Physico-chemical model for molecular diffusion from highly concentrated emulsions

Valery G. Babak,*[a,b] Marie-José Stébé[b] and Nathalie Fa[b]

[a] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5085; e-mail: babak@ineos.ac.ru*

[b] *Equipe Physico-Chimie des Colloides, UMR n°7565 CNRS / Université H. Poincaré, Nancy 1, Faculté des Sciences, BP 239, 54506 Vandoeuvre-lès-Nancy cedex, France*

10.1070/MC2003v013n06ABEH001794

A new physico-chemical model for the molecular diffusion of drugs from highly concentrated emulsions (gel emulsions) is proposed.

The use of highly concentrated emulsions for the encapsulation and prolonged release of drugs and other bioactive agents is of interest in medicine, pharmaceutics and cosmetics.[1,2] These emulsions, which are known as high internal phase ratio emulsions (HIPRE),[3] gel emulsions,[4,5] biliquid foams,[6] adhesive emulsions,[7,8] *etc.*, containing over $\varphi_v = 90\%$ internal phase by volume, have a swollen micellar (L_1 or L_2) solution of non-ionic[9,10] or ionic[6,7] surfactants as a continuous phase. With increasing the volume fraction φ_v of the internal phase, the specific area of the liquid films formed in the region of contact between the droplets increases, and for the values of $\varphi_v \sim 99$ % the interface is practically composed by these liquid films (this means that, like in foams, the continuous phase is practically localised in thin liquid films and Plateau borders formed by highly distorted droplets). The preparation and properties of these emulsion gels were reviewed elsewhere.[11]

The reverse water-in-oil (w/o) gel emulsions consisting of water droplets separated by thin layers and films of a hydrophobic (oil) phase are of special interest for the encapsulation and prolonged release of water-soluble drugs.[2,12,13] These drugs, which are usually insoluble in oils, slowly diffuse through oil films (bilayer membranes), which separate water droplets, to give a (sustained) prolonged release effect for these drugs.[14,15]

Taking into account, on the one hand, the highly developed internal surface of these emulsions, and, on the other hand, the interaction of drug molecules with the surface of droplets and with micelles, we expect a substantial effect of interfacial and colloid phenomena on the rate of drug release from these emulsions.

The aim of this study is to formulate colloid concepts for the elaboration of a model for the release of drug molecules from gel emulsions based on a systematic consideration of the effect of interfacial phenomena and the structure-mechanical properties of these emulsions.

The gel emulsions were obtained according to the standard method.[14,16] Perfluorodecalin (PFD) and decane were the continuous oil phases of fluorinated and hydrogenated emulsions, respectively (Table 1). The fluorinated surfactants $C_8F_{17}C_2H_4S$-$C_2H_4(OC_2H_4)_2OH$ ($C_8^F\,\Sigma\,E_2$)[9,10] and $C_{16}H_{33}(OC_2H_4)_4H$ ($C_{16}E_4$) were used. The mean radius of droplets R was determined using a microscope. The water content (φ_w) was equal to 95% for both types of emulsions. The oil/surfactant ratio ρ_{os} was equal to 2.3 or 1.5 for fluorinated or hydrogenated emulsions, respectively. The radius of micelles (r_{mic}) and the aggregation number (N_{ag}) were determined by SANS (PAXY spectrometer, LLB, CEA-CNRS: Saclay, France).[17,18] The solubilised water content (S_{wm}) of saturated inverse micellar solutions was 8 or 13 wt%. The interfacial tension (σ) was measured by a spinning drop method (Texas University instrument).[19] The water soluble active substance (AS), caffeine, was encapsulated in inverse gel emulsions. This AS is practically insoluble in fluorinated and hydrogenated oils, but it is very well solubilised by inverse micellar solutions (the partition coefficients K between the micellar and aqueous phases are equal to 8 and 14, respectively). The diffusion measurements were described elsewhere.[14,16] The diffusion coefficients were determined from the cumulative curves of caffeine release measured by spectrometry.[14]

Table 1 Physico-chemical parameters of fluorinated and hydrogenated emulsions at $T = 25$ °C.

Parameter	Fluorinated emulsion	Hydrogenated emulsion
Surfactant/oil	$C_8^F\,\Sigma\,E_2$/PFD	$C_{16}E_4$/decane
R/μm	1.5	1.5
φ_v	95%	95%
Stability time	months	weeks
σ/mN m^{-1}	2.2	0.5
N_{ag}	700	900
r_{mic}/nm	18	13

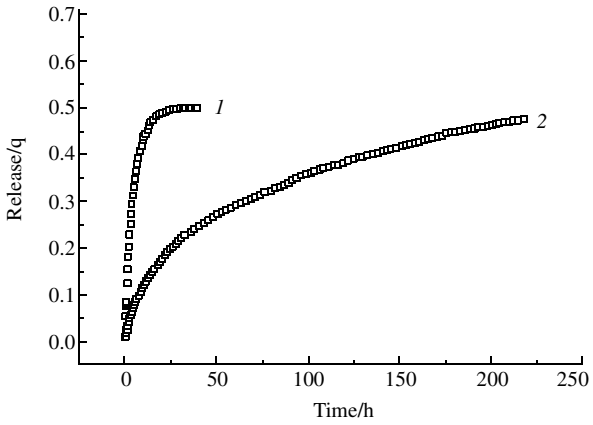

Figure 1 Release curves of caffeine from (*1*) hydrogenated and (*2*) fluorinated gel emulsions.

Figure 1 illustrates the difference between the caffeine release times caffeine from the hydrogenated and fluorinated gel emulsions, where q is the reduced released mass $q(t) = m(t)/m_0$, $m(t)$ is the drug amount (mass) released after time t, and m_0 is the initial mass contained in the emulsion.

The effective diffusion coefficients D_{ef} determined from experimental curves were equal to 4.2×10^{-10} m^2 s^{-1} and 2.4×10^{-11} m^2 s^{-1} for the hydrogenated and fluorinated emulsions, respectively.

We suggest a physico-chemical model, which explains the effect of different parameters characterising the properties of emulsion systems, as well as the properties of encapsulated drug molecules, on the rate of diffusion from gel emulsions. Here, we briefly describe main assumptions and conclusions of the model.

We consider a one-dimensional diffusion release of a drug from a w/o emulsion sample of the volume V_e to the exterior water volume $V_{aq} >> V_e$ through a semipermeable membrane with the area A_e^{ext} [Figure 2(*a*)]. The internal structure of a w/o gel emulsion consists of aqueous droplets separated from each other by a hydrophobic continuous phase (oil) containing inverted swelled micelles solubilised by water [Figure 2(*b*)]. The drug molecules are solubilised in the water phase (concentration C_w) and in the oil phase (concentration C_0), and they may also be adsorbed at the interfaces (adsorption amount Γ/mol m^{-2}).

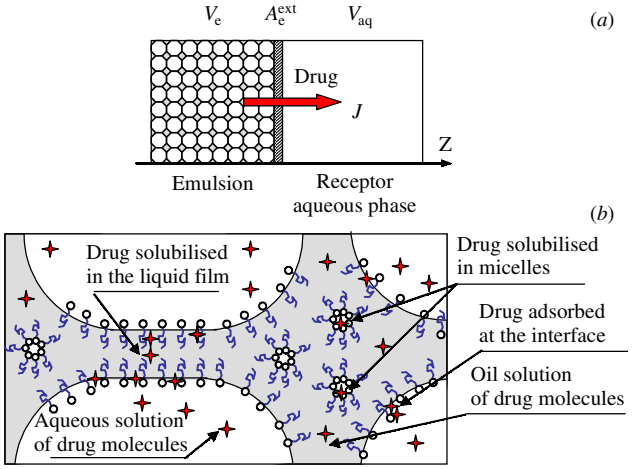

Figure 2 (*a*) Drug release by diffusion and (*b*) the distribution of a drug inside the gel emulsion.

The initial drug concentration $C_e^0 = m_0/V_e$ (m_0 is the mass of the encapsulated drug inside the emulsion volume V_e) may be expressed through the local drug concentrations C_w and C_0, and the adsorption amount Γ

$$C_e^0 = \varphi_w C_w + (1 - \varphi_w)C_0 + A_{sp}\Gamma, \quad (1)$$

where A_{sp} ($m^2\ m^{-3}$) is the specific internal area of the interfacial surface of the emulsion related to the mean droplet radius R as $A_{sp} \sim R^{-1}$. The drug concentration in the continuous oil phase is the sum $C_0 = C_{0,\,mol} + C_{0,\,mic}$, corresponding to the molecular and micellar solubilities of the drug in the oil phase.

The reduced mass $q = m(t)/m_0$ of the released drug may be written as

$$q = \frac{A_e^{ext}}{C_e V_e}\int_0^t j(\tau)d\tau,$$

where the flux of the drug is expressed through the macroscopic concentration gradient $\sigma_z C_e$, averaged over the characteristic length $L >> R$ (but $L << V_e^{1/3}$) according to the Fick law $j = -D_e\sigma_z C_e$, where D_e is the effective diffusion coefficient of the drug inside the emulsion.

On the microscopic level, the flux j of drug molecules from the emulsion to the receptor is the sum of two fluxes: (1) the flux j_f across thin liquid films of the area a_f^{ext} between the emulsion droplets and the aqueous phase of the receptor, and (2) the flux j_{ow} through the interfaces between the oil phase of the emulsion and the receptor aqueous phase (Figure 3). The relative contribution of these two fluxes is given by the relationship

$$j = \psi_f j_f + (1 - \psi_f)\, j_{ow}, \quad (2)$$

where $\psi_f = A_f^{ext}/A_e^{ext}$ is the relative area of emulsion films in contact with the receptor. The parameter ψ_f, depending on the volume fraction of the dispersed phase φ_w, determines the relative contribution of both fluxes to the final flux j and, consequently, to the release rate of the drug. With increasing φ_w, the parameter ψ_f varies from zero (for a 'cross-over' value $\varphi_w^* \cong 0.77$–0.80)[6] to 1 in the limit $\varphi_w \to 1$. For moderately high values of φ_w, this parameter scales as $\psi_f \sim (\varphi_w - \varphi_w^*)^\alpha$ with $\alpha \geq 1$.[20]

Inside the emulsion, the drug transport occurs through thin liquid films (j_f), as well as through free interfaces, from the droplets to the continuous oily phase and back ($j_{wo} + j_{ow}$) and by diffusion inside the continuous oily phase following the Plateau canals (j_{ob}).

Different limit cases may be considered. When the drug is weakly molecularly soluble in the continuous oil phase and the concentration of micelles in this phase is low, the drug is completely localised in the aqueous phase, *i.e.*, in water droplets. The fluxes j_{wo} through the water/oil interface are practically equal to zero, and the microscopic fluxes j_f through thin liquid films may be approximately expressed as

$$j_f = -k_f\Delta C, \quad (3)$$

where k_f has the meaning of the permittivity coefficient of the drug molecules through the film of thickness h_f relating to the difference of the concentration $\Delta C = C_1 - C_2 \cong h_f\sigma C_e$.

Assuming that the drug transfer through thin liquid films is an energetically activated process, the coefficient k_f may be expressed as

$$k_f = K_f \exp(-E_a/kT), \quad (4)$$

where $K_f \sim D_w/h_f$, and E_a is the activation energy of the transfer of drug molecules through a thin liquid film. When $E_a \cong 0$, the permittivity coefficient becomes $k_f = D_w/h_f$, and equation (3) acquires the well-known form of the Fick law for stationary fluxes: $j_f = -k_f\Delta C = (D_w/h_f)\Delta C = D_w\sigma C$.

The simplest way to estimate the activation energy E_a for the diffusion of a drug molecule through a liquid film of thickness h_f is to identify it with the work of formation of a 'hole' of the diameter δ equal to the size of the drug molecule. As found previously,[11] this work for stable emulsions may be estimated as

$$E_a \cong \pi\sigma h_f\delta, \quad (5)$$

where σ is the interfacial tension of the film. Thus, the effects of interfacial tension, film thickness, and drug molecular size on the release rate from gel emulsions can be taken into account.

In the alternative case of high molecular or micellar solubility of the drug in the oil phase, the contribution of the diffusion flux j_{ow} through the oil–water interface to the whole flux j in equation (2) should be considered. When the liquid films are impenetrable (very high E_a values), this drug transport mechanism is crucial. For its quantitative description, we need information on both the structural parameters of emulsions (φ_w, ψ_f, specific interfacial area A_{sp} and the concentration C_{mic} of micelles in the oil phase) and the parameters that characterise the micellar transport of drugs (*e.g.*, the kinetics of adsorption–desorption of micelles at the interface and of the micellar solubilization of drugs).[21]

When the fluxes j_f and j_{ow} are approximately equal, their contribution to the whole flux j will be determined, according to equation (2), by the parameter ψ_f. Nevertheless, for the emulsions with a water content of ~95–98%, this parameter is $\psi_f \sim 1$, which makes the contribution of the flux j_f as a determinant. In this case, the effect of physico-chemical factors on the whole flux may be estimated using equations (2)–(4):

$$j \cong \psi_f j_f \cong -D_{ef}\sigma C, \quad (6)$$

where

$$D_{ef} = kD_w(\varphi_w - \varphi_w^*)^\alpha \exp(-E_a/kT) \quad (7)$$

is the effective diffusion coefficient, and k is an adjustable parameter.

The significance of expression (7) for the effective diffusion coefficient D_{ef} consists in the possibility of explaining and systematising experimental data on drug release from gel emulsions. For example, the difference between the release rate of caffeine

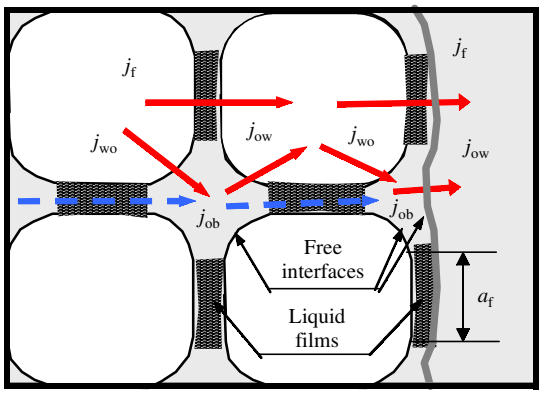

Figure 3 Drug transport from an emulsion to a receptor aqueous phase in a w/o gel emulsion.

from fluorinated and hydrogenated emulsions (Figure 1) can be explained by different activation energies of the diffusion of caffeine molecules through liquid films. According to equation (5), this difference is due to different interfacial tensions σ and film thicknesses h_f at a definite value δ of the size of the caffeine molecule.

According to the experimental data for the fluorinated and hydrogenated emulsions (Table 1), the interfacial tensions are $\sigma_{hyd} = 0.5$ mN m^{-1} and $\sigma_{fluor} = 2.2$ mN m^{-1}, respectively. Believing that the emulsion films thickness is of the order of the non-swelled micelles of the surfactant molecules, we may write[9,10] $h_f \cong 4.7$ nm (for the fluorinated surfactant $C_8^F \Sigma E_2$) and $h_f \cong$ $\cong 6.4$ nm (for the surfactant $C_{16}E_4$). Thus, the activation energy ratio for fluorianted and hydrogenated emulsions is ~3.1, which, according to equation (7), corresponds to a diffusion coefficient ~20 times lower than that of the fluorinated emulsion of the hydrogenated one. The numerical estimation obtained correlates well with the ratio $[D_{ef}(\text{hydro})/D_{ef}(\text{fluor}) = 17.5]$ of the diffusion coefficients $D_{ef}(\text{hydro}) = 4.2\times10^{-10}$ m^2 s^{-1} and $D_{ef}(\text{fluor}) =$ $= 2.4\times10^{-11}$ m^2 s^{-1} for the hydrogenated and fluorinated emulsions, calculated from the experimental release curves (Figure 1).

Note that the observed difference in the rates of drug release from the hydrogenated and fluorinated emulsions is due to not only the difference in the interfacial tension σ and the size of the surfactant molecules but also a higher cohesive energy between the fluorinated surfactant molecules in the bilayer membranes, which is manifested by an increase in the stability of the fluorinated emulsions with regard to the hydrogenated ones (Table 1). The release rate of the drug may also be influenced by the difference in the partition coefficients K of caffeine in the fluorinated and hydrogenated micellar solutions (Table 1).

We expect that the effects of physico-chemical parameters on the experimental drug release curves from the gel emulsions will be understood on the basis of the suggested model.

References

1 D. Attwood and A. T. Florence, in *Surfactant System*, Chapman and Hall, London, 1983, ch. 11.

2 M. Dias, A. Farinha, E. Faustino, J. Hadgraft, J. Pais and C. Toscano, *Int. J. Pharm*., 1999, **182**, 41.

3 K. J. Lissant, *J.Colloid Interface Sci*., 1966, **22**, 462.

4 C. Solans, J. G. Dominguez, J. L. Parra, J. Heuser and S. E. Friberg, *Colloid Polym. Sci*., 1988, **266**, 570.

5 R. Pons, J. C. Ravey, S. Sauvage, M. J. Stébé, P. Erra, C. Solans, *Colloids Surfaces, A*, 1993, **76**, 171.

6 H. M. Princen, *Langmuir*, 1987, **3**, 36.

7 J. Bibette, T. G. Mason, H. Gang, D. A. Weitz and P. Poulin, *Langmuir*, 1993, **9**, 3352.

8 L. Ramos and D. A. Weitz, *Langmuir*, 2001, **17**, 2275.

9 J. C. Ravey and M. J. Stébé, *Prog. Colloid Polym. Sci*., 1990, **82**, 218.

10 J. C. Ravey, M.J. Stébé and S. Sauvage, *Colloids Surfaces, A*, 1994, **91**, 237.

11 V. G. Babak and M.-J. Stébé, *J.D.S.T. (Special P. Becher Issue)*, 2002, **23**, 1.

12 P. Clement, C. Laugel and J.-P. Marty, *Int. J. Pharm.*, 2000, **207**, 7.

13 P. Clement, C. Laugel and J.-P. Marty, *J. Control. Release*, 2000, **66**, 243.

14 S. Rocca, M. J. Garcia-Celma, G. Caldero, R. Pons, C. Solans and M. J. Stébé, *Langmuir*, 1998, **14**, 6840.

15 G. Caldero, M. J. Garcia-Celma, C. Solans, M. J. Stébé, J. C. Ravey, S. Rocca and R. Pons, *Langmuir*, 1998, **14**, 1580.

16 S. Rocca, S. Muller and M.-J. Stebe, *J. Control. Release*, 1999, **61**, 251.

17 J. C. Ravey, M. J. Stebe and R. Oberthür, in *Surfactants in Solution*, eds. K. L. Mittal and P. Bothorel, Plenum, New York, 1987, p. 1421.

18 J. C. Ravey, M. J. Stébé, S. Sauvage and C. Elmoujahid, *Colloids Surfaces, A*, 1995, **99**, 221.

19 A. Langenfeld, V. Schmitt and M. J. Stebe, *J.C.I.S.*, 1999, **218**, 522.

20 M.-D. Lacasse, G. S. Grest and D. Levine, *Phys. Rev. E*, 1996, **54**, 5436.

21 A. Kabalnov and J. Weers, *Langmuir*, 1996, **12**, 3442.

Received: 6th May 2003; Com. 03/2120