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Research paper

# Nanoparticle layers controlling drug release from emulsions

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**Abstract**

The influence of interfacial layers of silica nanoparticles on the release kinetics of a model lipophilic drug (di-butyl-phthalate (DBP)) from polydimethylsiloxane droplets in water is reported. The nanoparticle layers are formed by self-assembly from solution and their structure is controlled by nanoparticle hydrophobicity and the solution conditions. For DBP loading levels resulting in released concentrations below the solubility limit, release is rapid from uncoated droplets whereas significant sustained release is facilitated by rigid interfacial layers of hydrophobic silica nanoparticles. Activation energies for release are in the range 580–630 kJ $mol^{-1}$, which is ten times greater than for barriers introduced by typical polymeric stabilisers. In contrast, at higher DBP loading levels (total concentration greater than the solubility level), both hydrophilic and hydrophobic nanoparticle layers increase the rate and extent of dissolution compared with uncoated droplets and pure DBP solutions. Nanoparticle layers are shown to significantly influence the release kinetics of lipophilic drugs from oil in water emulsions: either sustained or enhanced release properties can be introduced depending on the nanoparticle layer type and drug loading level. Thus, nanoparticle layers may be engineered to facilitate a range of release behaviours and offer great potential in the delivery of poorly soluble drugs.
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*Keywords:* Emulsions; Nanoparticles; Encapsulation; Drug release

## 1. Introduction

Surfactant and polymer stabilised emulsions have been widely investigated as carriers for lipophilic drugs, as well as intermediates in the production of micro/nanocapsules and particles for controlled release and drug protection [1–6]. It is well documented [7–13] that solid particles can act as excellent emulsion stabilisers, either solely or combined with surfactants and polymers. Furthermore, the self-assembly of nanoparticles at fluid interfaces that is driven by the reduction in interfacial energy grows in importance as a method for producing shells with desirable encapsulation properties [14–16]. Consequently, nanoparticle encapsulated emulsion systems may form the basis for design of alternative low surfactant or surfactant-free drug delivery systems.

There has been considerable interest in the *in vitro* release and *in vivo* fate of lipophilic drug molecules within oil droplets stabilised by classical and phospholipid emulsifiers [17–19]. The kinetics of release is mostly governed by the drug partition coefficient ($\log PC_{oct}$): drugs with $\log PC_{oct} > 9$ are generally retained in emulsion droplets and their *in vivo* disposition follows that of the droplet, whereas drugs with $\log PC_{oct} < 9$ are rapidly released under sink conditions and their bio-fate is consequently independent of the droplets [17]. Drug release kinetics is therefore driven by drug partitioning and lack of sustained release properties is a characteristic of conventional emulsions [17–19]. That is, commonly used emulsifiers such as lecithin and Pluronics® do not act as significant interfacial transport barriers and release of solute from such emulsion droplets typically occurs within 500 s [19].

Reports on the properties of particle stabilised emulsions and their potential as drug delivery systems,

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particularly for lipophilic drugs, are rarely described in the literature. Oza and Frank [20,21] investigated the preparation, characterisation and release behaviour of lidocaine in w/o/w multiple emulsions stabilised by microcrystalline cellulose and conventional surfactants. More recent reports on electrolyte release from w/o/w multiple emulsions [22–25] suggested that particle barriers at the oil–water interface could be particularly efficient for sustained release due to the formation of a better sealed interface. Dry adsorbed emulsions [26–28] have also been developed as a specific oral delivery system for controlled release of hydrophilic drugs. This delivery system is a free-flowing powder with nonporous particles of size from 125 to 710 μm, which consist of a random pack of hydrophilic and hydrophobic particles, containing a liquid-phase (aqueous and oily) adsorbed onto silica of the same polarity by weak bonds [26–28]. It is clear that self-assembled layers of nanoparticles offer much promise as coatings to stabilise and control drug release from emulsions; however there are currently no reported studies where the structure of the nanoparticle layer is systematically controlled and its influence on drug release ascertained over a wide range of drug loading levels.

Recently we have developed a model system where nanoparticle layers can be self-assembled at the polydimethylsiloxane (PDMS) droplet-water interface and have reported adsorption isotherms and layer microstructure for hydrophilic [29] and hydrophobic [30–32] silica nanoparticles (50 nm in diameter) under different solution conditions (electrolytes and pH). Hydrophilic silica nanoparticles adsorb as a monolayer, whereas hydrophobic silica nanoparticles form multilayers at PDMS droplet-water interfaces. Adsorption and interfacial layer structure are governed by interparticle lateral forces, i.e. the balance between attractive and repulsive forces. A schematic representation of how nanoparticle layer microstructure is critically determined by salt concentration and nanoparticle type is given in Fig. 1. Hydrophilic silica nanoparticles form densely packed layers without extensive interfacial aggregation at high salt concentrations when the double layer thickness is 2–3 nm (Fig. 1a). Hydrophobic silica nanoparticles may form multilayer coatings of non-aggregated nanoparticles (Fig. 1b), a rigid interfacial layer (Fig. 1c) or thick wall (Fig. 1d) depending on the salt concentration.

The present study aims to establish the interplay between layer microstructure of silica nanoparticles at the interface of PDMS droplets and the release behaviour of a model lipophilic molecule. This PDMS droplet system has unique properties not encountered in common emulsions that enable better insight into the role of nanoparticle layers in controlling release. That is, the PDMS droplets [33,34] are highly monodispersed, emulsifier free and stabilised exclusively by negative charge development due to the dissociation of silanol groups at the interface. Therefore, drug release can be assessed in the presence and absence of stabilising layers, and the role of nanoparticle layers can be isolated.

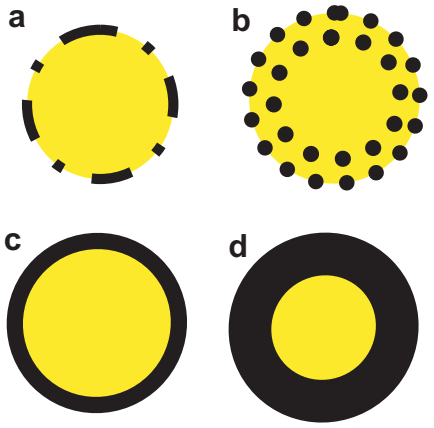


Fig. 1. Schematic representation of silica nanoparticle coatings at PDMS droplet interfaces: (a) partially aggregated, monolayer coatings of hydrophilic silica nanoparticle at $10^{-2}$ M NaCl, sample B; (b) multilayer coatings of non-aggregated hydrophobic silica nanoparticles at $10^{-4}$ M NaCl, sample C; (c) thick multilayer coatings of fully aggregated hydrophobic silica nanoparticle at $10^{-3}$–$10^{-2}$ M NaCl, samples D and E; (d) thick interfacial wall of hydrophobic nanoparticles at $10^{-1}$ M NaCl, sample F.

## 2. Materials and methods

### 2.1. Materials

High-purity water (Milli-Q) was used throughout the study. Diethoxydimethylsilane (DEDMS) was supplied by Sigma–Aldrich (Milwaukee, WI) and redistilled under nitrogen prior to use. Ammonia (Aldrich), $KNO_3$, NaCl (Merck, Darmstadt, Germany) and other reagents used were of analytical grade. Fumed silica nanoparticles [35]: Aerosil 380 and Aerosil 974R were kindly supplied by Degussa (their properties are given in Table 1). Dibutylphthalate (DBP) was supplied by Sigma–Aldrich, which is a liquid at room temperature with $\log P$ (octanol/water) = 4.68 and solubility in water of (1.0 mg/100 ml) [37].

Table 1
Properties of silica nanoparticles

| Trade name | Si–OH groups/nm$^{-2}$[a] | Contact angle (°)[b] | | BET surface area ($m^2g^{-1}$) | Average size (nm)[c] |
|---|---|---|---|---|---|
| Aerosil 380 | 2.5 | 14 | 0 | 380 ± 30 | 7 |
| Aerosil R974 | 0.39 | 117 ± 4 | 75 | 170 ± 20 | 12 |

[a] Determined from Li–Al-hydride method [35].
[b] Contact angles estimated from enthalpy of immersion [36]; first (left) number – at water/air interface, second (right) number – at toluene/water interface.
[c] Refers to primary particles according to the manufacturer specifications [35].

### 2.2. PDMS emulsions: preparation and DBP loading

DBP was chosen as a model poorly soluble drug because it is a liquid and readily miscible with PDMS (this was confirmed experimentally), hence it does not suffer from physical state changes when incorporated within the droplets. Release profiles were determined from both uncoated and nanoparticle coated droplets so as to establish the role of the nanoparticle stabilising layers in controlling release. DBP was incorporated into the PDMS droplets during the synthesis step. PDMS droplets were prepared using a modification of the methods reported by Obey and Vincent [33] and Goller et al. (without dialysis) [34]. That is, aqueous solutions containing 1.0 wt% DEDMS, which was previously mixed with 0, 0.025, 0.1 and 0.25 wt% DBP (i.e. weight ratio DEDMS: DBP is 1:0, 1:0.025, 1:0.1 and 1:0.25, respectively) in a nitrogen gas atmosphere with 0.1% ammonia, were sealed under nitrogen gas in a 250 ml reaction vessel, shaken vigorously for 30 s, and then tumbled at 30 rpm and 25 °C for 18 h. Drop size distributions were characterised by laser diffraction (Malvern Mastersizer X). Average drop sizes and size span [defined as $(d(v,0.9) - d(v,0.1))/d(v,0.5)$] are ~2.0 μm and 0.56. The presence of DBP did not significantly influence the drop size distribution. These emulsion samples were considerably more mono-dispersed than typical o/w or w/o emulsions prepared by homogenisation. Electrophoretic mobilities and hence ζ potentials were determined using phase analysis light scattering (PALS). Droplet ζ potential values were in the range $-71 \pm 10$ mV and independent of DBP inclusion. The partitioning of DBP into the emulsions was determined after ultracentrifugation at 10 000 rpm for 30 min and HPLC analysis. Log $P$ (PDMS droplets/aqueous phase of emulsion) was determined to be $3.18 \pm 0.2$ and is independent of the DBP concentration. The partition coefficient is lower for a droplet/water system than for an octanol/water system because of increased interfacial area and differences in the polarity of PDMS and octanol.

### 2.3. Nanoparticle coating (droplet encapsulation by nanoparticles)

A schematic representation of the drug encapsulation and nanoparticle layer formation processes is given in Fig. 2. Nanoparticle coated droplet samples were prepared by mixing 10 ml of the PDMS emulsions with 10 ml of sonicated Milli-Q water (bare droplets) and 1 wt% silica nanoparticle aqueous dispersions (coated droplets), respectively. Salt concentrations were adjusted in the range $10^{-4}$ to $10^{-1}$ M NaCl in order to control nanoparticle self-assembly and the nanoparticle layer structure. Samples were tumbled for 18 h at 30 rpm to attain nanoparticle coating and were subsequently investigated for drug release. Droplets were coated by silica nanoparticles in accord with previously reported isotherms [30,31]. It is noted that DBP partitioning was not significantly influenced by the nanoparticle coating process, i.e. $\log P = 3.18 \pm 0.2$. Furthermore, droplet size and zeta potentials were unaltered in the presence of nanoparticle layers.

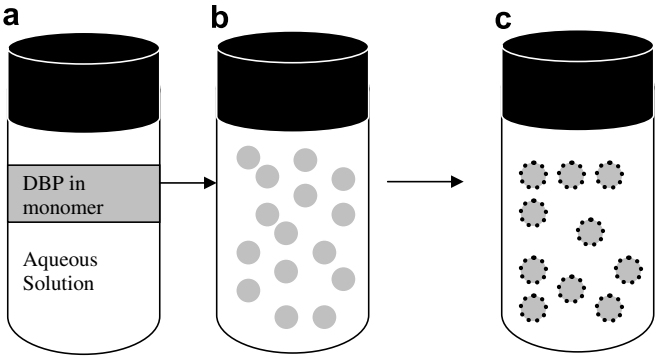


Fig. 2. Schematic representation of droplet and capsule preparation methodology: (a) Polymerisation and spontaneous emulsification of monomer containing DBP, (b) Nanoparticle self assembly, (c) Nanoparticle coated PDMS droplets.

### 2.4. Drug release studies

Drug release rate measurement from a colloidal carrier is not a trivial exercise. The major experimental difficulties are the rapid release from submicron-size carriers and appropriate separation of dissolved drug from the carrier components [38–40]. Many different methods have been described, such as the dialysis sac diffusion technique [38] and bulk equilibrium reverse dialysis [39]. It is claimed that with these methods, the carrier is never fully diluted with the release solution, and hence transport through the membrane may be a rate limiting step in the release process. Centrifugal ultrafiltration has no such drawback, but suffers from possible changes in drug distribution profile due to the strong centrifugal force. An ultrafiltration technique at low pressure has also been proposed [40]. In preliminary experiments we have determined that many dialysis membrane materials adsorb DBP and therefore we have used ultracentrifugation for separation.

The release profiles of DBP from emulsions were investigated using the USP rotation paddle method. 20 ml of emulsion samples was placed in the glass dissolution apparatus and filled with 900 ml of total volume dissolution medium (sonicated Milli-Q water). Two millilitre aliquots of medium were extracted with a syringe at certain time intervals and centrifuged at 10 000 rpm for 30 min in order to remove droplets and any non-adsorbed nanoparticles. Supernatants were analysed for DBP content by HPLC (655A-11 Liquid Chromatograph, Shimadzu) equipped with a UV detector. A Platinum® EPS C18, 5 μm, $150 \times 4.6$ mm (Alltech) reversed-phase HPLC column was used. The column was eluted with a solvent system containing sodium acetate 0.015 mol/L, pH = 4.5 and acetonitrile (3.5:6.5, v/v). Following injection of 20 μl sample volumes the eluent was run at a rate of 1 ml/min and monitored at

254 nm. The minimum concentration detected was $10^{-6}$ g/100 ml. Each sample was analysed in triplicate.

## 3. Results and discussion

### 3.1. PDMS droplets containing DBP and nanoparticle layers

A range of PDMS droplets were prepared with different levels of DBL loading and coatings composed of both hydrophilic and hydrophobic silica nanoparticles prepared under different solution conditions. The composition and properties of these droplets are given in Table 2. Samples B–F have structures that are schematically depicted in Fig. 1, i.e. sample B corresponds to Fig. 1a, sample C to Fig. 1b, samples D and E to Fig. 1c and sample F to Fig. 1d.

### 3.2. DBP release from bare and coated PDMS droplets

#### 3.2.1. Under sink conditions

Dibutylphthalate (DBP) is a poorly soluble lipophilic molecule with solubility in water of 1 mg/100 ml. When considering DBP release from PDMS droplets, sink conditions are defined as when the total DBP concentration in the dissolution medium is significantly below the solubility limit in water; this is the case for emulsion samples A–F with low DBP loading (Table 2) where the maximum DBP concentration in the dissolution medium is 0.28 mg/100 ml. DBP release from within uncoated droplets (sample A) is rapid and complete (Fig. 3): 70% is released after 10 min and 100% is released after 2 h. In comparison, DBP dissolution from coarse DBP liquid droplets required ~4 h to reach an equivalent concentration. It is well documented that both the saturation solubility and dissolution velocity are increased when the particle size of poorly soluble drugs is decreased or when the emulsion droplets that carry the poorly soluble drug are smaller [41]. The increase in saturation solubility can be explained by the Kelvin and the Ostwald–Freundlich equations [41]. The Noyes–Whitney equation describes the dissolution velocity $dc/dt$ which depends on the surface area $A$, the diffusional distance ($h$), and difference between the saturation solubility (cs) and the equilibrium concentration in bulk phase (cx):

$$dc/dt = A(cs - cx)/h \quad (1)$$

Table 2
PDMS droplets with and without nanoparticle layers

| Emulsion sample | Silica nanoparticle type | Salt concentration [NaCl] M |
|---|---|---|
| A | None | |
| B | Hydrophilic | $10^{-2}$ |
| C | Hydrophobic | $10^{-4}$ |
| D | Hydrophobic | $10^{-3}$ |
| E | Hydrophobic | $10^{-2}$ |
| F | Hydrophobic | $10^{-1}$ |

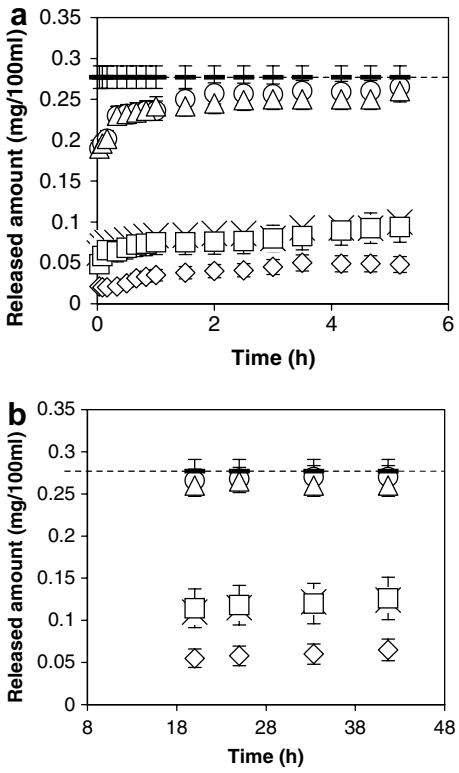


Fig. 3. DBL release profiles from PDMS emulsions with low DBP loading under sink conditions at 37 °C: ○ samples A and B; △ sample C; □ sample D; × sample E; ◇ sample F; dashed line represents 100% DBP dissolution (0.28 mg/100 ml): (a) release time first 6 h; (b) release time 48 h.

The diffusional distance is reduced for nanoparticles in comparison with micron-sized particles [41]. The simultaneous increase in cs and a decrease in $h$ lead to an increased concentration gradient $(cs - cx)/h$, thus enhancing the dissolution velocity in addition to any surface effects. In the case of DBP it is obvious that the dissolution rate is increased when DBP is incorporated into micron sized PDMS droplets rather than as coarse oil droplets. This is considered to be due to an increased surface area for dissolution. The release profiles of pure DBP and DBP in PDMS droplets are in accord with a number of previous reports [17,18,42,43] that drug release from emulsion droplets under sink conditions is rapid and driven by partitioning. It has also been well documented that commonly used emulsifiers, such as poloxamers and lecithin [19] as well as thin (10 nm) polymer layers [43] around oil droplets, do not act as strong barriers that prolong drug release. On the other hand, particle layers have been reported to significantly retard electrolyte release from w/o/w multiple emulsion droplets [24,25]. Barthel et al. [24] and Binks [25] theoretically and experimentally described the release kinetics of the electrolytes CsCl and NaCl from an inner water phase to an outer water phase in multiple w/o/w emulsions stabilised entirely by silica nanoparticles. The release followed first order kinetics with a rate constant (0.001 $min^{-1}$) 200 times lower than that theoretically calcu-

lated (0.2 $min^{-1}$) under the assumption that no interfacial barrier is present.

The presence of hydrophilic and hydrophobic silica nanoparticle layers prepared at a low salt concentration (samples B and C) does not significantly influence the release of DBP (Fig. 3), i.e. release is rapid. At higher salt concentrations (samples D and E) hydrophobic silica nanoparticles create a rigid interfacial layer that significantly retards the release of DBP (Fig. 3); the half release time is ~18 h. The release rate is further retarded in the presence of a thick interfacial particle wall prepared at $10^{-1}$ M NaCl (sample F). Thus, depending on the salt concentration during preparation, hydrophobic silica nanoparticle coatings can be engineered to be permeable or semipermeable.

Drug release from spherical devices under sink conditions can be discussed using two limiting models [19]. These models consider the situations where the rate of release is limited by either diffusion through the oil droplet or by an interfacial barrier. When no interfacial barrier is present, the release of drug over long time periods is approximated by:

$$M_t/M_0 = 1 - 6/\pi^2 \exp(-\pi^2\tau) \quad (2)$$

where $M_t$ is the amount of drug in the droplet at time $t$, $M_0$ is the initial amount of drug and dimensionless time $\tau$ is given by:

$$\tau = Dt/r^2 \quad (3)$$

where $D$ is the diffusion coefficient of the drug in the oil droplet and $r$ is the droplet radius.

This expression can be rearranged into the linear form:

$$\ln\,(1 - M_t/M_0) = \ln\,(6/\pi^2) - \pi^2 Dt/r^2 \quad (4)$$

Thus a plot of ln $(1 - M_t/M_0)$ against time will have a limiting slope at longer times of $-\pi^2 D/r^2$, enabling the diffusion coefficient to be determined.

When transport across the droplet interface is rate limiting, the long-time approximation for the released drug is given by:

$$M_t = 1/3\ Ac_0 r\ (1 - \exp\,(-3\kappa\tau)) \quad (5)$$

where $A$ is the surface area of the sphere, $c_0$ is the initial concentration of drug in the oil droplet and $\kappa$ is given by:

$$\kappa = k_1/D \quad (6)$$

where $k_1$ is the interfacial rate constant. Since the initial amount of drug in the droplet is $Ac_0 r/3$, this expression simplifies to:

$$M_t/M_0 = 1 - \exp\,(-3\ k_1 t/r^2) \quad (7)$$

hence:

$$\ln\,(1 - M_t/M_0) = -3\ k_1 t/r^2 \quad (8)$$

Thus a plot of ln $(1 - M_t/M_0)$ against time has a limiting slope at longer times of $-3k_1/r^2$, hence enabling the interfacial transport rate constant of the drug between the oil droplet and the release medium to be determined.

Considering that DBP release from bare PDMS droplets is rapid and significantly retarded when rigid interfacial layers of hydrophobic nanoparticles are present (Fig. 3), we may assume that interfacial transport is the rate limiting step, and therefore Eq. (8) may be applied. Plots of ln $(1 - M_t/M_0)$ against time for PDMS droplets with rigid hydrophobic coatings are presented in Fig. 4a. Correlation coefficients are >0.96 and release rate constants were calculated to be 0.3 $nm^2\ s^{-1}$ (samples D and E) and 0.05 $nm^2\ s^{-1}$ (sample F). These values are significantly lower than reported rate constants for drug release from Pluronic® stabilised emulsions (i.e. 4.5–45 $nm^2\ s^{-1}$) [19]. That is, nanoparticle coatings are a more significant barrier for molecular transport from an emulsion droplet than are adsorbed polymer layers.

It is also feasible to consider coated PDMS droplets with rigid nanoparticle layers as microcapsules in which the internal drug concentration decreases with time. In that case the drug release kinetics can be represented by an exponential relationship [19,28]:

$$\ln\,(Q_0 - Q) = \ln\ Q_0 - kt \quad (9)$$

where $Q_0$ is the initial amount of drug present in the droplets; $Q$ is the amount released at time $t$ and $k$ is the first-order kinetic constant ($min^{-1}$). Plots of ln $(Q_0 - Q)/Q_0$ vs. time (Fig. 4b) had $R^2$ values of 0.88, 0.894 and 0.936, respectively, and $k$ was calculated to be 0.0003 $min^{-1}$ (for samples D and E) and 0.0001 $min^{-1}$ (for sample F). These

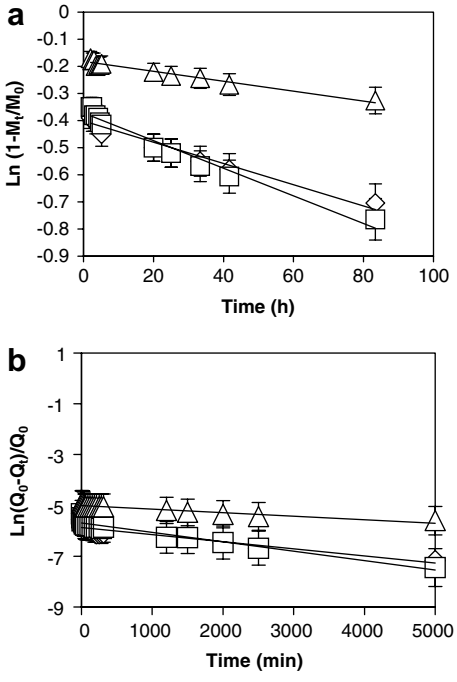


Fig. 4. Linearised DBL release profiles from hydrophobic nanoparticle coated PDMS emulsions (□ sample D; ◇ sample E; △ sample F) with low DBP loading under sink conditions: (a) long time approximation based on Eq. (8), (b) based on capsule release from, i.e. Eq. (8).

values are 1000 times lower than equivalent values for dry adsorbed emulsions [28], which further confirm that the sustained release effect is extensive for the system under investigation here.

The activation energy for interfacial transport was determined using an Arrhenius approach; this has been used previously for emulsions [19]. Kinetic release profiles for samples D and F were determined at four temperatures: 22, 27, 32 and $37 \pm 0.2$ °C. Kinetic rate constants were determined for each temperature from Eq. (8) and from the Arrhenius plots (Fig. 5) the activation energies ($E_a$) were calculated to be $580 \pm 60$ and $630 \pm 75$ kJ mol$^{-1}$, for samples D and F, respectively. These $E_a$ values are significantly higher than the value of 50 kJ mol$^{-1}$ reported for small lipophilic molecules to pass through Pluronic® barriers around oil droplets [19].

The linearity of the Arrhenius plots in Fig. 5 can be attributed to non-significant changes in the interfacial layer structure during the release process and as a function of temperature [19]. Washington and Evans [19] reported deviations from Arrhenius-type kinetics in Pluronic® stabilised o/w emulsions and suggested that temperature increase changes the hydration of Pluronic® polymer layers. The attachment energy of small particles with intermediate contact angles (close to 90° at oil–water interfaces) has an order of magnitude of $10^4$ kT, hence confirming irreversible attachment [9], i.e. changes in the interfacial barrier as a function of temperature are not likely to occur. Therefore, diffusion through the interfacial wall, not particle detachment, can be proposed as the release mechanism.

### 3.2.2. Non-sink conditions

*3.2.2.1. Medium DBP loading levels.* Medium DBP loading levels correspond to a DEDMS:DBP weight ratio of 1:0.1 (i.e. ~10 wt% DBP in PDMS droplet emulsion phase) and correspond to a maximum DBP level of 1.1 mg/100 ml in dissolution medium, i.e. 10% greater than the equilibrium solubility.

In comparison with the sink conditions described above, the release behaviour for the samples A–C and F at medium DBP loading (Table 2) is highly contrasting, see Fig. 6.

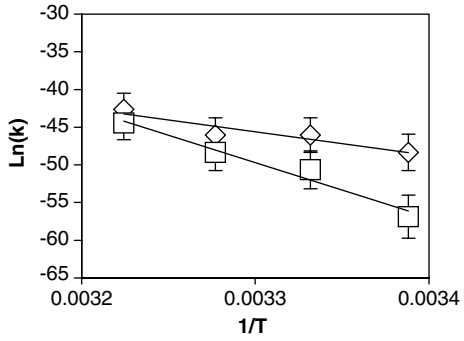


Fig. 5. Arrhenius plots for DBP release under sink conditions from hydrophobic nanoparticle coated PDMS emulsions with low DBP loading: ◇ sample D; □ sample F.

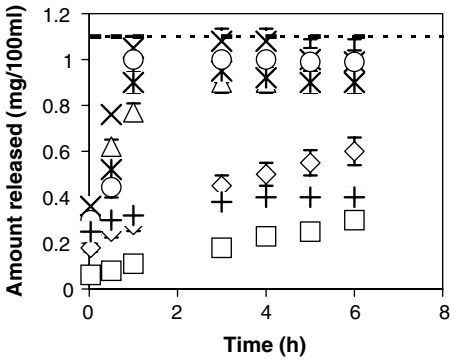


Fig. 6. DBL release profiles from PDMS emulsions with medium DBP loading under non-sink conditions at 37 °C: □ pure DBP; ◇ sample A; △ pure DBP with hydrophilic silica; ○ pure DBP with hydrophobic silica; ∗ sample B; × sample C; + sample F; dotted line correspond to 100% DBP dissolution/release (1.1 mg/100 ml).

When pure DBP oil phase (as coarse droplets) is added at 1.1 mg/100 ml into the dissolution medium, it takes ~20 h to achieve the equilibrium solubility level due to the slow rate of DBP dissolution. In line with the previous section, the dissolution rate is increased when DBP is incorporated into PDMS emulsion droplets (Fig. 6), e.g.: after 6 h 30% pure DBP and 60% DBP from PDMS droplets are released.

When the silica nanoparticles are present in coarse DBP emulsions or at the surface of PDMS emulsion droplets containing DBP, the dissolution velocity and soluble drug fraction are dramatically increased (Fig. 6). To illustrate the observed effect, the kinetic release rate constant calculated using Eq. (9) is 0.0015 min$^{-1}$ for bare PDMS droplets (sample A) and 0.03 min$^{-1}$ for silica nanoparticle coated droplets (samples B and C). The effect is strongly dependent upon the nature of the nanoparticle coating and is only significant when permeable nanoparticle coatings are present at the surface of the droplets (samples B and C); whereas when a thick nanoparticle wall is present at the droplet's surface (sample F) this effect is much less pronounced (Fig. 6). It has been demonstrated [44] that the release profile of tolbutamide from spray dried silica solid dispersions is dependent on the type of silica employed. Solid dispersions with hydrophilic silica showed enhanced dissolution properties, whereas the same dispersions with hydrophobic silica showed retarded dissolution in comparison to the original drug crystals; the effect was attributed to the amphiphilic nature and ability to form hydrophobic bonds between drug and silica that retard release. Our results presented here show that both hydrophilic and hydrophobic silica nanoparticles in the presence and absence of PDMS droplets (Fig. 6) improved the dissolution properties of DBP. A release retarding effect is operative only when rigid hydrophobic layers are present at droplet interfaces. This effect is considered to be due to specific interactions between rigid interfacial silica nanoparticle multilayers and PDMS, where oil/DBP retards release. Alternatively, diffusion across rigid multilayers may be the rate limiting step for release.

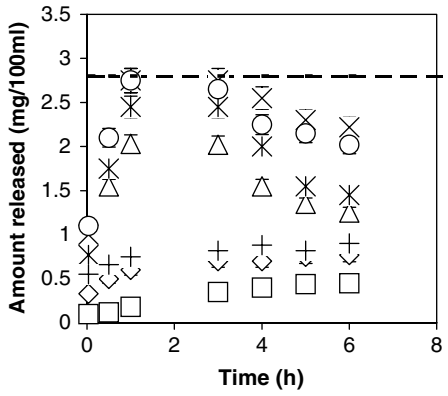


Fig. 7. DBL release profiles from PDMS emulsions with high DBP loading under non-sink conditions at 37 °C: □ pure DBP; ◇ sample A; △ pure DBP with hydrophilic silica; ○ pure DBP with hydrophobic silica; ∗ sample B; × sample C; + sample F; dotted line correspond to 100% DBP dissolution/release (2.8 mg/100 ml).

*3.2.2.2. High DBP loading levels.* In this case the DEDMS: DBP weight ratio is 1:0.25 and corresponds to a maximum DBP level of 2.8 mg/100 ml in the dissolution medium, i.e. 280% of the equilibrium solubility.

For emulsion samples A–C and F (Table 2) with high DBP loading, the release behaviour (Fig. 7) follows similar trends of increased rate and extent as was observed for medium levels of DBP inclusion. For the higher loading levels supersaturated DBP solutions are initially formed and then the concentration is reduced towards the aqueous DBL solubility limit. The supersaturated state is thermodynamically unstable state and DBP precipitates (DBP is an oily liquid and it is considered that reduction of supersaturation will result in droplet formation, droplet growth and then phase separation). The intensity and duration of the "supersaturation" effect is more pronounced for hydrophobic silica nanoparticle layers (sample C). For hydrophilic nanoparticle layers (sample B) the DBP concentration reaches a maximum after 2 h and decreases to the solubility limit over the next 6 h (Fig. 7); for hydrophobic silica nanoparticle layers this process requires 10 h. A plausible explanation for the different kinetic processes observed is that hydrophobic silica nanoparticles have an amphiphilic nature and facilitate hydrophobic binding to DBP, hence a potentially higher amount of DBP is adsorbed into surface pores and a higher amount released in solution upon desorption. Our observation here for nanoparticle coated droplets is in contrast to investigations [44] reporting that solid dispersions of poorly soluble drugs and hydrophobic silica retard release due to hydrophobic bonding, whereas equivalent dispersions with hydrophilic silica enhances the release. Considering that saturated and supersaturated DBP solutions occur for either pure DBP or DBP within PDMS droplets in the presence of silica nanoparticles (Figs. 6 and 7), we might propose that physisorption of DBP onto the silica nanoparticle layers at the surface of the droplets occurs, and upon dilution in the release medium DBP is desorbed and released. For medium and high levels of DBL loading, the increase in solubility is negligible when thick interfacial layers of nanoparticles are present at the surface of the droplets (Figs. 6 and 7).

Hydrophilic silica has previously been reported to be an excellent additive to accelerate the dissolution of poorly soluble actives, and thus potentially improve biological availability [45–47]. Adsorbates of hydrophilic silica and poorly soluble drugs (etinyl estradiol and griseofulvin [47]) were produced, so that non-polar solvents form loosely packed sorption layers and supersaturated solutions are formed upon contact with water [45–47]. Considering that there are no surfactants present to support the drug in a soluble state, the supersaturation effect is short lived and drug precipitates. This is commonly observed in solid dispersions of poorly soluble drugs with particles [45–47] and polymers [48]. A similar effect of improved dissolution properties has been reported for spray-dried silica solid dispersions with tolbutamide [44], indomethacin [49], carbamazepine and nifedipin [50] and glibenclamide [51]. Here, we have demonstrated a similar effect when either hydrophilic or hydrophobic silica nanoparticles are present as a permeable layer at the surface of emulsion droplets, thereby providing a strategy for increasing the bioavailability of poorly soluble drugs from a carrier system.

## 4. Conclusions

Correlation between interfacial nanoparticle layer structure at the surface of emulsion droplets and release properties of a lipophilic molecule (dibutylphtalate-DBP) has been established. The layered microstructure of interfacial nanoparticle layers has been controlled by nanoparticle self-assembly from the aqueous phase and is critically dependent on nanoparticle properties and electrolyte concentrations. When DBP is present within the droplets at concentrations significantly below the solubility limit in water, release is rapid if permeable layers of hydrophilic or hydrophobic silica nanoparticles are present at the interface. Significant sustained release effects can be achieved when hydrophobic silica nanoparticles are present as rigid multilayers. When the DBP concentration is close to or above the solubility limit in water, the presence of either hydrophilic or hydrophobic silica nanoparticle permeable layers can dramatically increase the dissolution rate and the amount dissolved. This effect is so pronounced that supersaturated DBP solutions can be formed. Nanoparticle coating of emulsion droplets could be a useful strategy in solving the formulation problem of low bioavailability of poorly soluble drugs. In vivo studies are underway to confirm improved bioavailability and will be the subject of subsequent publications.

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