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An evaluation of a mass transfer rate at the boundary of different release mechanisms in complex liquid dispersion

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ABSTRACT

The paper focuses on the development of the criteria for modelling mass transfer during release process at the boundary of diffusion and fragmentation in complex liquid dispersion, such as double emulsions. The proposed model for predicting release rates accounts for the effect of mass transfer resistance coupled with the emulsion structure and external release environment. The criteria of the applicability of the proposed model were formulated after verification by studies of drug release from O1/W/O2 emulsions, prepared in a Taylor–Couette flow bioreactor. It has been found that one or more mechanisms may dominate at different release stages, depending on the mixing intensity of the release medium and internal structure of double emulsions. The experimental analysis of release rates and the changes in the emulsion structure during the release process, revealed the existence of three mechanisms: (i) diffusion, (ii) diffusion and fragmentation—loss of the original structure from double emulsions to single emulsions and (iii) fragmentation. The criteria covering the diffusion release model have been formulated, as the shear rate ranges at the boundary of different mechanisms, and correspond to the values of the critical capillary numbers, which seemed to depend on the volume fraction of internal droplets of multiple emulsions.

1. Introduction

The mathematical description of an active agent (e.g. a drug) release process is an important consideration in the design of advanced active substance delivery systems. Release modelling can also be helpful in providing an interpretation of the experimental data and a better understanding of the mechanisms of drug release. Most of the research devoted to this subject refers to the release rate of drugs from therapeutic delivery systems, such as liposomes, micro-emulsions, multiple emulsions, nanoparticles, or polymeric implantable devices. In this paper we discuss double emulsions, which are emerging as a viable alternative to controlled release systems that have been shown to deliver therapeutic concentrations of various potent chemopreventives and drugs. Multiple emulsions are hierarchically structured liquid dispersed systems of "drops in drops" (see Table 1), which allow one or more active agents to be incorporated and then released in a controlled manner, through their size and physicochemical parameters drops form a liquid-permeable membrane separating the internal droplets from the continuous external phase. Multiple emulsions can have a double, triple, quadruple, quintuple, or even more complex structures. These complex liquid dispersions have been extensively studied due to their potential application in separation processes, and for the controlled release of chemical species (e.g. hydrophobic or hydrophilic drugs), initially encapsulated in the internal droplets [1–5]. Other applications include chemistry, cosmetics, pharmaceutics, food, and the use of multiple emulsions as intermediate templates in preparing lipid nanoparticles or polymersomes, polymeric, and biodegradable microspheres, or gel microbeds [6–10]. Most applications refer to the double structured emulsions. Two main drug release mechanisms from multiple emulsions have been recognised diffusion of an active agent through the permeable membrane phase drops, and the breakdown of the emulsion membrane due to shear forces, an osmotic gradient (a swelling-breakdown phenomenon), or the presence of surfactants, or additives [1,11–17]. The bursting mechanisms of an emulsion membrane lead to the fragmentation of double emulsions i.e. loss of their complex primary structure, result in simple emulsions, as shown in Fig. 1.

Theoretical and experimental analysis of the deformation and breakup of double emulsions allowed several pathways of instability to be determined [1,13,14,16,17]. The most likely mechanisms are (i) coalescence of the internal droplets, (ii) coalescence of membrane phase drops and (iii) coalescence of the

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Nomenclature

a	Interfacial area of the internal phase drops, m^{-1}
a_n	Parameter in Eqs. (14)–(16)
b_n	Parameter in Eqs. (14)–(16)
C	Concentration of a drug within the membrane phase of double emulsions, $g\,m^{-3}$
Ca	Capillary number, ($Ca = \mu_{ea}\,(D_{43}/2)\,\gamma_e/\sigma_{stat.}$)
C^*_S	Concentration of a drug in the pseudo-homogenous phase in an equilibrium with the membrane phase, $g\,m^{-3}$
C^*_{S0}	Initial concentration of a drug in the pseudo-homogenous phase in an equilibrium with the membrane phase, $g\,m^{-3}$
$C_{S.in.}$	Drug concentration in the internal phase at the CTF contactor inlet, wt%
d, D	Diameter of internal and membrane phase drops of double emulsion, m
D_{10}, d_{10}	Arithmetic mean diameter of membrane, internal phase drops, m
D_{32}, d_{32}	The Sauter mean diameter of membrane, internal phase drops, m
D_{43}, d_{43}	The de Brouckere mean diameter of membrane, internal phase drops, m
D_e	Effective diffusion coefficient of substance in the membrane phase drop, $m^2\,s^{-1}$
d_m	Stirrer diameter, m
D_{modal}	Modal diameter of membrane phase drops, m
D_S	Molecular diffusion coefficient of substance in membrane phase drop, $m^2\,s^{-1}$
D_T, H	Diameter and high of tank, m
$F_{\Sigma.in.}$	Total area of the internal phase droplets of radius r_i, m^2
h	Mass transfer coefficient in continuous phase, $m\,s^{-1}$
$k_L\alpha$	Volumetric mass transfer coefficient in the membrane phase, s^{-1}
m	Partition coefficient of drug between membrane/external phases
M_∞	Cumulative mass of drug released at the infinite time t_∞, g
M_t	Cumulative mass of drug released at the time t, g
M_{t0}	Initial mass of drug, g
M_{t+}	Dimensionless cumulative mass of drug released at the dimensionless time (t^+)
$M_{t+=1}$	Dimensionless cumulative mass of drug released at the infinite time ($t^+ = 1$)
n, N	Rotational frequency of an inner cylinder of the CTF contactor and the stirrer, rpm
q_i	Volume content of drops of i-class in population, %
R, r_i	Radius of membrane and internal phase drops of double emulsions, m
Re_e	Effective Reynolds number ($Re_e = n\,d_m{}^2\,\rho/\mu_{ea}$)
t	Release time, h
t_0	Initial release time, h
u	Superficial velocity of fluid (liquid mixture) in convection-diffusion Eqs. (1), (2) and (5), $m\,s^{-1}$
V_Σ	Volume of the drop of radius R (diameter D), m^3
$V_{\Sigma.in.}$	Total volume of the internal phase droplets of radius r_i, m^3
$V_{memb.}$	Volume of the membrane phase in the drop of radius R, m^3

Greek symbols

α_n	Parameter in Eqs. (14)–(16)
$\dot{\gamma}_e$	Effective value of shear rate, s^{-1}
δ	Layer thickness representing mass transfer resistance in the membrane phase, m
θ	Parameter in Eqs. (15) and (16)
κ	Structure parameter, equivalent to volumetric mass transfer coefficient, s^{-1}
λ_n	Solution of the transcendental equation $\lambda_n = (1-h)\,\mathrm{Tan}(\lambda_n)$ for $n = 1,2\ldots$
μ	Fluid viscosity, Pa s
ρ	Fluid density, $kg\,m^{-3}$
$\sigma_{stat.}$	Static interfacial tensions of aqueous gelatin solution (membrane phase) in contact with liquid paraffin, $mN\,m^{-1}$
ϕ	Volume packing fraction of internal droplets in the membrane phase drops
$\phi_{m.p.c.}$	Close packing—the maximum volume fraction for monodisperse internal drops
Φ_n	Parameter in Eqs. (14)–(16)

Subscripts

a	Apparent value
cr	Critical value
e	Effective value
E1, E2, E3, E4	Double emulsions E1, E2, E3, E4
expt.	Experimental value
ext.	External phase of double emulsions
in.	Internal phase of double emulsions
memb.	Membrane phase of double emulsions
s	Pseudo-homogenous phase

Superscripts

+	Dimensionless values

internal drops with the external continuous phase of double emulsions. These mechanisms may influence the release rate of substances from the internal phase of double emulsions and should be taken into account in modelling the release process under shearing. If a drug is released only via diffusion through the membrane phase of multiple emulsions, to determine the release rate the models developed for solid micro/nanospheres can be used [18–20]. These models assume that geometric properties, an internal structure, transport parameters, and physicochemical properties of micro/nanospheres are constant during the process. The approach to diffusional release modelling requires us to consider the initial concentration of the drug (C_0), and its solubility within the matrix material of microparticles (C_S), or in the case of multiple emulsions, within the membrane phase [18–22]. Generally, two different cases are considered: with the initial drug concentration at either below or above the drug solubility within the system. In the first case ($C_0 < C_S$), an active agent (a drug) is uniformly dissolved within the solid matrix, or within the drops forming the liquid membrane of the multiple emulsion. The second case ($C_0 > C_S$) refers to the co-existence of the dissolved drug molecules with an excess of the drug, which is dispersed as aggregates and/or crystals. The second case is a more complex problem, and it is usually treated mathematically by a moving diffusion front of a dispersed drug (see Table 1). Diffusion models for both cases are based on solutions of the first and second Fick's laws with appropriate boundary and initial conditions, and require the assumption that the substance is molecularly dispersed within the whole volume of the membrane, or matrix phase. The concepts of modelling of an active agent diffusive release from the microspheres with different structures (type I–IV), as reported in the literature, are summarised in Table 1. In the modelling of a release process either infinite mass transfer conditions are