaming cell: (a) stored at 5° C, (b) stored at 25° C, (c) stored at 45° C.

Malthusian growth. This law may hold in the initial stages of population increase. However, in the long run of course there must be some adjustment to such exponential growth, i.e., a self-limiting process should operate when a population becomes too large. The Verhulst model for logistic growth in a population is written as:

$$\mathrm{d}N/\mathrm{d}t = KN(1 - N/C) \qquad (6)$$

where K and C are positive constants. The constant C is the carrying capacity of the environment, which is usually determined by the available sustaining resources, and determines the size of the stable steady-state population. If $N_{(\mathrm{o})} = N_{\mathrm{o}}$, the solution of Eq. 6 is (Murray, 1993):

$$N_{\mathrm{o}} = \frac{N_{\mathrm{o}} \cdot C \cdot \exp(Kt)}{C + N_{\mathrm{o}} \cdot (\exp(Kt) - 1)} \qquad (7)$$

The sigmoidal curve obtained from Eq. 7 is called the logistic curve. The point about Eq. 6 and 7 is that it is more likely representative for a class of population models with a density-dependent regulatory mechanism. It is a particularly convenient form to take when seeking dynamic behaviour in systems in which $N = 0$ is an unstable steady state and $N_{(t)}$ tends to a finite stable steady state. Keeping this in mind for creaming events the terms occurring in Eq. 6 and 7 can be interpreted as follows. With regard to the carrying capacity of the environment (constant C) creaming is limited due to the available free space for the droplets at the top of the emulsion. The upper asymptote is understood as the maximum achievable volume fraction of dispersed phase, $\phi_{\max}$. Again, the constant K is interpreted as the creaming rate constant, which expresses the volume fraction of dispersed phase that creams in a given unit of time. With these definitions Eq. 7 is rewritten in the following equation:

$$\phi_{(t)} = \frac{\phi_{\mathrm{o}} \cdot \phi_{\max} \cdot \exp(Kt)}{\phi_{\max} + \phi_{\mathrm{o}} \cdot (\exp(Kt) - 1)} \qquad (8)$$

Eq. 8 is illustrated in Fig. 2 for ϕ_{o} values of 0.1 and 0.4 (for both cases $\phi_{\max} = 0.6$ and $K = 0.0075$). In Eq. 8 there is a qualitative difference depending on whether $\phi_{\mathrm{o}} > \phi_{\max}/2$ or $\phi_{\mathrm{o}} < \phi_{\max}/2$ (Fig. 2). With $\phi_{\mathrm{o}} < \phi_{\max}/2$ the form has a typical sigmoidal character, but not for $\phi_{\mathrm{o}} > \phi_{\max}/2$. With regard to the value of $\phi_{\max}$, Scott (1960) studied the random packing arrangements of uniform size spheres and concluded that the values of $\phi_{\max}$ lie between two well-defined limits: 0.601 (loose random packing) and 0.637 (dense random packing). Finally, as can be proven easily, Eq. 8 agrees with Eq. 5 for a short observation period of time.

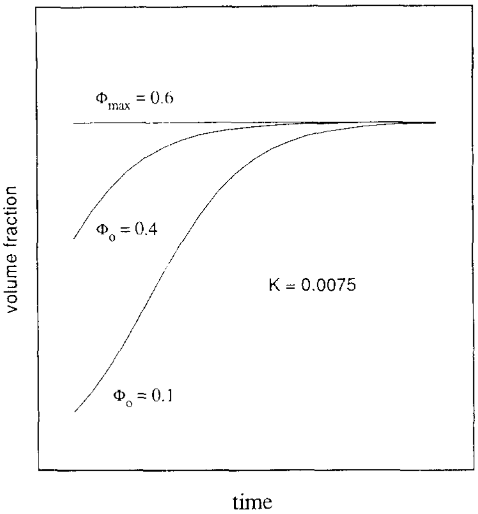

Fig. 2. Logistic growth curvatures according to Eq. 8 (Verhulst equation) for emulsion systems with $\phi_{\mathrm{o}} = 0.1$ and 0.4 (for both cases $K = 0.0075$ and $\phi_{\max} = 0.6$).

To test the reliability of Eq. 8 for modelling creaming events of the fluid emulsions, the following initial values were used in the statistical analysis: ϕ_{o} as given in Table 2, $\phi_{\max}$ as 0.6 and K as 0.01. For the 5° C samples $\phi_{\max}$ was set to a constant value as obtained from the corresponding 25° C samples. The result of the regression analysis is summarized in Table 3. As indicated by the high R^2 terms the fitting to Eq. 8 of the various creaming profiles is very satisfactory. As is apparent from Table 3, the maximum volume fraction of dispersed phase seems to be temperature dependent, e.g., the higher the storage temperature the higher is the $\phi_{\max}$. In the F 20, F 30 and F 40 samples stored at 25° the corresponding $\phi_{\max}$ values were calculated as 0.47, 0.55 and 0.63 and in the 45° C samples as 0.65, 0.66 and 0.68. The higher $\phi_{\max}$ as compared with the abovementioned values for loose and dense random packing may be explained due to some polydispersity of the emulsions.

According to these results, Eq. 8 is regarded as a suitable kinetic model for creaming events. In the following Eq. 8 is studied for its application in temperature stress testing. In chemical kinetics this testing approach is coupled with the use of the Arrhenius equation, which relates in its logarithmic form the logarithm of the kinetic constant linearly to the reciprocal of the elevated temperature:

$$\ln(k) = \ln(A) - E_a/RT \qquad (9)$$

where E_a is the activation energy measured in cal/mol and the coefficient A denotes the frequency factor. R is the gas constant (1.987 cal K^{-1} mol^{-1}) and T represents the temperature in K. The dependence of the creaming rate constant K on temperature can be expressed by an equation analogous to the Arrhenius equation (Eq. 9) as has also been described for viscosity and diffusion (Eyring, 1936; Brandt, 1959). The activation energy E_a in Eq. 9 is interpreted as the activation energy for creaming, E_c:

$$\ln(K) = \ln(A) - (E_c/R)(1/T) \qquad (10)$$

The value of (E_c/R) is obtained from linear regression analysis as the slope.

The primary requirement of this accelerated test is that the temperature stress applied should speed up, but not alter the mechanism of deterioration operating under normal storage conditions (Parkinson and Sherman, 1972). As is apparent from Eq. 1 the macroscopic shear viscosity of the external phase η should be considered as one major cause for the change of the creaming rate constant with temperature. However, since the viscosity of bulk liquids usually has a temperature dependency fairly well represented by an Arrhenius-type equation (Berry et al., 1980), only special occurrences in the storage temperature interval of the emulsion system such as phase transitions have to be considered. To detect such occurrences the conductivity-temperature profiles of emulsions F 10 and F 50 were recorded during manufacturing (Fig. 3). For both emulsions linear profiles were obtained, indicating that the requirement for applying Eq. 10 is fulfilled.

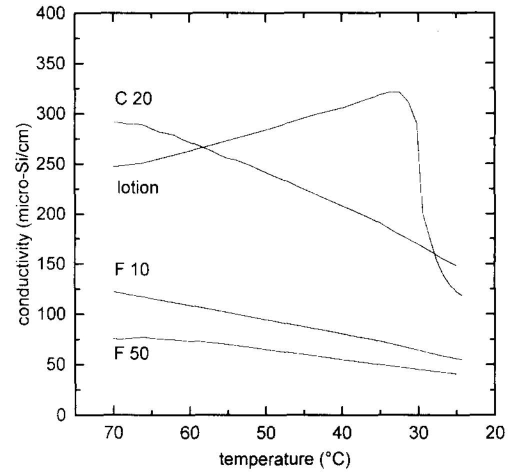

Fig. 3. Conductivity-temperature profile during manufacturing of the emulsions F 10, F 50 and C 20 and the lotion.

In Fig. 4 the ln(K) values of the fluid emulsions are plotted against $(1/T)$ and in Table 4 the result of linear regression analysis is compiled according to Eq. 10. For all five fluid emulsions the fits are highly significant as reflected in the F-test values. Therefore, the temperature stress method can principally be applied in a quantitative manner on the basis of Eq. 8 and 10.

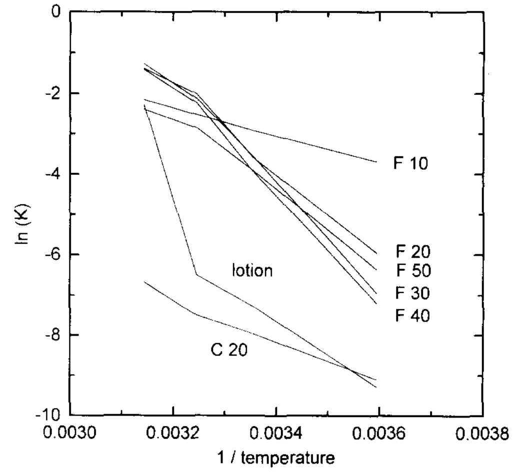

Fig. 4. Arrhenius plot of the fluid emulsions, emulsion C 20 and the lotion.

Table 4
Arrhenius analysis (Eq. 10) of creaming rate constants with the various emulsions

Emulsion	E_c (kcal/mol)	R^2	F [a]	Q_{10} [b]
F 10	6.73	0.9989	1826	1.45
F 20	20.76	0.9898	194	3.12
F 30	25.47	0.9916	235	4.03
F 40	26.10	0.9925	266	4.18
F 50	18.02	0.9844	126	2.68
C 20	10.31	0.9879	119	1.76
Lotion [c]	15.90	0.9994	773	2.39

[a] $F(2,99) = 98.4$
[b] As defined in Eq. 11.
[c] Without the 45° C sample.

3.2. *Applications of the kinetic model to model systems*

As is clear from Stokes' equation (Eq. 1), an increased viscosity of the external phase reduces the creaming rate. The most practical method for controlling creaming is to use viscosity increasing agents like carbomer 934 Ph. However, the thickener level required cannot be easily predicted, since this thickener is non-Newtonian in its flow behaviour, and may form a network in the continuous phase with a yield value. Thus, the level required for a particular formulation has to be found by a 'trial and error' procedure. The present method was investigated for the fast determination of the required polymer concentration.

The effects of various carbomer 934 Ph concentrations on the creaming behavior were determined at 25° C (emulsions C 5, C 10 and C 20) in comparison with that of emulsion F 10 (Fig. 5). Creaming was detected already after a few days with the emulsions containing carbomer 934 Ph concentrations up to 0.1%. The observed profiles for the low carbomer concentration, where creaming occurs even more rapidly than in the carbomer free emulsion F 10, can be explained in terms of 'bridging', a mechanism involving multiple droplet adsorptive attachment to the soluble polymer. On the other hand, by adding 0.2% carbomer 934 Ph only a very slight change in the volume fraction of dispersed phase could be detected over 120 days storage.

The statistical determination of the creaming constant of emulsion C 20 (Table 3) was performed according to Eq. 5 (Malthus equation), since only an increase in its exponential phase could be observed. The volume fraction data obtained with 120 days storage at 25° C of emulsion C 20 and their statistical fit to Eq. 5 ($\phi_0 = 0.1181$ and $K = 0.000353$) were used to extrapolate the further change in volume fraction of dispersed phase at the top electrode:

Initially	0.118
120 days	0.123
1 year	0.134
2 years	0.152
5 years	0.223

As indicated by these extrapolations, emulsion C 20 is considered not to be stable against creaming over 5 years if no moderate shaking can be applied. To prevent any creaming a slightly higher concentration of carbomer 934 Ph should be used such as 0.25%. As major conclusion, the conductivity method is sensitive to small changes in the volume fraction of dispersed phase already with room temperature testing. Additionally, these creaming profiles can be analyzed with the kinetic model of Eq. 5 or 8, allowing extrapolations

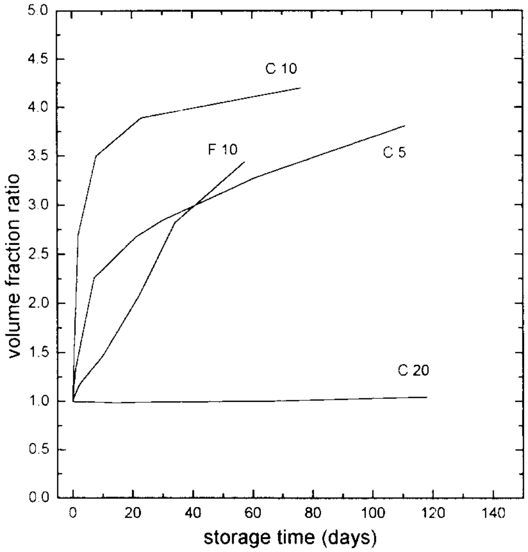

Fig. 5. Volume fraction of dispersed phase of emulsions C 5, C 10 and C 20 compared with that of emulsion F 10 at the top electrode of the creaming cell stored at 25° C.

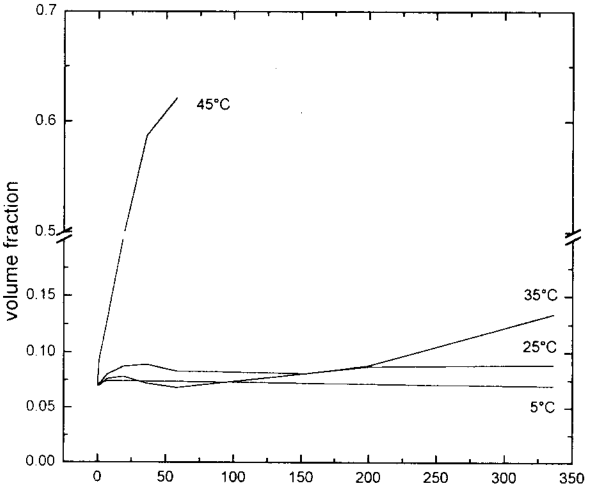

Fig. 6. Volume fraction of dispersed phase of the lotion stored at 5, 25, 35 and 45° C.

for long-term stability predictions. With this procedure the necessary polymer concentration to prevent creaming can be detected in a short period of time.

To investigate the thermal influence on creaming, the creaming behavior of emulsion C 20 was determined under different storage conditions. The creaming profiles were again analyzed applying Eq. 5 (Malthus equation). The requirement for applying Eq. 9 is fulfilled for emulsion C 20 as depicted in the conductivity-temperature profile (Fig. 3). The Arrhenius analysis (Table 4) showed that the fit is highly significant as reflected by the F-test value. To express the change in the creaming rate constants corresponding to a 10 K temperature change, a Q_{10} value is defined as follows:

$$Q_{10} = \exp(E_c/R(1/T_1 - 1/T_2)) \tag{11}$$

Accordingly, the Q_{10} value is a function of the activation energy, E_c, and the considered temperature interval. In the present study T_1 corresponds to 25° C or 298.16 K and T_2 to 35° C or 309.16 K. The creaming of emulsion C 20 is accelerated by a Q_{10} value of 1.8.

As another model system for temperature stress test evaluation a lotion was chosen. As shown in Fig. 6, the 5 and 25° C samples showed over 340 days storage no significant change in the volume fraction of dispersed phase whereas in the 35° C sample a 2-fold increase in the volume fraction could be detected. The 45° C sample was completely creamed after about 2 months.

With the help of the conductivity-temperature profile obtained during manufacturing (Fig. 3), viscosification of the system could be observed at about 35° C. Therefore, the 45° C sample was rejected for the Arrhenius-type analysis. Although the 35° C sample was in the range of the observed phase transition, a good fit was obtained with the remaining three storage samples as reflected by the F-test value. A Q_{10} value of 2.4 was calculated.

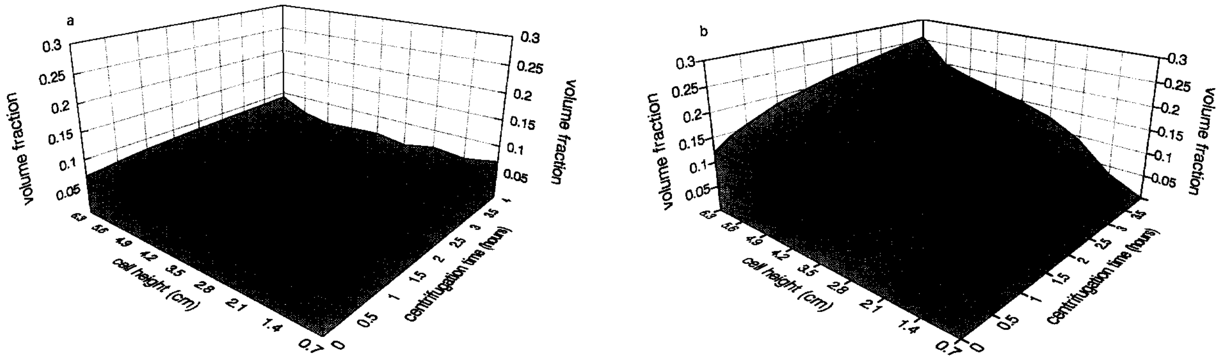

Fig. 7. Volume fraction of dispersed phase $\phi_{x,t}$ under a centrifugational field of 4000 rpm for a period of 4 h: (a) lotion, (b) emulsion C 20.

The Q_{10} values of the different investigated emulsions (Table 4) fall within the range between 1.5 and 4. As stated by Rieger (1986), an emulsion should be visibly stable for at least 2–3 months at 45° C, and 12–18 months at room temperature. This recommendation, which is apparently based on a Q_{10} value of 3, seems to be justified as an empirical mean value, but can deviate for a particular system to a higher or lower value. However for a particular emulsion system, one takes a considerable risk for long-term predictions if creaming experiments are performed only at high temperature storage without determination of the Q_{10} value.

3.3. Centrifugational stress testing

As a further stress test a centrifugational field of 4000 rpm up to 4 h was applied to emulsion C 20 and to the lotion to study its effect over the six electrode heights. With the lotion no creaming could be observed (Fig. 7a). On the other hand, the creaming of emulsion C 20 was drastically accelerated (Fig. 7b) as compared to the 25° C sample (Fig. 5). As indicated by Becher (1965), centrifugation at 3750 rpm in a 10 cm radius centrifuge for a period of 5 h would be equivalent to the gravity effect of about 1 year. Although the centrifugational fields are not identical (Becher's study: about $1500 \times g$; present study: about $1150 \times g$ at the top electrode and $2150 \times g$ at the bottom electrode), Becher's suggestion for emulsion C 20 is not fulfilled, in that centrifugation seems to overstress the system. An explanation can be seen in the presence of carbomer, forming a network in the continuous phase leading to a yield value. With the applied centrifugational field this creaming barrier may be overcome, but not with the gravitational one.

Comparing the results of both model emulsions, the following conclusion is drawn: If under centrifugation no creaming can be observed, it is normally correct to assume that it will be comparably stable under the normal gravitational field. However, as observed with emulsion C 20, the reverse argument does not always apply.

This phenomenological technique already allows long-term predictions for stability assessment. Nevertheless, quantitative predictions based on kinetic models would add a higher value. Generally, centrifugation of an emulsion greatly exaggerates the effect of gravity, and therefore accelerates the creaming rate. Under these circumstances Stokes' Law (Eq. 1) becomes:

$$v_o = \frac{2r^2(\rho - \rho')}{9\eta}\omega^2 R \qquad (12)$$

where the acceleration due to gravity g has been replaced by $\omega^2 R$. ω is the angular velocity of the centrifuge (with rpm $(\pi/30)$), and R denotes the distance of the sample from the rotation center. The degree of acceleration of creaming will obviously depend upon the speed of centrifugation (Eq. 12). If it is assumed that the creaming rate is directly proportional to the strength of the gravitational field, it should be possible to establish a direct relationship between speed and time of centrifugation, and normal storage conditions. A study in this direction was performed by Garrett (1962) demonstrating that rates of emulsion clearing (meniscus kinematics) can be stated as a function of the ultracentrifugational field and that the rate of clearing under simple gravity can be predicted for the emulsion. However, with the used conductivity cells an exposure to higher centrifugational forces was not possible due to tightening problems with the electrodes being integrated in the creaming cell and exposed also to the centrifugational field. Other experimental techniques for monitoring the $\phi_{x,t}$ profiles (Williams et al., 1990) may be useful for these type of experiments where the detector can be installed outside of the creaming cell, and thus not be exposed to the centrifugational field.

4. Conclusion

A kinetic model based on equations used in modelling biological population dynamics is proposed to describe the creaming behavior of oil-in-water emulsions. Fluid emulsions were used to verify successfully the reliability of this model.

This kinetic model was applied to model emulsions, to analyze the most reliable test scheme for stability assessment (room temperature storage, temperature stress test, and low centrifugational stress test). With regard to room temperature testing, the conductivity method for determining the creaming profile is sensitive to small changes. This creaming profile can be analyzed with the kinetic model allowing extrapolations for long-term predictions and shortening the time needed for stability assessments.

Temperature stress testing has been employed to accelerate the creaming of the investigated emulsions. The primary requirement is that the viscosity-temperature profile of the emulsion system obeys an Arrhenius type relation. The measurement of the conductivity-temperature profile during manufacturing seems to be an appropriate and fast method to detect linearity respectively non-linearity of the thermal behavior of the system. An Arrhenius-type analysis can principally be performed on the basis of the creaming rate constants obtained from the proposed kinetic model. The change in the creaming rate constants corresponding to a 10 K temperature change (expressed as Q_{10} value) were determined for the various investigated emulsions lying in the range between 1.5 and 4. Due to this large range, one takes a considerable risk for long-term predictions if creaming experiments are performed only at high temperature storage without knowledge of the particular Q_{10} value for extrapolation to room temperature storage.

With regard to the centrifugation stress test, the employed centrifugational field may lead to overstressing an emulsion system. Therefore, if under centrifugation no creaming can be observed, it is normally correct to assume that it will be stable under normal gravitational field. However, the reverse argument does not always apply.

Finally, the present method was used for the fast determination of the required concentration of viscosity increasing agents like carbomer 934 Ph. With this method the necessary polymer concentration to prevent creaming of an emulsion can be detected in a short period of time.

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