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Environmentally-induced degradation of solid-lipid nanoparticles

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ABSTRACT
Solid lipid nanoparticles (SLN) have been widely studied as drug and nutrient delivery vehicles. Due to their solid core, they are especially suited to oral delivery. In this paper, we examine—using Monte Carlo simulations—the effect of environmental agents such as enzymes on the degradation of SLNs. The process is dominated by surface erosion, since the solid nature of the core suppresses diffusion. As may be expected, smaller particles degrade more quickly than larger ones with a rate that is dominated by the surface area of the nanoparticle. As a result, particles with the same surface area degrade at approximately the same rate regardless of their asymmetry (length to width to height ratio). Quite surprisingly, the rate of reaction between the degradation agent and the lipids comprising the core does not significantly affect particle degradation. However, the rate of degradation is highly sensitive to the concentration of degradation agents in the surrounding solution.
Keywords: *Solid-lipid nanoparticles (SLN); Monte Carlo simulations; degradation; oral delivery.*

1. INTRODUCTION
Drug-carrying nanoparticles have been widely investigated as a method for enhancing the delivery dosage of poorly soluble, hydrophobic compounds and allowing control over the release rate and location [1-11]. Most importantly, encapsulation in nanocarriers protects the drugs from potentially harmful environmental agents such as free radicals or enzymes [1-11], which is essential when considering oral delivery [12-15].

Solid lipid nanoparticles, or SLNs, are composed of a lipid core phase that is solid in the storage and application temperature [10, 16-18]. The solid nature of SLNs imparts mechanical stability, and thus long shelf life [16, 19-21]. (Note: In the literature, the term 'lipid' is used for both 'oils' such as chain triglycerides, and for amphiphilic phospholipids, that are sometimes used to emulsify and stabilize drug-delivery nanoparticles. In this paper we will consistently use the term SLN or 'oil phase'). As a result, SLNs are especially promising when considering oral delivery of drugs that may be degraded when exposed to the conditions in the stomach or GI tract [22-26]. Understanding the process of degradation is important also as a measure of drug release from the SLNs: Since diffusion in the particle core is suppressed, release can occur only through disintegration of the solid core.

Solid nanoparticles can degrade via two mechanisms: Bulk or surface erosion. In the case of bulk erosion, environmental degradation agents (e.g. free radicals, UV light) penetrate throughout the particle core, reacting with the particle matrix and causing disintegration. Such mechanism is typical for polymeric nanoparticles such as those composed of poly(lactic-co-glycolic acid), PLGA [13, 27-31], resulting from partial swelling and /or relatively easy mobility within the polymeric matrix. In dense, solid particles such as SLNs diffusion into the particle is suppressed, so that degradation occurs at the particle/solution interface—surface erosion.

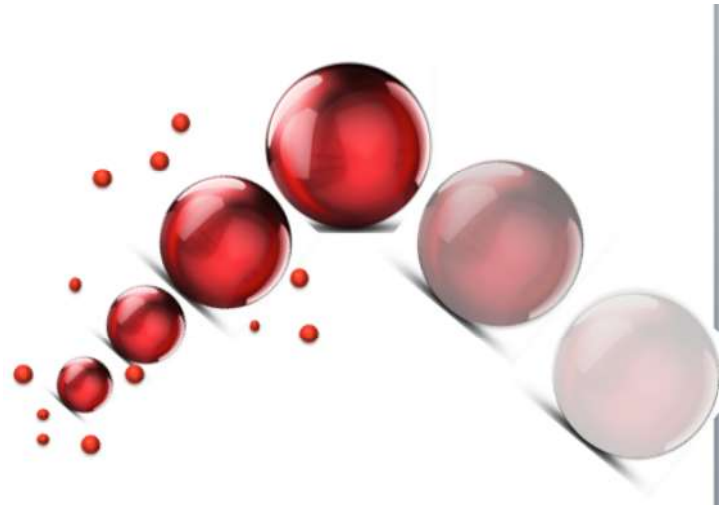

Figure 1. Mechanisms for degradation of solid nanoparticles. Right: Bulk erosion, where the particle disintegrates uniformly throughout the core. Left: Surface erosion, where degradation occurs only at the solution/particle interface. In bulk erosion, the overall size of the particle remains relatively constant, but the density decreases with time. In surface erosion, the particle size decreases with time while the density remains constant.

Despite their potential utility and importance as nanocarriers, few studies examined the degradation of SLNs. Muller, et al [32] investigated the degradation of SLNs in pancreatic lipase and co-lipase solutions, finding that the rate of degradation depends on the type of lipid core, as may be expected. Bonnaire, et al [33] compared the rate of SLN degradation to that emulsions (where the core is composed of similar lipids that are in the liquid state). Interestingly, they find that the lipid hydrolysis (in both liquid and solid nanoparticles) reached a constant rate after a period of time [33]. Jannin, et al [34] investigated the effect of the solution conditions by comparing the effects of lipase/colipase assay with porcine pancreatic extract. Nik, et al [35] found that lipolysis was much more significant, under the

same conditions, in liquid emulsions when compared to SLNs. Thus, these studies show that the rate of SLN degradation depends on the particle chemistry (type of lipid phase) and the solution chemistry (degradation agent). Studies of other nanoparticle systems suggest that particle size and geometry may play a role as well [27, 36, 37].

Surface erosion is typically analysed, theoretically, in combination with bulk erosion as applied to polymeric nanoparticles [38]. Little is known regarding the effect of system parameters on the degradation rate of SLNs, where surface erosion is the likely dominant mechanism. In this paper we examine the degradation of SLNs using Monte-Carlo based simulations, as a function of parameters that include the solution conditions (concentration of degradation agent and the reaction kinetics), the size of the nanoparticle and its shape. The results are compared to a simply geometric model. The results help identify the dominant parameters controlling surface erosion, thereby enabling the design of particles that would suit specific needs.

2. SIMULATION METHODS

The simulations were conducted as follows: The nanoparticle is taken to be a 3D object of dimensions L_x x L_y x L_z, with values ranging from 5 to 40 in simulation units. The nanoparticle is situated in a box that contains mobile degradation 'molecules' at a pre-determined concentration (defined by number of molecules per solution volume, namely, the box volume that is not occupied by the nanoparticle). The molecules move randomly in solution, obeying a reflecting boundary condition at the box boundary, so that at each time step all molecules are moved randomly by one lattice site. When a diffusing molecule lands on a site that is occupied by the nanoparticle, it may be reflected or it may 'react' with the particle, depending on a random probability that defines the rate of reaction (namely, if the probability of reaction is 1, that is, it always occurs, the rate of reaction is instantaneous. If the probability of reaction is zero- i.e. the reaction never occurs, the rate of reaction is infinite). If the reaction occurs, the particle site is 'degraded', namely, converted to a solution site, and the molecule eliminated from the site. To maintain a constant concentration of degradation agents, any time a diffusing molecule is eliminated due to reaction a new one is placed randomly at the box boundary.

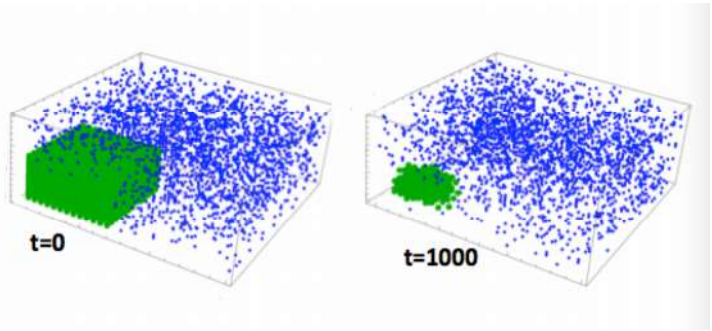

Figure 2. The simulation scheme: The nanoparticle is located at the (0,0,0) corner, and the degradation molecules are distributed randomly throughout the simulation box (except for where the nanoparticle is located). As the degradation agents move in the box, those that encounter a particle site may react with it with a specified probability, thereby causing it to 'degrade'. The degradation causes the nanoparticle to shrink with time, as shown by comparing t=0 (left) and t=1500 simulation steps (right). In the system shown the particle size is 13 x 13 x 16, the concentration of degradation molecules in the box is held at C=0.1, the probability of reaction is 1, and the box size is 30.

3. RESULTS SECTION

We first examine the effect of nanoparticle size on the degradation of symmetrical cube-like particles where L_x=L_y=L_z=L. As shown in Figure 3, the degradation of smaller particles, as defined by the fraction of particle that remains intact, is much more rapid than that of larger ones. This is as may be expected: Degradation occurs at the interface between the particle and the solution. Smaller particles have a larger surface to volume ratio, which would suggest that they would degrade faster.

Next we examine in Figure 4 the effect of the reaction rate and the concentration of degradation molecules on the nanoparticle degradation rate. As expected, increasing the probability of reaction (which is equivalent to increasing the rate) reduces the time required to degrade the particle (see Figure 4.A). However, the effect is not as large as may be expected: Reducing the probability of reaction from 1 (namely, when each encounter between particle and molecule leads to degradation) to 0.1 (where 10 encounters are needed, on average, to produce a reaction) only mildly increases the time required for degradation: The time required to degrade ½ of the particle volume increases from ~450 time steps to ~700 time steps. In contrast, increasing the concentration of degradation agents has a much more significant effect, as shown in Figure 4.B: Doubling the concentration from 0.05 to 0.1 changes the time required to degrade ½ the particle volume from ~450 to ~280 time steps.

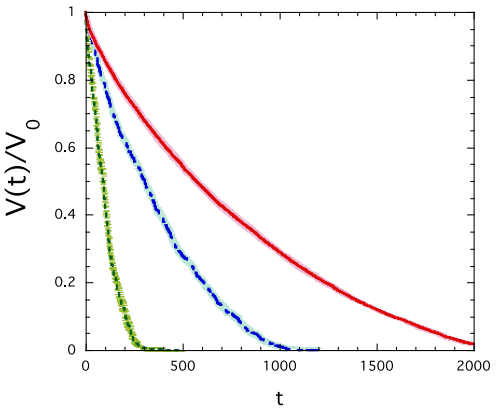

Figure 3. Degradation of symmetrical, cube-like nanoparticles as a function of particle size. L_x=L_y=L_z=L. V_0 is the volume of the particle at time 0 (=L^3), and V(t) the volume remaining at time t. Green dotted line: L=5. Blue dot-dashed line: L=10. Red continuous line: L=15. The concentration of degradation molecules is 0.1, box size=30, and the probability of reaction is 1, namely, instantaneous reaction rate. Curves are based on an average of 3 simulation runs, with the light colored region outlining the standard deviation.

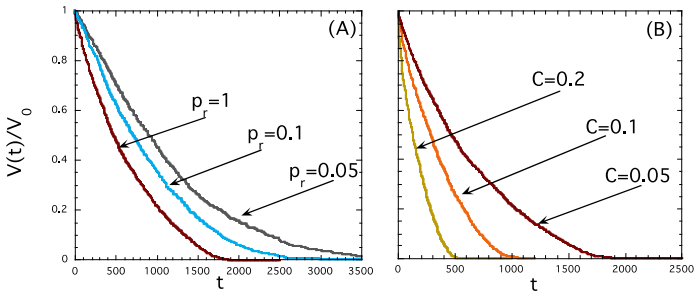

Figure 4. Degradation of symmetrical, cube-like nanoparticles as a function of the probability of degradation reaction p_r and the concentration of degrading molecules C. The cube size is L=10 in all cases, and box size=30. (A) Molecule concentration, C= 0.05, and the probability of reaction as noted. (B) Probability of reaction =1, and the concentration as noted. Curves are based on an average of three runs, with standard deviation of the same order as shown in Figure 3.

This result is somewhat unexpected: It may be thought that 10 molecules with a probability of reaction (each) of 0.1 would be equivalent to 1 molecule with a 100% probability of reaction. Indeed, this is the case for any given reaction. However, once the reaction occurred, the reacting molecule is eliminated and further degradation requires the appearance of new molecules at the site- thus increasing the sensitivity to the molecule concentration.

Another parameter that is thought to affect the degradation of nanoparticles is their shape, or aspect ratio. Generally, it may be expected that highly asymmetric elongated particles may degrade more rapidly than compact, symmetrical ones. However, it is not clear whether this is inherently related to the particle asymmetry, or to differences in the effective surface area (or surface to volume ratio). To examine this, we first compared the degradation rates of various asymmetrical particles with the same surface area, but different volumes and aspect ratios. To simplify the comparison, we focus on systems where $L_x=L_y\neq L_z$.

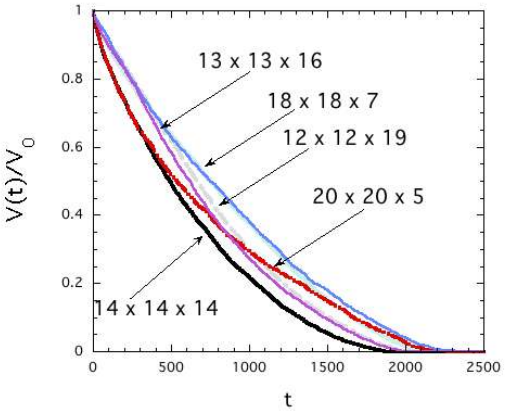

Figure 5. Degradation of asymmetrical nanoparticles with the same surface area but different volumes/aspect ratio. Particle sizes are as marked. Particle volumes range from 2000 (20 x 20 x 5) to 2744 (14 x 14 x 14). In all cases, C=0.1, probability of reaction =1 (instantaneous rate) and box size=45.

As shown in Figure 5, the fastest degradation occurs in the symmetrical particle. However, the differences in rate are not highly significant between the asymmetric ones, or between the asymmetric and symmetric nanoparticles. Furthermore, we do not see a direct correlation with the particle volume.

To understand the effect of system parameters on the degradation rate, we consider a simple geometric model. Defining the rate of surface reaction as R per unit area, we have:

$$\frac{dV}{dt} = -RA \qquad (1)$$

where V is the particle volume and A the surface area. For a sphere where $V=4\pi r^3/3$ and $A=4\pi r^2$ (where r is the radius, which depends on time) this yields

$$\frac{dr}{dt} = -R \rightarrow r(t) = r_0 - Rt \qquad (2.a)$$

so that

$$\frac{V(t)}{V_0} = \left(1 - \frac{R}{r_0}t\right)^3 \qquad (2.a)$$

where r_0 is the radius at t=0. An identical expression is obtained for a cube (such as the symmetric particle used in the simulation), where L(t) replaces r(t). In the case of asymmetric shapes, this is slightly modified to

$$\frac{V(t)}{V_0} = \left(1 - \frac{R}{L_{x,0}}t\right)\left(1 - \frac{R}{L_{y,0}}t\right)\left(1 - \frac{R}{L_{z,0}}t\right) \qquad (2.b)$$

These expressions are based on the assumption(s) that the degradation reaction rate does not change with time, and is the same for all faces of the nanoparticle.

To test equation (2) we fit the measured release rates of symmetrical nanoparticles (Figure 3). We see that the form of equation (2) provides a good fit (see Figure 6) to the degradation profiles. However, the values of R, which should be the same in the three cases, vary: For L=5, R≈0.015, for L=10 R≈0.007, and for L=15 R≈0.005. Since the actual reaction rate is the same (instantaneous) in all cases, this suggests that there is some effect that 'increases' the observed reaction rate in smaller particles when compared to larger ones.

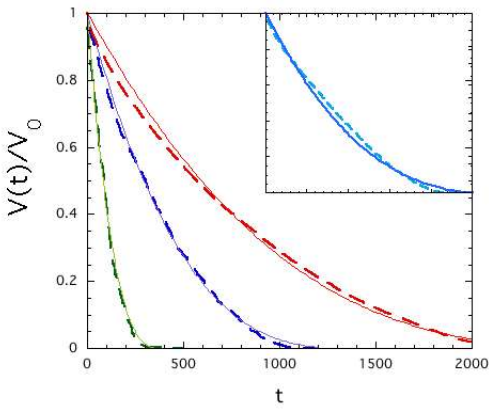

Figure 6. Fitting the degradation of symmetrical particles to equation (2). Green dotted line: L=5. Blue dot-dashed line: L=10. Red continuous line: L=15. The concentration of degradation molecules is 0.1, box size=30, and the probability of reaction is 1, namely, instantaneous reaction rate. Inset: Asymmetric box with 10 x 16 x 16. The free parameter used for the fit to equation (2) is the reaction rate: For L=5, R≈0.015, for L=10 R≈0.007, and for L=15 R≈0.005. For the asymmetric box in the inset, the two associated rates are R=0.0017 for L=10 and R=0.006 for L=16.

Even more significant deviations were found in the case of asymmetric particles: As illustrated in Figure 6 (inset), the rate associated with the smaller dimension of a 10 x 16 x16 box is 0.0017, while that associated with the longer dimension is 0.006. To understand the failure of equation (2) in describing the surface-erosion induced degradation of nanoparticles, we look at the particle-solution interface as a function of time. As illustrated in Figure 7, the degradation front is not uniform: The randomness of the distribution of degrading molecules leads to the development

of channels and isolated regions, even at relatively short times; while the actual surface reaction rate of smaller sections is the same, equation (2) suggests that the rate of volume decrease of smaller regions is faster than that of larger ones. As a result, the effective, observable rate can vary. Unfortunately, it is difficult to quantify the effect of non-uniform surface degradation. However, it is more likely to dominate shapes that are elongated (with, for example, two dimensions that are smaller than the third one), as seen by the fit for the asymmetric particle in Figure 6 (inset). Yet, the effect of asymmetry is still minor (for particles with the same overall surface area) when compared to the effect of the particle surface area (Figure 3).

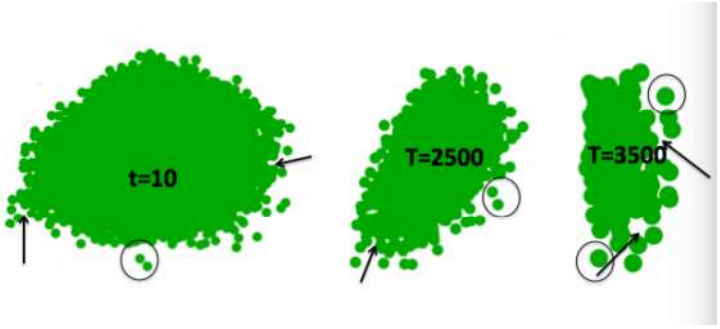

Figure 7. Snapshots of a degrading nanoparticle. The initial particle size is 20 x 20 x 20. The concentration of molecules in the solution is C=0.1, and the probability of reaction is ½. The number of time steps is as noted. Circles illustrate isolated nanoparticle units, and arrows indicate 'channels'.

4. DISCUSSION

The parameters controlling the degradation of nanoparticles are important when designing carriers for oral delivery.

The surface to volume ratio of the particles is expected to play an important role in determining the rate of degradation. Indeed, as shown in Figure 3 smaller particles (with larger surface to volume ratio) degrade more quickly than larger ones. This would suggest that particles with larger surface to volume ratio—namely—asymmetrical/elongated ones—would degrade more quickly than symmetrical ones. Yet, as shown in Figure 5, the shape of nanoparticles with the same volume does not significantly affect the rate of degradation. Analysis of the rate (Figure 6) shows that the *effective* rate of reaction degradation depends on the particle size and asymmetry, despite the fact that the molecular reaction rate is the same. Examining 'snapshots' of the degrading particles suggests that this effective rate may be due to the development of degradation channels in the particle (Figure 7), that affect the actual surface of the particle that is exposed to the solution and its degradation agents. The properties of the degradation agents also play a significant role. Increasing the rate of reaction increases the rate of particle degradation (Figure 4.A), but in a surprisingly weak manner. In contrast, the concentration of degradation agent in solution significantly affects particle degradation (Figure 4.B). This is due to the type of degradation reaction examined here, where we assumed that once a molecule reacts with the particle it is changed and cannot react anymore. As a result, the probability that the reaction occurs is more sensitive to whether a degradation molecule reached the surface (a function of the concentration), rather than how long it will take until the reaction took place. We expect that in the case of degradation by enzymes, which recover their activity after reaction, the concentration would play a weaker role.

As a rule, studies of SLN particles for oral delivery focus on the choice of lipid [32-35]; This will affect the rate of reaction between environmental agents and the particles. However, as this study suggests, this rate may play a lesser role is controlling particle degradation rate than the particle size or the concentration of degradation agents.

5. CONCLUSION

In this paper we use Monte-Carlo simulations to examine the surface erosion and degradation of SLNs. We find that the rate of particle degradation is highly sensitive to its surface area and the concentration of degradation molecules in solution. In contrast, particle asymmetry and the rate of the degradation reaction between the solution and the particle affect degradation only weakly. Although degradation occurs only at the interface between the solution and the particle, we find that the process does not occur uniformly.

These findings suggest that when choosing SLNs for a particular application, larger rather than smaller particles are preferred since their degradation will be slower, but their exact shape is not important. When choosing the lipids composing the SLN, the rate of reaction between the degradation molecules and the lipid is less important than the concentration of the relevant molecule. Thus, it is preferable to choose a lipid that reacts with an enzyme whose concentration is low in the digestive system, even if the reaction is rapid, than a lipid that reacts with an enzyme whose concentration is high even if that reaction is slow.

The stability imparted by the solid core of SLNs makes them ideal for oral delivery. However, their utilization requires better understanding of their interactions with the harsh environments and highly degrading conditions associated with the process. The results presented here allow better understanding of surface erosion in such particles, which can be used to design efficient drug carriers.

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