

DRUG RELEASE FROM COLLOIDAL-COATED MICRO- OR NANO- CAPSULES

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ABSTRACT

Self-assembly of colloidal particles at liquid/liquid interfaces leads to the formation of mesoporous shells that can be used to coat nano- and micro drug carriers: Pickering emulsions are composed of a hydrophobic core that delivers oil-soluble drugs, while the aqueous core of colloidosomes allows delivery of hydrophilic drugs. Various studies investigated such carriers as drug delivery systems, finding that the rate of drug release depends on the shell properties. This paper presents the results of Monte-Carlo simulations of the release of encapsulated molecules from such microcapsules, and examines the validity of a previously-developed analytical model.

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1. INTRODUCTION

Micro or nano-scale carriers for controlled, long term drug delivery of drugs must provide protection from the immune system while allowing release at a proscribed rate (Stolnik, Illum et al. 1995, Kumar 2000, Moghimi, Hunter et al. 2001, Oh, Drumright et al. 2008, Mora-Huertas, Fessi et al. 2010, Ma and Su 2013). Effective carrier performance relies, therefore, on the properties of the carrier shell, or coating.

Carrier shells form by self-assembly at the interface between the drug-containing core and the surrounding solution. Typically, amphiphilic molecules are used for shell formation, since the dual hydrophilic/hydrophobic nature of these molecules drives the formation of interfacial films: Small molecule surfactants are used for the stabilization of emulsions, namely drops of oil in water (Sjoblom 2005), while aqueous drops in a continuous aqueous phase are coated by lipid (liposomes) (Torchilin 2005) or block copolymer (polymersomes) (Discher and Eisenberg 2002) bilayers. The advantage of such molecules is that they easily self-assemble at interfaces and suppress drop coalescence. However, controlling the properties of the shell is possible only through changes in the molecular structure of the amphiphilic molecules.

Colloidal particles have been found to aggregate at interfaces between hydrophobic and hydrophilic phases, thereby stabilizing emulsions. These 'Pickering emulsions' (Zeng, Bissig et al. 2006, Tcholakova, Denkov et al. 2008, Dickinson 2010, Niu, He et al. 2010, Dickinson 2012) are composed of oil in water or water in oil drops, stabilized by a shell of colloidal particles. A similar process produces aqueous drops in an aqueous medium, termed 'colloidosomes' (Shilpi, Jain et al. 2007, Patra, Sanyal et al. 2010, Dan 2012). Both Pickering emulsions and colloidosomes have been investigated as drug carriers (Shilpi, Jain et al. 2007, Lee and Weitz 2008, Mohanraj, Barnes et al. 2010, Miguel and Behrens 2011, Simovic, Ghouchi-Eskandar et al. 2011, Cejkova and Stepanek 2013, Porta and Kros 2013, Nan, Wu et al. 2014): The former for the delivery of hydrophobic drugs, the latter for hydrophilic ones.

Self-assembled colloidal shells are mesoporous structure with pores that allow transport (i.e. the voids between the particles) and impenetrable regions (the particles). The rate of transport through the colloidal shells is controlled by three parameters: The shell thickness, the colloidal packing density (or, alternately, the void fraction) and the colloidal particle size (Rosenberg and Dan 2010, Dan 2012, Rosenberg and Dan 2013). These parameters set the characteristic pore size, which determines the maximal size of diffusants that can cross through the shell, as well as the shell permeability to smaller molecules. Small-molecules or particles were found to diffuse through shells (Dinsmore, Hsu et al. 2002, Thompson, Armes et al. 2010), although at a slower rate when compared to uncoated cores (Simovic and Prestidge 2007, Zhao, Dan et al. 2013). Larger

molecules or particles do not cross the shell (Dinsmore, Hsu et al. 2002, Thompson, Armes et al. 2010).

Colloidal-based carriers are composed of an inner core volume that is separated from the continuous solution by the shell. Diffusion and release requires transport in the three corresponding regions. Transport in the continuous phase is usually neglected if the solution is dilute so that infinite sink conditions may be assumed. Analysis must therefore consider the diffusion of the encapsulant in the core and the finite amount of diffusant in the core, as well as the permeability of the shell (a function of the colloidal particle size, packing density, shell thickness).

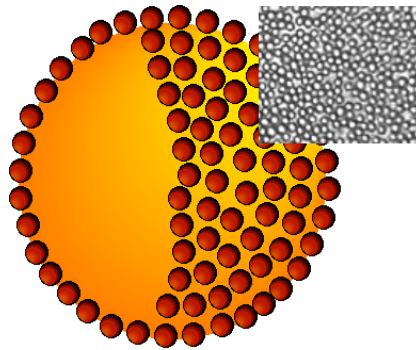


Figure 1. Colloidal shells as coatings for drug carriers. The micrograph shows 3.3 μm Amidine PS colloidal particles assembled at a water/hydrogel interface.

One approach simplifies the process by neglecting transport in the core, so that the flux across the shell (molecules per unit area per time) is given by (Yow and Routh 2009)

$$j = -4\pi D_s c \frac{R+h}{h} \quad (1)$$

where c is the average diffusant concentration in the core, D_s the diffusion coefficient through the shell, R the core radius, and h the shell thickness. This corresponds to a release profile, as defined by the amount of drug remaining in the core as a function of time, that follows an exponential decay:

$$f(t) = \frac{M(t)}{M_0} = 1 - \exp\left(\frac{-3tD_s \{R+h\}}{hR^2}\right) \quad (2)$$

$M(t)$ is the amount of drug remaining in the core at time t , and M_0 is the initial amount. This profile has been shown to fit experimental data, providing an estimate of D_s (Yow and Routh 2009, Miguel and Behrens 2011).

Equation (2) does not provide, however, a way to estimate the effect the shell parameters on the release rate. These have been accounted for in a model we developed that accounts for several features of the colloidal shell structure (Rosenberg and Dan 2011, Rosenberg and Dan 2013), including the finite size of the voids where transport occurs, the *surface area* available for transport, and the composite-like structure of the shell. Combining these contributions, while assuming that the core size is much larger than the colloidal particle size yields an effective permeability, L given by (Rosenberg and Dan 2011, Rosenberg and Dan 2013)

$$L = \frac{RD_s}{hD} \approx \frac{R}{2b} \frac{\left(1 - \frac{R_D}{b \left\{ \frac{11}{50} - \frac{\phi}{4} \right\}}\right)^4}{\left\{1 + \phi^{\frac{2}{3}} \left(\frac{\pi}{6}\right)^{\frac{1}{3}}\right\} \left\{1 + \frac{R\phi}{\pi b(1-\phi)}\right\}} \quad (3)$$

D is the diffusion coefficient through the voids phase (which is typically water), b the colloidal particle radius and ϕ the volume fraction of the particles in the shell. For uncoated cores where $\phi=0$ and there is no barrier to transport, L is infinite. In the limit where there are no pores, or voids so that $\phi \approx 1$ the permeability $L=0$ and transport is inhibited.

Equation (3) has been found to agree, qualitatively, with experiments measuring transport thorough monolayer-thick, dilute shells (Rosenberg and Dan 2010, Rosenberg and Dan 2011) and multi-layered, dense ones (Kim, Fernandez-Nieves et al. 2007). However, quantitative testing was not possible since, although parameters such as the colloidal particle size, shell thickness and core size are known or measurable, the packing density ϕ cannot be measured directly but only inferred either from micrographs (see Figure 1) or from the release data.

In this paper we present the results of a Monte Carlo simulation developed to examine the release of small (point-like) molecules from cores coated by a monolayer-thick colloidal shell. The simulation data are compared to the results of experiments and the predictions of equation (3), which is found to be effective throughout a broad range of parameters.

2. METHOD

The release profile of an encapsulated drug through a colloidal shell is simulated using a Monte Carlo scheme (Dan 2014). Colloidosomes or Pickering emulsion drops are modeled as two-dimensional cores of size $R \times R$ that contain, initially, M_0 point-like drug molecules. Each drug molecule moves one step,

randomly, in the x / y plane at each time step, thereby following a diffusive/random walk. The shell is modeled as an ordered array of n square-like particles of size $b \times b$ (see Figure 2). Therefore, the volume fraction of the particles in the shell is given by $\phi=nb/R$.

Drug molecules that reach the shell's inner edge at $x=R$ or $y=R$ in a location where there is a particle are reflected back. Drug molecules that reach the boundary where a pore is present- that is-where there is no particle - is allowed to proceed into the pore. Any step that places the molecule where a particle is present is reflected back, until the molecule reaches the shell edge at $R+b$.

Once molecules reach the shell edge, they are eliminated. This simulates infinite sink, where those molecules are eliminated (Higuchi 1963, Enden and Schroeder 2009). For simplicity, the diffusion step-size rate in solution is similar to that in the core and voids. Thus, the scheme is most appropriate for colloidosomes where all liquid volumes are aqueous. However, it can be adapted to account for oil/water emulsions by modifying the step-size in the core vs. solution.

At each time step, the number of drug molecules remaining inside the core is counted and compared to the initial value. This yields the fraction of drug molecules that are released at each time point, $f(t)=I-M(t)/M$, where $M(t)$ the number of molecules that remain within the liposome area at that time.

The overall process is as follows:

- The colloidosome characteristics (size R , number of particles n , size of particle b and the number of encapsulated drug molecules M_0 is chosen.
- The M_0 drug molecules are randomly placed in the core.
- The location of the particles is set, the first particle is placed at $x=0$ and $y=R$, the next one at a distance $(R-nb)/n$ from it, etc.
- The diffusion process is started: Each of the M_0 molecules is moved 1 step in a randomly chosen direction, and its new location tested: If it is inside the core, no other action is taken. If it is on the core edge in a location where a particle edge is located, the molecule is 'reflected' back to its original position. If it is on the edge in a location defined as a pore, the molecule is allowed to proceed into the core.
- Molecules in pores are allowed to proceed unless their trajectory leads them 'into' a particle, in which case they are reflected to the previous position. Molecules that reach the edge of the shell are either eliminated or continue diffusing.
- The number of molecules remaining in the core is counted and the fraction $f(t)$ calculated.

The calculation was conducted using Wolfram's Mathematica ©.

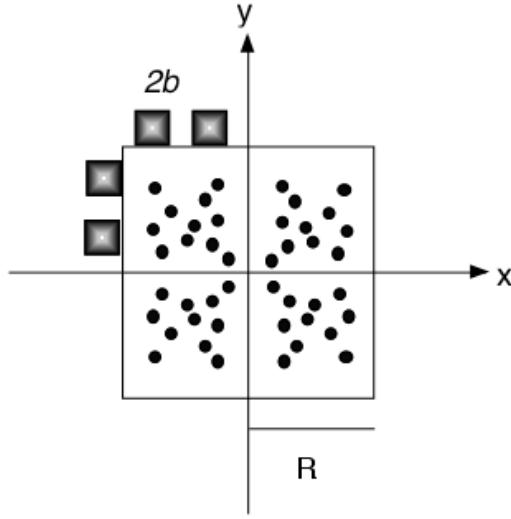


Figure 2: The simulation scheme: M_0 point-like diffusants are placed randomly in a core of size $R \times R$. In each time step, every diffusant ‘molecule’ moves one step in a random direction. The shell is represented by an array of n impenetrable box-like particles of size b . The particle volume fraction ϕ of in the shell is given by nb/R . A diffusant that reaches a colloidal particle is bounced back to its previous position. Diffusants that reach a distance of $R+2b$, namely, the outer edge of the core, are considered ‘in solution’ and eliminated.

We focus on simulating point-like, uncharged molecules to determine the effect of the shell on the flux. Previous analysis examined the effects of molecular size, charge, and pore characteristics on transport through a single pore (see, for example, (Beck and Schultz 1970, Chen, Lear et al. 1997, Bezanilla 2000, Eisenberg 2003, Ramirez, Aguilera-Arzo et al. 2006, Dan 2012)), so that once the effect of the shell structure is understood these could be accounted for through a pore resistance coefficient. For example, size exclusion—that is, the reduction in flux when the drug size is of the same order of magnitude as the pore diameter—is given by $(1-R_D/R_p)^4$ (Beck and Schultz 1970), one of the contributions in equation (3).

As noted in Section 1, the release from core/shell nano- or micro- particles follows an exponentially-decaying profile. Although equation (2) is useful, we use here a more detailed diffusion model where $f(t)$ is given by (Crank 1975)

$$f(t) = 1 - \frac{\sum_{n=0}^{\infty} \frac{\exp\left(\frac{-\beta_n^2 Dt}{R^2}\right)}{\beta_n^2 (\beta_n^2 + L^2 - L)}}{\sum_{n=0}^{\infty} \frac{1}{\beta_n^2 (\beta_n^2 + L^2 - L)}} \quad (4)$$

Where the Eigen values are defined by $(\beta_n \cot \beta_n + L - 1) = 0$.

Equation (4) accounts for the fact that the liposome interior may not be well mixed: drug molecules need to diffuse *in* the liposome interior until reaching the shell, and for the surface to volume ratio. Tests of the simulation with no shell where $L = \infty$ yield good agreement between the simulation data and the predictions of equation (4) with a single fit parameter, D for a range of core sizes ($2 < R < 50$) and M_0 values of 250-1000 (Dan 2014). The value of D , 1.5 in simulation units is consistent with our expectation based on the simulation set-up (Crank 1975).

3. RESULTS AND DISCUSSION

We first test the validity of the simulation by examining the rate of release from uncoated cores immersed in an infinite-sink solution; In this case, the resistance to release is zero, so that the permeability L is infinite. However, the release is not instantaneous, since drug molecules must diffuse through the core until reaching the core/solution interface.

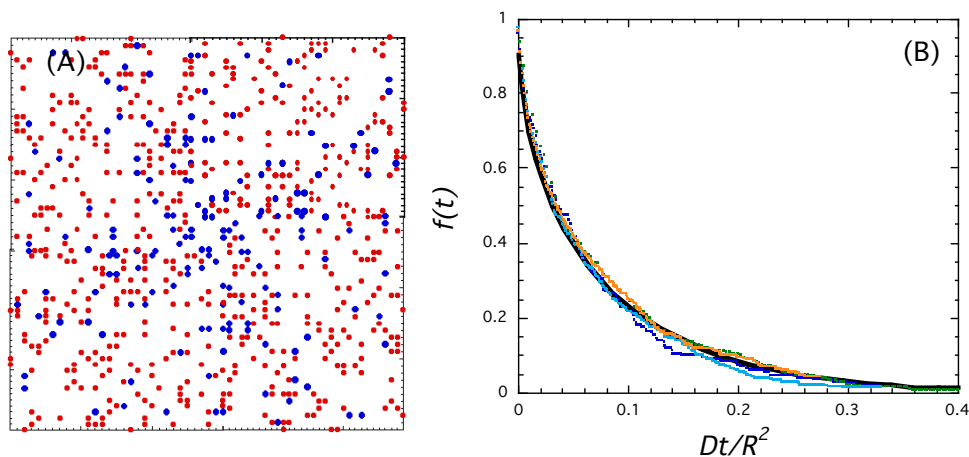


Figure 3: Monte Carlo simulations of release from uncoated cores (where $\phi=0$). (A) The distribution of drug molecules initially at $t=0$ (red) and after 500 time steps (blue). Box size $R=30$, and $M_0=250$. We see that the initial distribution is random but relatively uniform, while the later distribution is depleted near the core boundaries. (B) The fraction of drug molecules remaining in the core, f , as a function of dimensionless time for box sizes R from 10 to 40 and M_0 values from 250 to 500. The black line shows the predictions of equation (4) with $L \rightarrow \infty$. $D=1.5$ in simulation units for all systems. Repeat runs yield a scatter of order $\pm 5\%$.

As shown in Figure 3.A, initially the drug molecules are distributed randomly and relatively uniformly through the core. However, after a period of time their

number is reduced, and they are depleted near the edges. Plotting the fraction of drug molecules remaining in the core f as a function of dimensionless time Dt/R^2 (Figure 3.B) collapses all the release profiles onto one ‘master’ curve, regardless of the core size R or the initial number of drug molecules M_0 . Furthermore, the release profile is fit well with equation (5) when $L \rightarrow \infty$.

We next examine the effect of the packing density of the release rate. As expected, the presence of a shell reduces the rate of release when compared to the uncoated case (see Figure 4). Increasing the colloidal particle packing density reduces the release rate, due to the associated reduction in voids the voids available for diffusion. The release profiles can still be fit well by equation (4), with values of the shell permeability L that decrease with increasing particle volume fraction ϕ (see Table I). Determining the effect of colloidal particle size on the release rate does not yield an obvious trend (see Table I); similarly unclear is the effect of the core size. The model we derived previously for the permeability (Rosenberg and Dan 2010, Rosenberg and Dan 2011, Rosenberg and Dan 2013), as presented in equation (3) should, if correct, enable us to understand these correlations.

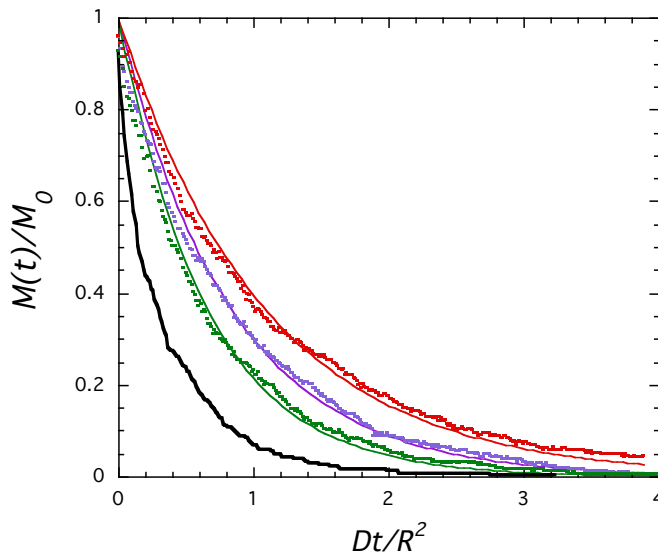


Figure 4: Monte-Carlo simulations for the release from colloidosomes with monolayer-thick shells: Effect of particle packing density. Core size $R=10$, particle size $b=1$, and $D=1.5$ in simulation units for all systems. Black: $\phi=0$; Green: $\phi=0.1$; Purple: $\phi=0.2$. Red: $\phi=0.33$. The lines describe a fit to equation (4) with different values of the permeability L , as listed in Table I. Repeat runs yield some distribution in the data, with error of order $\pm 5\%$.

Table I: The effective permeability L through a colloidal shell, as a function of core and shell parameters for some of the simulated systems.

Core size R	Colloidal particle size b	Shell particle packing density ϕ	Effective permeability L ($\pm 15\%$) [*]
10	1	0.1	3.5
10	1	0.2	2
10	1	0.33	1.75
30	1	0.033	10
30	1	0.1	9
30	1	0.125	7
30	2	0.33	3
30	3	0.33	1.25
30	2	0.5	0.2
30	4	0.5	0.85
30	5	0.5	0.2
40	1	0.1	70

^{*}Calculated by fitting the release profile to equation (4).

To test the validity of the model for L we plot the value of the permeability obtained from fitting the simulation release profiles by equation (4)—as shown for example in Figure 4—to the predicted value based on equation (3). Note that, since the drug molecules are point-like in these systems, $R_D=0$. As shown in Figure 5, we find good agreement (i.e. clustering near the 45° line) for most of the parameter range. Significant deviations are found, however, in the limit where the

simulation-fit permeability becomes relatively high, namely, when the colloidal shell does not significantly hinder transport.

The model's failure in the limit of high shell permeability is due to the fact that it was developed using the assumption that $R \gg b$. Thus, in the limit of $\phi \rightarrow 0$, the model that $L \approx R/2b$ which, in most experimentally-studied systems where R is of order $100 \mu\text{m}$ or more, and the particles of order $1 \mu\text{m}$ or less (Dan 2012) yields a relatively high value for L (as shown, for example, by Crank, the release profiles for $L=100$ and $L \rightarrow \infty$ are practically identical (Crank 1975)). However, in the simulated systems the ratio of $R/2b$ is, at most, or order 20, and therefore cannot accurately capture the correct value.

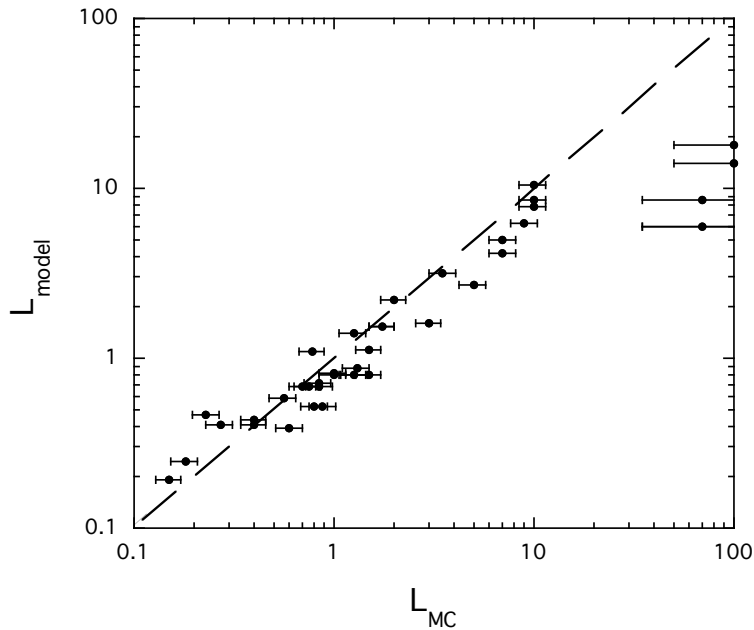


Figure 5: Comparison between the model predictions for the permeability, L_{model} (based on equation 3) and the permeability obtained from the Monte Carlo simulation fit to equation (4). Values near the 45° line indicate good agreement; values far from this line show significant deviations. Note that the model predicted value is exact, since all the values (R, b, ϕ) are pre-set in the simulation. However, the permeability obtained by the fit has a deviation that is of order $\pm 15\%$ except in the limit of high L where it may be larger (Crank 1975)

4. CONCLUSION

Colloidal shells can self-assemble at liquid-liquid interfaces, thereby providing a coating for micro- and nano- drug carriers that provides protection to the encapsulated drug, and controls the rate of transport into and out of the carrier. The shell permeability is set by the size of the colloidal particles, their packing density (or volume fraction), and the shell thickness.

In this paper we examined the effects of colloidal particle size and packing density on the rate of release of point-like drug molecules from a carrier using Monte Carlo simulations. We find that, as may be expected, increasing the particle packing density in the shell—which reduces the fraction of voids available for transport—reduces the permeability. However, the dependence of the permeability on the core size and the particle size is less clear. To that end, we compared the permeability obtained from the simulations to the predictions of our theoretical model (equation 3). We find good agreement throughout a wide range of parameters, except in the limit of low colloidal particle volume fraction, where the model deviates from the observed data due to the small size of the core.

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