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Controlling the *in vitro* release profiles for a system of haloperidol-loaded PLGA nanoparticles

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Abstract

We have used a systematic methodology to tailor the *in vitro* drug release profiles for a system of PLGA/PLA nanoparticles encapsulating a hydrophobic drug, haloperidol. We applied our previously developed sonication and homogenization methods to produce haloperidol-loaded PLGA/PLA nanoparticles with 200–1000 nm diameters and 0.2–2.5% drug content. The three important properties affecting release behavior were identified as: polymer hydrophobicity, particle size and particle coating. Increasing the polymer hydrophobicity reduces the initial burst and extends the period of release. Increasing the particle size reduces the initial burst and increases the rate of release. It was also shown that coating the particles with chitosan significantly reduces the initial burst without affecting other parts of the release profile. Various combinations of the above three properties were used to achieve *in vitro* release of drug over a period of 8, 25 and >40 days, with initial burst <25% and a steady release rate over the entire period of release. Polymer molecular weight and particle drug content were inconsequential for drug release in this system. Experimental *in vitro* drug release data were fitted with available mathematical models in literature to establish that the mechanism of drug release is predominantly diffusion controlled. The average value of drug diffusivities for PLGA and PLA nanoparticles was calculated and its variation with particle size was established.

Keywords: Controlled release; Haloperidol; Nanoparticles; PLGA end groups; Drug diffusivity; Drug release mechanism

1. Introduction

Time-controlled drug delivery can be achieved through polymeric drug delivery systems, using the widely accepted biodegradable polymer PLGA (Bala et al., 2004). Two promising candidates among the PLGA-based polymeric drug delivery systems include microparticles (defined here as particles of mean diameter greater than 1 μm) and nanoparticles (defined here as particles of mean diameter less than 1 μm) containing the active pharmaceutical agent encapsulated in PLGA matrix. PLGA-based microparticles have been studied extensively and several products are available on market (Woo et al., 2001; Dong et al., 2003). However, for site-specific controlled drug delivery, nanoparticles offer additional advantages due to their submicron size, which makes extravasation possible and occlusion of terminal blood vessels unlikely (Barratt, 2003).

While the drug release behavior has been studied for PLGA-based microparticles and nanoparticles encapsulating various hydrophobic drugs (Avgoustakis, 2004), there have been few attempts to develop a systematic methodology to understand and modulate the drug release profile. Previous attempts to tailor the release profiles include that of Ravivarapu et al. (2000), who utilized polymer and microparticle blending to achieve desired release profiles for a system of peptide-loaded PLGA microparticles. They blended PLGA polymers of different molecular weights to make microparticles and also produced peptide-loaded microparticles from different molecular weight PLGA. This is a good strategy to control the drug release from a microparticulate system since the drug release is affected by dif-

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fusion as well as polymer degradation and the latter is strongly affected by polymer molecular weight. However, the release profile of our haloperidol-loaded PLGA nanoparticles is not expected to be a strong function of polymer molecular weight and we need to develop other strategies to tailor the release profiles.

The primary objective of our research is to achieve drug release profiles with desired characteristics in terms of time period and rate of drug release. This is realized by first interpreting the effect of particle and polymer properties on drug release in terms of the pertinent scientific principle and then employing these effects to tailor the release profiles. For our system of haloperidol-loaded PLGA/PLA nanoparticles, we have previously hypothesized the mechanism to be predominantly diffusion controlled for particles with bimodal size populations (Budhian et al., 2005). Here, another objective is to verify this hypothesis by collecting *in vitro* release data from unimodal PLGA/PLA nanoparticles of various sizes and fitting it to mathematical models in literature based on Fick's second law of diffusion (Ritger and Peppas, 1987a,b; Siepmann et al., 2005). It was determined that the initial burst and induction period were most significantly altered by manipulating the polymer hydrophobicity, the coating on the particle surface and/or particle size.

2. Materials and methods

2.1. Materials

Poly(D,L-lactic-*co*-glycolic acid) (PLGA) 50:50 DL (inherent viscosity, 0.37 dL/g), 50:50 DL (0.44 dL/g), 75:25 DL (0.55 dL/g) and 100:0 DL (0.68 dL/g) were purchased from Alkermes, USA. Polyvinyl alcohol (PVA) (MW, 25,000, 88% hydrolyzed) was purchased from Polysciences Inc., USA. Haloperidol, phosphate buffered saline (PBS), ammonium acetate, 1-piperazineethane sulfonic acid, 4-(2-hydroxyethyl)-monosodium salt (HEPES), gelatin and chitosan were purchased from Sigma, USA. Acetonitrile, dichloromethane (DCM) and acetone were purchased from Fisher scientific. All the solvents were HPLC grade.

2.2. Nanoparticle preparation

Nanoparticles were prepared by using two methods: (1) emulsification by homogenization-solvent evaporation and (2) emulsification by sonication-solvent evaporation. Henceforth, these methods will be referred as simply homogenization and sonication. Both methods involve preparation of an organic phase consisting of polymer (PLA or PLGA) and drug (haloperidol) dissolved in organic solvent (DCM). The organic phase is added to an aqueous phase containing a surfactant (PVA) to form an emulsion. This emulsion is broken down into nanodroplets by applying external energy and these nanodroplets form nanoparticles upon solvent evaporation. Details of both methods have been discussed in our earlier publications (Budhian et al., 2005; Budhian, 2006). Particles thus prepared are referred as uncoated nanoparticles.

Unless otherwise mentioned, all the experiments are conducted by varying one parameter while keeping all the other processing parameters at the standard condition: 10 mg/mL of PLGA 50:50, MW 51 kDa and 0.5 mg/mL of haloperidol in DCM as the organic phase and 50 mL of 1% PVA solution as the aqueous phase. The aqueous to organic ratio and the surfactant to PLGA ratio is 10:1 and polymer to drug ratio is 20:1. Solvent volume is 5 mL. Sonication is carried out at a power of 7 for 7 min.

2.3. Coating of nanoparticles

Particles were coated with chitosan, L101 or gelatin. The coating was done by two methods. In the first method, the coating was done by first freeze drying a batch of particles and then carefully spreading a drop of 1% solution of chitosan, L101, or gelatin on the surface of particles and then mixing it to ensure that the particles are coated evenly. Henceforth, this method is referred as coating by freeze-drying method. In the case of chitosan, the coating protocol was done by a second method, henceforth referred as the *in situ* coating method, where chitosan was added to the nanoparticulate aqueous suspension of particles prepared in Section 2.2 to form a 1% chitosan solution. This promotes a uniform chitosan coating on the particle surface and prevents agglomeration of the particles. Particles thus prepared are referred as coated particles.

2.4. Nanoparticle characterization

Nanoparticles were characterized for size, size distribution and drug content as detailed in our earlier publication (Budhian et al., 2005). The size and size distribution were measured by laser dynamic light scattering. The haloperidol content was measured using HPLC. Briefly, the nanoparticle suspension (coated or uncoated particles) was completely dissolved in the mobile phase of HPLC and injected into the machine as detailed in our earlier publication (Budhian et al., 2005). Drug content was calculated as the ratio of the mass of drug inside the nanoparticles to the total initial mass amount of the polymer.

2.5. In vitro release studies

The *in vitro* release study of the haloperidol-loaded PLGA nanoparticles was carried out in triplicate in stirred dissolution cells at 37.4 °C by suspending 1–2 mL of the nanoparticulate suspension in a large quantity (100–200 mL) of pH 7.4 PBS solution such that the total amount of haloperidol inside the suspended nanoparticles is less than 10% of its solubility limit in PBS buffer. This ensures the correct *in vitro* conditions to study the release behavior of a hydrophobic drug (Chorny et al., 2002a,b). One-milliliter aliquots were taken out of the dissolution cells at pre-determined time intervals, replaced by fresh PBS buffer and analyzed for released haloperidol by HPLC. The cumulative %release profiles were obtained by taking the ratio of the amount of haloperidol released to the total drug content in the same volume of sample.

3. Results and discussion

3.1. Particle size and drug content of coated and uncoated particles

We used our method of sonication to produce 220 nm particles with very narrow size distribution. We were also able to produce uniformly sized particles of desired mean diameter by our homogenization method for various polymer types and drug contents by selecting the materials and/or controlling the processing conditions as described in our previous publication (Budhian et al., 2007; Budhian, 2006). The polydispersity index of the particle size ranges from 0 to 0.3, where 0.3 refers to the most polydisperse population. The polydispersity indexes of these haloperidol–PLGA nanoparticles, particularly those prepared by sonication, are low and show little variability between different batches of particles prepared under various conditions. Unless otherwise mentioned, the polydispersity indexes of unimodal particles prepared by sonication are 0.05–0.07, while those from homogenization are 0.10–0.14. Particle size measurements of coated particles produced by the *in situ* method show similar values of mean diameter and polydispersity index as uncoated particles indicating that this method prevents agglomeration of particles post-coating. The *in situ* coating method is superior to the freeze-drying coating method, which results in higher polydispersity index post coating (data not shown). Hence, the *in situ* coating method was used for most of this study.

We now present the isolated effects of L:G ratio, drug content, surface coating and particle size on the kinetics of drug release. For all the figures, each point represents the mean value from one batch of nanoparticles from multiple dissolution cells and error bars indicate the standard deviation within a batch. Error bars are omitted when the error is <10% of the mean. The particle size and drug content of each set of particles used for a release study is mentioned in the subsequent sections.

3.2. Effect of L:G ratio

Fig. 1a shows the cumulative %haloperidol released as a function of time from three batches of nanoparticles made from PLA using the sonication method. The size of particles from each batch is 220 nm and the drug content is 1.7%.

Fig. 1a demonstrates our capacity to produce a system of small nanoparticles (~220 nm) that releases haloperidol consistently with an extraordinary reproducibility across different batches. The drug release profile from nanoparticles can be divided into four zones: (i) initial burst period, during which the surface drug is dumped into the release medium; here it is taken as 1 day; (ii) induction period, during which the drug is released at a gradually decreasing fast rate; (iii) slow release period, during which the drug is released at a steady slow rate; (iv) final release period (not shown), during which the particle disintegrates to release the remaining drug at a fast rate.

Fig. 1b shows the haloperidol release profiles from nanoparticles made from PLGA 50:50 and PLA. The size of particles is 220 nm and the drug content is 1.3% for PLGA particles and 1.7% for PLA particles.

The drug release process over a long period of time is expected to be influenced by the polymer L:G ratio since the process is controlled by the degradation rate of polymer, which is affected by polymer hydrophobicity. Strong L:G dependence of release profile has been reported by Bodmeier et al. (1989) for water-soluble drugs (salicylic acid, caffeine and quinidine) incorporated in PLGA and PLA films and microspheres and by Mu and Feng (2002) for a hydrophobic drug (paclitaxel) incorporated in PLGA nanoparticles. For both these cases the drug release mechanism was a combination of drug diffusion and polymer degradation.

However, the drug release mechanism in the haloperidol–PLGA system is suspected to be predominantly diffusion controlled (Budhian et al., 2005). Hence the influence of L:G ratio cannot be attributed entirely to slow polymer degradation. During the drug release process, the drug diffuses through the hydrated polymer matrix into the aqueous phase. The process of hydration relaxes the polymer chains and enhances the diffusion of drug molecules. The rate of water uptake (hydration) of polymer particles increases with the hydrophilicity of polymer. Hence, the initial burst is higher for more hydrophilic (PLGA) particles than less hydrophilic (PLA) particles. The induction period is also affected by polymer hydrophobicity. Decreasing the hydrophobicity increases the

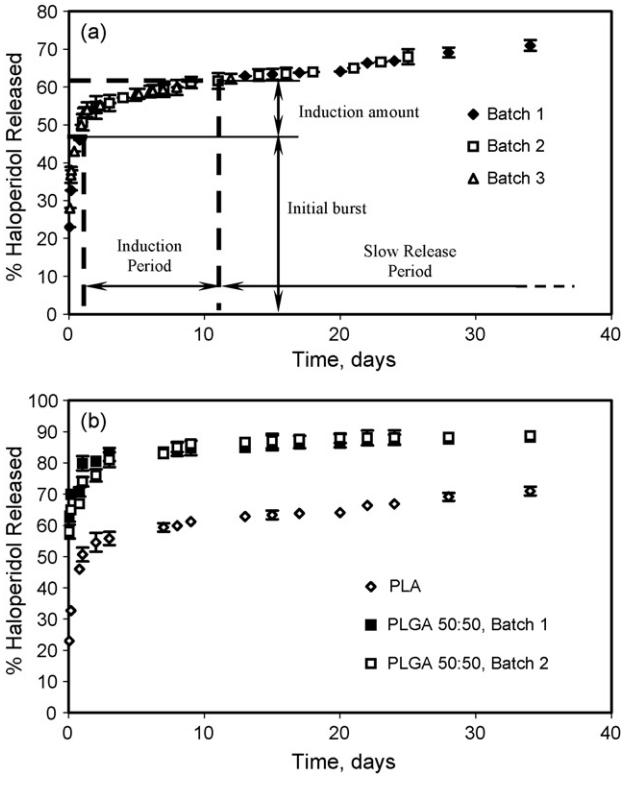

Fig. 1. (a) Overall haloperidol release profiles from three batches of PLA nanoparticles. Each batch has a mean diameter of 220 nm and a drug content of 1.7%. (b) Haloperidol release profiles from PLA (◊) and PLGA (■, □) particles having a mean diameter of 220 nm. Drug content is 1.7% for PLA particles and 1.3% for PLGA particles. In this and subsequent figures, each point represents a batch and error bars indicate the standard deviation of the mean reading within a batch. Error bars are omitted when the error is within 10% of the mean reading.

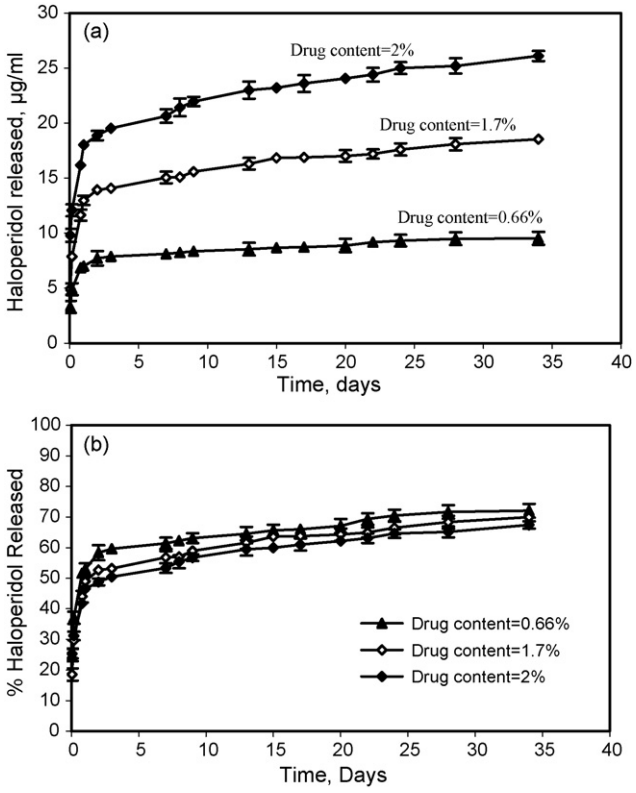

Fig. 2. (a) Absolute and (b) normalized haloperidol release profiles from 220 nm PLA particles having a drug content of 2% (◊), 1.7% (♦) and 0.66% (▲).

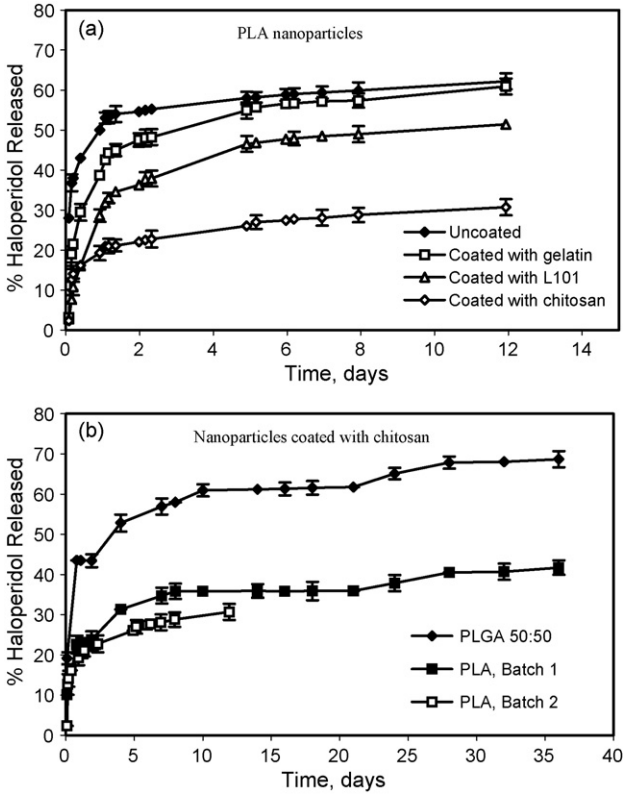

Fig. 3. (a) Haloperidol release profiles from 220 nm PLA particles: uncoated (♦) and coated with gelatin (□), chitosan (◊) or L101 (△). (b) Haloperidol release profiles from 220 m particles coated with chitosan and prepared from PLGA 50:50 (♦) or PLA (■, □). PLGA and PLA particles have a drug content of 1.3 and 1.7%, respectively.

rate at which the diffusion front (of the release medium) moves from the surface to the core, which makes more drug available for diffusion in a less time and thus reduces the induction period.

3.3. Effect of drug content

Fig. 2a and b shows the haloperidol release profiles from 220 nm PLA particles prepared by sonication and having a drug content of 0.66, 1.7 and 2%. As the drug content increases, the absolute initial burst increases from 7 to 17 μg/mL. The %release profile is not significantly affected by change in drug content (Fig. 2b).

The increase in drug content in the particles influences the absolute release profiles such that both, the cumulative amount of drug released at any time (including initial burst) and the induction period increases. The increase in drug content increases the amount of drug close to the surface as well as the drug in the core of nanoparticles. The former is responsible for an increased initial burst while the latter causes an increase during the induction period.

For the cumulative %haloperidol release profiles, the increase in the drug released is offset by the increase in the total amount of drug contained in the particles. The final effect on release profile is determined by the larger of the above-mentioned ratios. The drug released during initial burst is predominantly the drug located close to the surface. For our system, the slight decrease in initial burst on increasing the drug content probably happens due to uneven drug distribution inside the particles. On increasing the drug content, the marginal increase in this surface-associated drug is less as compared to the marginal increase in the total drug. Hence, the initial burst given as a %haloperidol decreases on increasing the drug content. Similar trend has been previously reported (Avgoustakis et al., 2002; Ruan and Feng, 2003) for various nano- and microparticulate systems. The opposite trend has also been reported (Allemann et al., 1993; Huang et al., 1999; Chorny et al., 2002a,b) for some PLGA microparticle and nanoparticle systems with different drugs. The discrepancy occurs probably due to excess drug at the nanoparticle surface in the latter case that is immediately released.

3.4. Effect of coating the particles

Fig. 3a shows the haloperidol release profile from 220 nm PLA particles: uncoated or coated with gelatin, chitosan, or L101, prepared by sonication. Particles have a drug content of 1.3%. The %haloperidol released at the end of day 1 (initial burst) from uncoated particles is 46%, while that from particles coated with gelatin, L101 and chitosan is 30, 20 and 17%, respectively. Fig. 3b shows the haloperidol release profile from 220 nm particles coated with chitosan and prepared from PLGA 50:50 and PLA using the method of sonication. The initial burst is ∼20% for PLA particles and ∼43% for PLGA particles.

All the particles are physically coated with various coating agents and the coating process is solely due to physical adsorption or electrostatic interactions between the polymer chains and the coating material. On coating the particles with a thin layer of different substances (chitosan, L101, gelatin) the drug molecules have to pass through an additional layer of diffusional resistance created by the coating substance. This slows down the release process and, in particular, reduces the initial burst. A reduction in initial burst for a hydrophobic drug (lidocaine) encapsulated in PLGA films or microspheres coated with gelatin or chitosan has been reported (Huang et al., 1999; Chiou et al., 2001). Similarly, a reduction in initial burst for coated PLGA microspheres containing a hydrophilic drug (bovine serum albumin) has been reported (Park et al., 1992). In all these case, the coating was achieved by simply dipping the polymer films or microparticles in the coating solution, which is impractical for a nanoparticulate system due the increased tendency of agglomeration post-coating. We overcome this issue of particle agglomeration by using the *in situ* coating method, which is better suited for particles of such small size.

Chitosan was chosen as the coating material for further studies since it reduces the initial burst most effectively. Chitosan is a polysaccharide having a number of –OH and –NH groups that provide opportunities of intermolecular hydrogen bonding with PLGA and PVA. Chitosan forms an entangled network layer on the particle surface and restricts the infiltration and diffusion of water. Further, the solubility of chitosan is a function of pH and at a pH of 7.4 it is practically insoluble in water, which further reduces the rate of water absorption by the particles. The diffusion of drug molecules from nanoparticles surface to the surrounding medium is limited by the entanglements caused by chitosan layer, which reduces the initial burst. The burst is also reduced because now the surface region contains less drug since the coated chitosan layer is devoid of drug. Comparison of Fig. 3b with Fig. 1b clearly shows the reduction in burst release achieved by coating 220 nm PLGA or PLA particles with chitosan. The batch-to-batch variation for PLA particles (Fig. 3b) might be attributed to different coating methods (coating of freeze-dried particles versus *in situ* coating of nanosuspension). The *in situ* method was used for further studies. Coating the particles with chitosan can significantly reduce the initial burst in the release profiles obtained from various haloperidol-loaded nanoparticles.

3.5. Effect of particle size

Fig. 4a compares the haloperidol release profiles from PLA particles with 1.8% drug content having different diameters. The 220 nm particles were prepared using sonication at standard conditions, while the 450 and 1300 nm particles were prepared using homogenization at different speeds. As the size increases, the initial burst decreases and the induction period increases.

The burst is reduced because on increasing the size, the total surface area of a constant weight of particles decreases. Increasing the size of particles increases the length of diffusion pathways for the drug molecules. For the same amount of drug inside the particles, increasing the length of diffusion pathways exercises two opposing effects on the induction period. The induction period increases because the drug molecules have to traverse a longer distance within the polymer matrix to reach the surface. However, the products of polymer degradation also have to travel a longer distance before they can dissolve in the release medium. The trapped products increase the local pH within the polymer matrix, which accelerates the polymer degradation due to autocatalysis (Siepmann et al., 2005). This accelerates the rate of loss of molecular weight within the matrix leading to faster drug diffusion. This has an effect of reducing the induction period. The final value of induction period depends on the dominating mechanism. For our small sized particles (<1000 nm), autocatalysis is insignificant and the overall impact of increasing the diffusion pathways (by increasing the particle

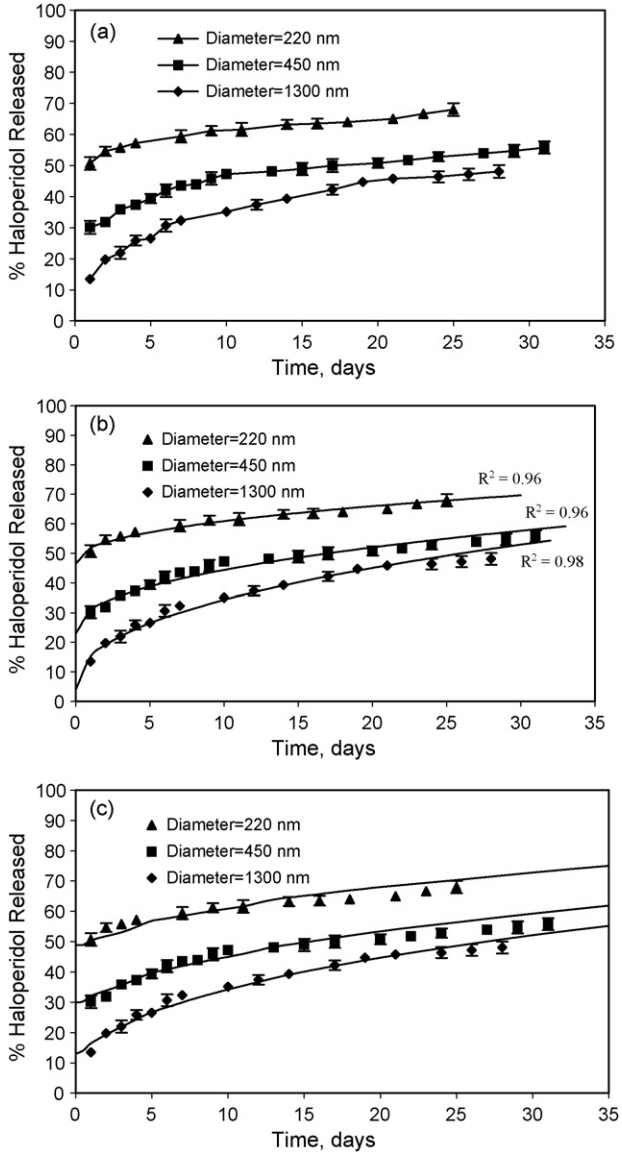

Fig. 4. Haloperidol release profiles from PLA particles having diameters of 220 nm (▲), 450 nm (■) and 1300 nm (♦). All particles have ∼1.8% drug content. (b and c) Theoretical fit to experimental release data shown in (a). Symbols indicate experimental data and solid lines indicate release profile according to Eq. (1) (b) and Eq. (6) (c).

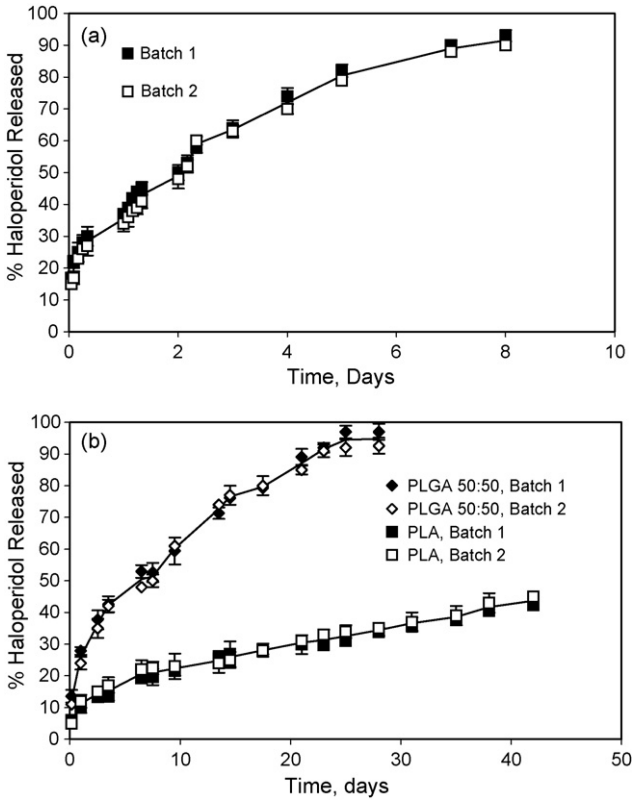

Fig. 5. Haloperidol release profiles from chitosan coated (a) 400 nm PLGA 75:25 particles (■, □) having a drug content of 2% and (b) 900 nm PLGA 50:50 (♦, ◇) and PLA (■, □) particles having a drug content of 2.4 and 2.7%, respectively.

diameter) is an increase in induction period and the induction amount.

3.6. Tailored release profiles

Fig. 5 shows the haloperidol release profiles for two batches of chitosan coated particles prepared by using homogenization and made from PLGA 75:25, PLGA 50:50 and PLA. The chitosan coated PLGA 75:25 particles have a mean particle size of 400 nm, polydispersity of 0.11, and a drug content of 2%. The chitosan coated PLGA 50:50 particles have a mean particle size of 900 nm, polydispersity of 0.14, and a drug content of 2.4%. The chitosan coated PLA particles have a mean particle size of 900 nm, polydispersity of 0.14, and a drug content of 2.7%. These results demonstrate our capacity to tailor the *in vitro* drug release profiles to achieve specific objectives in terms of drug release period and the release rate. We would ideally want to have a zero initial burst and a steady and constant rate of drug release over a desired period of release.

As we have demonstrated above, the release profile is mainly a function of polymer hydrophobicity, particle size, particle surface and specific interactions in the system. However, each parameter exercises multiple effects on each part of the release profile and getting a desired release profile involves identifying the dominant influences and manipulating multiple parameters simultaneously to reach the desired objective. We can adjust the parameters so that the entire drug is released in the induction period itself and the usual triphasic profile is reduced to a single continuous profile. The next step is to reduce the initial burst so as to maximize the induction amount. Finally, the induction period is adjusted in accordance with the given objectives. For example, if the objective is to design a release system for medium release times (∼7–8 days), then we can take the following steps: (i) increase the polymer hydrophilicity to reduce the triphasic profile into a continuous profile, (ii) coat the particles with appropriate agent to reduce the initial burst and maximize the induction amount without significantly affecting the slope of the release profile and (iii) adjust the period of release by increasing/decreasing the effective drug diffusivity out of the polymer matrix by changing the size of the particles and/or utilizing specific interactions in the system. For example, for our haloperidol–PLGA system, the objective of achieving continuous release for medium release times can be achieved with the following multifaceted approach. (i) Given that the release is strongly affected by the haloperidol–PLGA end group interaction, we chose the polymers having acid end group so as to reduce the burst and prolong the induction period for small (<1000 nm) particles. Since PLA polymer is highly hydrophobic and it gives a typical triphasic profile that extends for longer periods (>35 days), we decide to use the hydrophilic acid end group PLGA polymers. (ii) After selecting the end group, we fix the size of the particles to the smallest possible size (∼220 nm). (iii) Next, we realize that the induction amount can be substantially increased by reducing the high initial burst associated with small sized (<1000 nm) PLGA 50:50 nanoparticles. So we coat the particles with chitosan to reduce the initial burst. (iv) Finally, we increase the induction period to the desired value (∼7–8 days) by increasing the size as well as hydrophobicity of the polymer. The increase in hydrophobicity further reduces burst and increases the induction period at the cost of reducing the induction–release slope. This is overcome by increasing the size of particles, which reduces burst, increases the induction period and also increases the drug release slope during the induction period and compensates for the decrease in slope caused by polymer hydrophobicity. After a careful manipulation of hydrophobicity and size, we find that chitosan coated PLGA 75:25 particles of diameter 400 nm can achieve the desired objective (Fig. 5a). Note that we can also achieve this objective by utilizing other combinations of polymer characteristics and particle properties if there are other constraints on size, hydrophobicity or any other property of the system. This release-profile-tailoring scheme is based on general scientific principles governing the release of any hydrophobic drug from a biodegradable polymer system and can be applied to a model hydrophobic drug–polymer system after taking into account the specific interactions/properties present in the system.

4. Mathematical modeling of drug release

The aim of this section is to utilize the already existing mathematical models in literature to verify our earlier hypothesis that the release from our nanoparticulate system is predominantly diffusion controlled (Budhian et al., 2005)

and to understand how the diffusion mechanism is affected by the size and hydrophobicity of the particles. This would also enable us to calculate drug diffusivities for haloperidol–PLGA nanoparticulate system, which is a fundamental property of such a system and can prove to be very useful for future studies.

4.1. Verification of diffusion hypothesis

The drug release from polymeric micro/nanoparticulate systems is usually considered as a combination of Fickian (diffusion) and non-Fickian movement of drug molecules through polymer chains (Kosmidis et al., 2003). Ritger and Peppas (1987a,b) gave the semi-empirical equation to describe the release of solute when the prevailing mechanism is a combination of Fickian and non-Fickian mechanisms:

$$\frac{M_t}{M_\infty} = kt^n + \alpha \tag{1}$$

where M_t is the drug released at time t, M_∞ the quantity of drug released at infinite time, k the kinetic constant, n an exponent and α represents the drug released at zero time and accounts for the initial burst (Huang and Brazel, 2001). The value of n is related to both the geometrical shape of the formulation and the release mechanism. For drug release from spherical particles, the value of n is equal to 0.43 for pure Fickian and 0.85 for pure non-Fickian mechanisms.

We fit our experimental release data to theoretical release profiles given by Eq. (1) and determine the value of the exponent n so as to test our hypothesis. Fig. 4b shows the theoretical fit to experimental release data for haloperidol-loaded PLA nanoparticles of various diameters. The symbols indicate experimental results and solid lines indicate the best fit as described by Eq. (1). The values of different parameters corresponding to the best-fit lines are given below.

$$\frac{M_t}{M_\infty} = 0.053\ t^{0.433} + 46 \tag{2}$$

$$\frac{M_t}{M_\infty} = 0.078\ t^{0.438} + 23 \tag{3}$$

$$\frac{M_t}{M_\infty} = 0.112\ t^{0.435} + 4 \tag{4}$$

The value of n is ~0.43 for various particle sizes indicating that the drug release is diffusion controlled. The experimental and theoretical profiles for PLGA 50:50 particles start deviating at ~10 days (data not shown), after which the release becomes slower than predicted by the diffusion equation. This deviation of release profiles starts at a much later time for PLA particles. This deviation suggests that the release mechanism is diffusion controlled for the initial few days, after which the role of polymer degradation becomes important in PLGA 50:50 particles. The polymer degradation is faster for PLGA particles than for PLA particles and hence the deviation from experimental profiles is observed much earlier for PLGA particles.

4.2. Analysis of drug release by diffusion

Once the mechanism of drug release is established as diffusion controlled, we can calculate the drug diffusivity using Fick's second law of diffusion:

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r}\right) \tag{5}$$

where c denotes the concentration of drug, t the time, D the diffusion coefficient and r is the radial coordinate. The initial value problem described by Eq. (5) is solved by applying appropriate boundary conditions (Siepmann et al., 2005):

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{n^2\pi^2}{R^2}Dt\right) + \alpha \tag{6}$$

Fig. 4c shows the theoretical fit of Eq. (6) to our experimental release data for haloperidol-loaded PLA nanoparticles of various diameters. The values of drug diffusivity corresponding to the best-fit lines are as given in Table 1 for both PLA and PLGA 50:50. The diffusivity of drug molecules in PLGA 50:50 particles is approximately 16 times the diffusivity in PLA particles.

The increase in drug diffusivity in degrading PLGA particles as compared to PLA particles can be understood in terms of established results in literature for degrading PLA/PLGA micro- and nanoparticles without any encapsulated drug. For a given particle size, the diffusivity is a function of polymer molecular weight (Raman et al., 2005), which varies with time for a degrading polymer system (Belbella et al., 1996). For very small nanoparticles (~220 nm diameter), the molecular weight of PLA particles remains constant for about 10 weeks, while the molecular weight of PLGA particles gradually decreases until they are completely degraded in about 8 weeks (Zweers et al., 2004). Thus, the drug diffusivity in 220 nm PLA particles

Table 1
Drug diffusivities, D, from the haloperidol–PLGA/PLA nanoparticles in Fig. 4c and other PLA–hydrophobic drug systems in literature

Polymer	Drug	Mean diameter (nm)	Diffusivity, D (cm^2/s)	Reference
PLGA 50:50	Haloperidol	220	8×10^{-18}	This paper
PLA	Haloperidol	220	5×10^{-19}	This paper
PLA	Haloperidol	450	3×10^{-18}	This paper
PLA	Haloperidol	1300	4×10^{-17}	This paper
PLA	Lidocaine	225	5×10^{-16}	Polakovic et al. (1999)
PLA	Lidocaine	200	7.7×10^{-17}	Rouzes et al. (2003)
PLA	Tyrphostin AG-1295	170	4×10^{-16}	Chorny et al. (2002a,b)

stays constant with time (in the range tested), while it increases with time for 220 nm PLGA particles. Hence, the average value of drug diffusivity in 220 nm PLGA particles is higher than in PLA particles.

The value of haloperidol diffusivity in PLA matrix for small sized PLA particles is of the order of 10^{-19} to 10^{-18} cm^2/s, which is about two orders of magnitude less than the diffusivity of some other system of nanoparticles reported in literature (Table 1) (Polakovic et al., 1999; Chorny et al., 2002a,b; Rouzes et al., 2003). The primary reason for this discrepancy may be the strong hydrogen bonding interaction between haloperidol and the carboxylic acid group of PLA (Budhian et al., 2005). The drug release rate and hence the apparent diffusivity is reduced due to this strong drug–polymer interaction. Hence, the drug diffusivity in polymer matrix for a system of haloperidol-loaded PLGA/PLA nanoparticles is a complex function of polymer molecular weight, polymer hydrophobicity and particle size.

5. Conclusions

Haloperidol-loaded PLGA/PLA particles were produced by sonication or homogenization and tested for their *in vitro* release behavior. The effects of various particle properties including, polymer hydrophobicity, particle drug content and surface coating, on the release behavior were understood separately. Subsequently, this understanding was integrated to achieve desired haloperidol release profiles. The three most important properties affecting release behavior were identified as: polymer hydrophobicity, surface coating and particle size. Polymer hydrophobicity reduces the initial burst and prolongs the period of release. For example, the initial burst and the %drug released in 35 days is 46 and 70% for 220 nm PLA particles as compared to 70 and 90% for 220 nm PLGA particles. Coating the particle surface with chitosan considerably reduces the initial burst, without significantly affecting the release rate. For example, the initial burst from 220 nm PLGA particles with 1.3% drug is reduced from 70 to 36% by coating them with chitosan. Increasing the size of the particles reduces the initial burst and increases the rate of release. For example, increasing the size from 220 to 450 nm reduces the initial burst from 48 to 28% and results in a steady release of drug over a 10 day time period as compared to 4 days. We successfully integrated these three properties to produce nanoparticles having a release profile with reduced burst and steady release over a desired time period. For example, 400 nm PLGA 75:25 particles, coated with chitosan provide steady release for 8 days with an initial burst of just 30%. The predominant mechanism of drug release was confirmed to be diffusion controlled by the application of mathematical models and the corresponding drug diffusivities were established to be a function of both polymer hydrophobicity and particle size. Hence, the release profile from haloperidol-loaded PLGA/PLA nanoparticles can be tailored to achieve desired objectives by selective manipulation of particle properties. These principles can be applied to a general hydrophobic drug–polymer system after taking into account the specific interactions involved in the system.

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