Chitin/PLGA blend microspheres as a biodegradable drug-delivery system: phase-separation, degradation and release behavior

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Abstract

A novel chitin-based microsphere was developed for anti-cancer drug-delivery purpose in the present study. These biodegradable microspheres were prepared by directly blending chitin with different contents of poly(\(d,\text{,}l\)-lactide-co-glycolide 50:50) (PLGA 50/50) in dimethylacetamide–lithium chloride solution, and following it by coagulating in water via wet phase inversion. Scanning electron microscopy (SEM) micrography of the blend microsphere showed that there are numerous PLGA particulates homogeneously dispersed in chitin matrix, suggesting the occurrence of obvious phase separation from the blended chitin and PLGA 50/50 phase due to their thermodynamic incompatibility. Degradation of the chitin/PLGA 50/50 blend microsphere depends on the surface erosion of chitin phase and bulk hydrolysis of PLGA phase, according to the examinations of SEM and differential scanning calorimetry studies. Weight loss of the chitin/PLGA 50/50 blend microsphere increases with the increase of chitin content in the microsphere. A two-phase drug-release model is observed from the release of chlorambucil from chitin/PLGA 50/50 blend microspheres. The initial stage of drug-release rate increases with the increased chitin content due to the hydration and surface erosion of hydrophilic chitin phase; however, the following stage of slow release is sustained for several days, mainly contributed by the bulk hydrolysis of hydrophobic PLGA phase. In conclusion, such a chitin/PLGA 50/50 blend microsphere is novel and interesting, and may be used as a special drug-delivery system. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Recently, synthetic biodegradable polyesters such as the polymers of lactic acid (PLA) and glycolic acid (PGA), and their copolymers (PLGA) have attracted much attention in the use for special drug delivery [1–7]. As the polymers are safe in the body and are hydrolyzed into metabolic by-products, surgery is not required for their removal after complete drug release. Poly(\(d,\text{,}l\)-lactide-co-glycolide) (PLGA) among them is one of an important polyester because it is a commercially available product approved for human application. It has been reported that the degradation rate of such a copolymer is significantly affected by the lactic acid/glycolic acid composition, and the degradation rate may be a dominant factor to successfully deliver drugs in a controlled way. In an attempt to modify the degradation behavior of these polymers, different LA/GA compositions of PLGA have been synthesized and characterized [8–12].

One attempt to control the degradability of a device based on PLA, PGA or PLGA is blending the polyesters with other biodegradable polymers. Blending may be used effectively to modify physical and mechanical properties that each individual polymer does not have. Depending on the thermodynamic properties of the chosen polymers, different degrees of phase separation can be observed from the blended polymers, leading to the variation of their degradation behaviors. In the past studies, PLA was blended with degradable and non-degradable polymers such as poly(glycolic acid) (PGA), poly(ethylene oxide) (PEO), poly(propylene oxide) (PPO)
(PPO) and poly(ethylene-vinyl acetate) in an effort to modify degradation and drug-release behaviors of PLGA-based polymeric drug-delivery systems [13]. Besides, the miscibility, degradability and drug-release property of the PLGA/polyphosphazene and PLGA/PVA blends were also studied, respectively [14–15].

Natural polysaccharide such as chitin [poly β(1–4)-D-glucosamine] is also biodegradable, and has recently been found to be a useful material for biomedical application [16]. Chitin is degraded via the cleavage of β-glycosidic bond between β-acetylglucosamine unit [17–18]. Due to the reason that chitin has a thermodynamic property which is significantly different with the properties of PLGA, one can expect to observe significantly phase-separated morphologies from the chitin/PLGA blending. Furthermore, chitin is more hydrophilic than PLGA, the chitin/PLGA blends may exhibit different degrees of hydration depending on the ratio chitin:PLGA in the blends. In particular, hydration plays an important role determining polymer degradation via hydrolysis of ester backbone [13]. Accordingly, drug release from the chitin/PLGA blendings may be affected by their hydrophilicity.

In the present study, we report the preparation and characterization of a novel biodegradable drug-delivery device based on chitin/PLGA 50/50. A series of chitin/PLGA 50/50 microspheres are prepared by coagulating the droplets of chitin/PLGA 50/50 blends in deionized water (a wet phase-inversion method). Physical and morphological studies such as differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) of the resultant microspheres are carried out to examine the phase separation of chitin/PLGA 50/50 blending. It can be found that the phase-separated microspheres consisting of numerous PLGA particulates dispersed in the chitin matrix. Based on the understanding of characteristics of phase separation and hydration of the blended microspheres, the degradation properties are investigated in the present work. A model anti-cancer agent, chlorambucil, is loaded in the chitin/PLGA 50/50 blend microspheres, and the effects of physicochemical and morphological changes on drug-release patterns are also examined.

2. Experimental

2.1. Materials

Chitin was purchased from Tokyo Chemical Industry (Japan). PLGA 50/50 (Mw is about 40,000, lactide/glicolide ratio is 50/50) and chlorambucil were obtained from Polyscience (USA) and Aldrich Chemical Company, Inc. (USA). All other reagents and solvents used were of reagent grade.

2.2. Preparation of chitin/PLGA 50/50 blended solution

Chitin solution (1.0% by weight) was prepared by suspending chitin powder (2 g) in 200 ml of dimethylacetamide (DMAc)–5% lithium chloride (LiCl) solution. The chitin/DMAc–LiCl mixed suspension was prepared by stirring for 2 h. The bath contained a large amount of deionized water, which provides a sink of nonsolvent (coagulant) for the phase separation of chitin/PLGA 50/50 blends. The chitin/PLGA 50/50 blend solution was slowly added with the nonsolvent (water) for the separation of chitin and PLGA 50/50 phase. The PLGA domain of the phase-separated chitin/PLGA 50/50 blend was extracted by dichloromethane to characterize the phase separation.

2.3. Preparation of chitin/PLGA 50/50 blend lump

Deionized water was used as a nonsolvent (coagulant) for the phase separation of chitin/PLGA 50/50 blends. The chitin/PLGA 50/50 blend solution was slowly added with the nonsolvent (water) for the separation of chitin and PLGA 50/50 phase. The PLGA domain of the phase-separated chitin/PLGA 50/50 blend was extracted by dichloromethane to characterize the phase separation.

2.4. Preparation of chitin/PLGA 50/50 blend microspheres

To prepare microspheres, the chitin/PLGA 50/50 blend solution was added dropwise through syringe into the coagulation bath. The bath contained a large amount of deionized water, which provides a sink of nonsolvent tank for completely replacing DMAc–LiCl solution from the droplet of chitin/PLGA 50/50 blend. The gelled microspheres were allowed to harden in the coagulation bath for 6 h. After coagulation, the microspheres were filtered, rinsed with deionized water again and dried in air overnight, then stored in desiccator for future analysis.

2.5. Preparation of drug-loaded chitin/PLGA 50/50 microspheres

Chlorambucil was dissolved in the chitin/PLGA 50/50 blend solution by stirring to prepare a homogeneous solution. The chlorambucil/chitin/PLGA 50/50 homogeneous solution was added dropwise through a syringe into the coagulation bath according to the process for the preparation of raw chitin/PLGA 50/50 blend microspheres described above. During the coagulation of polymeric chitin/PLGA 50/50 solution, the dissolved chlorambucil is precipitated in the phase-separated chitin/PLGA 50/50 microspheres. The microspheres
were filtered, rinsed with deionized water again and dried in air overnight, then stored in desiccator for drug-release analysis.

2.6. Scanning electronic microscopy (SEM)

The chitin/PLGA 50/50 blend microspheres prepared by the wet phase-inversion method were attached onto a double-sided adhesive tape and fixed to an aluminum stage, respectively. The microspheres were cut by a razor, and then were sputter-coated with gold for the thickness of 500 × 10⁻⁸ cm using a Hitachi coating unit (IB-2 coater). Subsequently, the morphologies of surface and cross section of the microspheres were examined using a Hitachi S-2300 SEM.

2.7. Differential scanning calorimetry (DSC)

DSC (Perkin-Elmer Series 7) thermograms were taken using a standard aluminum pan. Nitrogen was used as a sweeping gas, and the heating rate was 5°C/min. Samples (5 mg) were loaded without further treatment. The initial and final temperatures are -50°C and 200°C, respectively. All the samples for DSC analysis were original chitin/PLGA 50/50 blend microspheres without drug loading.

2.8. Hydration of chitin/PLGA 50/50 blend microspheres

The water uptake capacity of each chitin/PLGA 50/50 blend microsphere was determined by the hydration of microsphere in deionized water at room temperature. The chitin/PLGA 50/50 blend microsphere (200 mg) was placed in deionized water for a required period of time. At preset time intervals, hydrated samples were taken and weighed after blotting the surface water with a filter paper, then weighed immediately on an electronic balance. The percentage water content of the chitin/PLGA 50/50 blend microsphere was calculated as follows:

\[ P_{WC} = \left( \frac{W_e - W_0}{W_0} \right) \times 100\% \]

\( P_{WC} \) is the percent water content of chitin/PLGA 50/50 blend microsphere at equilibrium. \( W_e \) denote the weight of the chitin/PLGA 50/50 blend microsphere at equilibrium of water uptake and \( W_0 \) is the initial weight of the chitin/PLGA 50/50 blend microsphere. Each water uptake experiment was repeated 3 times and the average value was taken as the percentage water content value.

2.9. Degradation of chitin/PLGA 50/50 blend microspheres

The degradation study of the chitin/PLGA 50/50 blend microspheres was conducted in vitro by incubating the microspheres in deionized water in test tube with known weights, respectively. The test tubes were placed in a 37°C shaking water bath. At predetermined time intervals, the chitin/PLGA 50/50 blend microspheres were separated from the medium and dried in vacuum oven to a constant weight at 40°C. The biodegradation rate was expressed as the weight loss of the chitin/PLGA 50/50 blend microspheres after incubation. Each biodegradation experiment was repeated 3 times and the average value was taken as the remaining weight of chitin/PLGA 50/50 blend microspheres. The variation of morphologies and chemical compositions of the chitin/PLGA 50/50 blend microspheres after degradation was examined by SEM (Hitachi S-2300) study.

2.10. Drug release from chitin/PLGA 50/50 blend microspheres

The release of chlorambucil from chitin/PLGA 50/50 blend microsphere was measured using the dissolution (Hanson research, Dissoette II) and autosampling (Hanson research, SR6) systems. The dissolution medium was 500 ml of deionized water. The medium was placed in a 11 round flask fitted with a pump for autosampler to remove the medium and was stirred with a mechanical stirrer at a rate of 100 r.p.m. The dissolution medium temperature was maintained at 37°C. An equivalent quantity of 100 mg chitin/PLGA 50/50 blend microsphere was dispersed in the dissolution medium. After a predetermined period, 5 ml of the medium was removed and the amount of chlorambucil was analyzed spectrophotometrically at 320 nm. In order to maintain the original volume, each time 5 ml of the medium was replaced with fresh deionized water.

3. Result and discussion

3.1. Morphology of chitin/PLGA 50/50 blend lump

The chitin/PLGA blend solution was coagulated by the addition of deionized water. From the cross-section view of coagulated chitin/PLGA blend (Fig. 1(a)), it reveals that the coagulated gel is composed of numerous particulates dispersed in the matrix. To examine the dispersed (particulates) and continuous phases (matrix), PLGA domain of the phase-separated chitin/PLGA 50/50 blend was extracted by dichloromethane. As can be seen from Fig. 1(b), it is found that homogeneously dispersed pores are formed in the gel after extraction by dichloromethane. The result suggests that the dispersed phase is composed of PLGA 50/50 and the continuous phase is composed of chitin. This is a simple method to characterize the phase separation of chitin/PLGA 50/50 blend; however, the phase-separated chitin/PLGA 50/50 blends were lump and not microsphere. Microspheres are prepared by
dropping the chitin/PLGA 50/50 blend solution through a syringe into water, contrarily.

3.2. Phase separation in chitin/PLGA 50/50 blend microspheres

Different approaches have been adopted to prepare PLGA-based materials for biomedical application in the previous articles. In the present study, chitin/PLGA 50/50 blend microspheres were prepared using a wet phase-inversion method as illustrated in Fig. 2. The microspheres prepared from various chitin/PLGA 50/50 blends have various morphologies, and may demonstrate different hydration properties and biodegradability. These factors significantly affect the drug-release characteristics of the blend microspheres. The investigations about the chitin/PLGA 50/50 microspheres were all evaluated for future use as a novel drug-delivery system.

The thermodynamic compatibility between PLGA 50/50 and chitin is expected to depend on the miscibility of two types of polymers. The basic requirement for compatibility of a two-component polymer blend is that the enthalpy term $\Delta H_{\text{mix}}$ must be negative to achieve miscibility:

$$\Delta H_{\text{mix}}/V = (\delta_1 - \delta_2)\Phi_1\Phi_2,$$

where $V$ is the molar volume of the mixture, $\delta_{1,2}$ are the solubility parameters and $\Phi_{1,2}$ are the volume fractions of components 1 and 2. The solubility parameter of PLGA 50/50 has been reported to be 25.11 J$^{1/2}$/cm$^{3/2}$ [15]; however, the solubility parameter of chitin is estimated to be 17.8 according to the parameters of Hoy’s group molar attraction constants. The difference in the $\delta$ values of PLGA 50/50 and chitin leads to the expectation that $\Delta H_{\text{mix}}$ will be positive. Since the existence of hydrogen bonding between PLGA 50/50 and chitin is not significant, except for those between the hydroxyl and carboxyl end groups in PLGA 50/50 and the amide functional groups in chitin, a high degree of phase separation can be observed from the chitin/PLGA 50/50 blending. DSC studies were carried out to examine the phase separation. The chitin/PLGA 50/50 blend microspheres exhibit two endothermal peaks around 50°C and 170°C which correspond to the glass transition temperature ($T_g$) of PLGA 50/50 and
β-chitin [16], respectively (Fig. 3). No obvious shift in $T_g$ provides a direct evidence of polymer immiscibility.

The crystalline melting temperature ($T_m$) of a polymer is also used to evaluate the extent of phase separation in the blend. When two polymers are compatible in the amorphous state, $T_m$ is depressed as a result of the disturbed order in the crystalline phase. PLA is a semi-crystalline polymer with $T_m$ around 170°C; however, there is no evidence of an endothermal melting observed from the DSC study, which suggests that the 50:50 PLGA used in this work is not crystalline. The absence of a $T_m$ is consistent with the racemic structure of the dilactide monomer and the copolymerization of dilactide and diglycolide is largely random, with the result that long sequences of glycolide capable of crystallization are not formed in the 1:1 copolymer [17,18]. An exothermic peak around 185°C corresponding to the crystalline temperature ($T_c$) of chitin is observed from the chitin/PLGA 50/50 blends, which are almost the same as the $T_c$ of original chitin. The $T_m$ of chitin is above 200°C which is not found in the present DSC analysis. These results indicate that PLGA 50/50 and chitin phase in the blended microsphere exhibit a high degree of phase separation.

### 3.3. Morphologies of chitin/PLGA 50/50 blend microspheres

Fig. 4 shows the SEM micrographs of the cross-section view of all chitin/PLGA 50/50 microspheres prepared by a wet phase-inversion method. It can be clearly found that there are numerous PLGA 50/50 particulates homogeneously dispersed in chitin matrix of the blend microsphere. In five types of blends, the domain size of PLGA phase significantly increases from hundred nanometers to several micrometers with the increase of PLGA 50/50 content in the blends. Phase separation of a polymeric blend in the coagulant depends on a number of factors including the composition of the blend, the history of coagulants, and the interactions between polymer–solvent–coagulant (nonsolvent) three phase, such as polymer–polymer (PLGA 50/50–chitin), polymer–solvent (PLGA 50/50–DMAc, chitin–DMAc) and polymer–nonsolvent (PLGA 50/50–water, chitin–water) miscibility. As described previously, chitin and PLGA 50/50 were immiscible according to the estimation of their solubility parameters. Being immersed in water, PLGA 50/50 precipitates from the chitin/PLGA 50/50-blended droplet much quicker than chitin because that water, which is used a coagulant for PLGA 50/50, is a poor solvent (nonsolvent) more severe than that used for chitin, therefore, PLGA phase of the chitin/PLGA 50/50 blend forms a domain (dispersion phase) and chitin phase forms matrix (continuous phase) after phase separation. In addition, the surface tension of PLGA and the interfacial tension between DMAc/PLGA 50/50 solution and water may be large enough to maintain the sphericity of phase-separated PLGA 50/50 particulates. Owing to the reasons, a novel microsphere containing numerous PLGA 50/50 particulates dispersed in chitin matrix can be obtained by the coagulation of chitin/PLGA 50/50 blend (dissolved in DMAc) solution in water. Aggregation into larger domain is possible for the increase of PLGA 50/50 content in the chitin/PLGA 50/50 blend, due to the great driving force for solidification. The chitin/PLGA 50/50 blends have distinct boundaries between domains and matrix, implying poor interfacial adhesion. As described previously, no significant hydrogen bonding between PLGA 50/50 and chitin is responsible for the poor interfacial adhesion.

Fig. 5 shows SEM micrographs of the cross-section view of the microspheres prepared by phase inversion of the chitin/PLGA 50/50 blended solutions, in the presence of dissolved chlorambucil. After phase separation, the PLGA 50/50 particulates are found to be embedded in cellular pores of chitin matrix of the blend microspheres. A void space between the PLGA 50/50 particulate and cellular pore of chitin matrix can be observed from the chlorambucil-loaded microspheres. These results can be due to the leaching out of dissolved chlorambucil from both chitin and PLGA 50/50 phase, after phase separation of the chitin/PLGA 50/50 blends in deionized water, which is responsible for the formation of a void space between the PLGA 50/50 particulate and cellular pore of the chitin matrix, after drying.
3.4. Hydration properties

The degradation of PLGA 50/50 proceeds via hydrolytic breakage of the ester backbone bond. Water accessibility to these bonds will determine the rate of degradation. Accordingly, the rates for the degradation of dispersed PLGA 50/50 phase may depend on the hydrophilicity and crystallinity of the chitin/PLGA 50/50 blends. PLGA 50/50 is relatively hydrophobic, but has very low degree of crystallinity in its structure. Chitin unlike PLGA 50/50 is more hydrophilic and it has a semi-crystalline structure. Blending of PLGA 50/50 with chitin is expected to produce different degrees of matrix hydration depending on the choice of various chitin/PLGA 50/50 blend ratios. Fig. 6 shows the hydration degrees of microspheres prepared from different ratios of chitin/PLGA 50/50 blends. All the chitin/PLGA 50/50 blends showed a high water uptake capability relative to pure PLGA 50/50; the water content increases with increase in the amounts of chitin phase in the blends. Deformation is not observed from all the chitin/PLGA 50/50 blend microspheres, except for a low degree of swelling.

3.5. Degradation studies

PLGA 50/50 has been known to degrade slowly because of its hydrophobic property. Nevertheless, the degradation rate of PLGA 50/50 is quicker than PLA, due to its amorphous structure allowing fast water penetration. The bulk hydrolytic chain scission of PLGA is proportional to water and ester concentration, and is autocatalyzed by the generated carboxylic end groups. When PLGA is blended with a hydrophilic polymer in good miscibility, it is expected to bring about a rapid increase in the PLGA hydrolysis rate due to the soaking of PLGA with water in the same phase. However, for the immiscible chitin/PLGA 50/50 blends, the adsorbed water in the polymer bulk will be primarily associated with the chitin phase and will not contribute significantly to the chain scission process in the separated PLGA phase. Fig. 7 shows the change in weight of the chitin/PLGA 50/50 blend microspheres after being incubated in deionized water. Weight loss of the chitin/PLGA 50/50 microspheres increases with the increase in hydrophilic chitin content, and suggests that the hydrolysis of PLGA may be accelerated after being...
Fig. 5. SEM micrographs of phase-separated chitin/PLGA 50/50 blend microsphere in the presence of chlorambucil; chitin/PLGA 50/50 blend ratios: (a) pure chitin, (b) 3/1, (c) 2/1, (d) 1/1, (e) 1/2, and (f) 1/3.

Fig. 6. Hydration degrees of chitin/PLGA 50/50 blend microsphere.
blended with the hydrophilic chitin. These results seem to be inconsistent with the expectation based on the theory described above.

Figs. 8 and 9 show the SEM micrographs of various chitin/PLGA 50/50 blend microspheres after different periods of degradation. As can be seen from Figs. 8(a–d), it is of interest to find that the surface morphology of microspheres prepared from pure chitin become porous under 1–5 weeks of degradation; however, the inside structure of chitin microsphere remains intact (Fig. 8e). Surface erosion of the chitin microsphere is accompanied with the reduction of its diameter. The degraded chitin microsphere decreases to about half of its original volume at week 5 (Fig. 8d). Figs. 9(a–c) show the surface morphologies of degraded chitin/PLGA 50/50 microspheres which are prepared from highest chitin content of chitin/PLGA 50/50 blended solutions (blending ratios chitin:PLGA 50/50 are 3:1). These microspheres become more porous than those prepared from the lowest chitin content (blending ratios chitin:PLGA 50/50 are 1:3) after degradation (Figs. 9(d–f)). These results suggest that the degradation of the chitin/PLGA 50/50 blend microspheres should be mainly dominated by the erosion of chitin phase.

There are many cracks, but no pores, on the surface of a microsphere prepared from the lower chitin content of chitin/PLGA 50/50-blended solution (blending ratios chitin:PLGA 50/50 is 1:3) after degradation (Figs. 9(d–f)), reveals that surface erosion of such a blended microsphere is inhibited. As shown in Figs. 9(g–i), deformation and aggregation of the PLGA 50/50 particulates within the chitin matrix are observed from the cross-section of degraded microspheres after 5 weeks of degradation. This suggests that the hydrated chitin polymer chains in amorphous region is excessively intermixed with the degraded PLGA 50/50 molecule. Fig. 10 shows the DSC studies of degraded chitin/PLGA microspheres. In the blend microspheres, the peaks at
glass transition temperature ($T_g$) of PLGA 50/50 phase and the crystallization temperature ($T_c$) of chitin phase disappear after 7 weeks of degradation. The results reveal that PLGA 50/50 phase in the chitin/PLGA blends has transferred from a glass state to amorphous state due to a bulk degradation, and the degraded PLGA 50/50 molecules are indeed intermixed with the chitin phase of the blend microspheres.

3.6. Drug release

As mentioned above, phase separation in the chitin/PLGA 50/50 blend microspheres is observed from the examination of SEM micrography and DSC study. The chitin phase is more hydrophilic than PLGA phase and it is degraded by surface erosion; however, the PLGA phase is hydrophobic and it is degraded by bulk degradation. Accordingly, the characteristics of drug released from the chitin/PLGA 50/50 blend microspheres after 7 weeks of degradation.

Fig. 9. SEM micrographs of chitin/PLGA 50/50 blend microsphere after different periods of degradation; (a)–(c) are the surface morphology of microspheres prepared from chitin/PLGA 50/50 blend ratio 3/1; (d)–(f) and (g)–(i) are, respectively, the surface and cross-section morphology of microspheres prepared from chitin/PLGA 50/50 blend ratio 1/3.

Fig. 10. DSC thermogram of the chitin/PLGA 50/50 blend microsphere after 7 weeks of degradation.
microspheres may be affected by the hydrophilicity and degradability of both PLGA and chitin phase. The release of chlorambucil from a hydrophilic chitin matrix, via the penetration of water into the amorphous region to leach out the incorporated drug, is much quicker than the release of chlorambucil via surface erosion of chitin matrix. Chlorambucil release from the hydrophobic PLGA 50/50 particulates via bulk degradation is another factor that affects drug release. Owing to the different hydrophilicity and degradability of chitin and PLGA phase, drug-release mechanism of the blended microsphere becomes very complex.

The overall rate of drug release is decided by ultimately depending on the partition of drug in different phases (chitin or PLGA phase) of the blend microsphere. If the dissolved chlorambucil is mainly incorporated in the chitin matrix after phase separation, then kinetics of drug release may be illustrated by a diffusion-controlled release model. On the contrary, chlorambucil is mainly incorporated in the PLGA domain after phase separation. The chitin matrix serves to protect the entrapped PLGA 50/50 particulates from the external aqueous environment until such a time as the erosion front reaches the PLGA domain. A slow release rate with evident delay time can be observed from this type of drug release. In general, chlorambucil will be homogeneously dispersed in both chitin and PLGA phase of the blend microsphere. For such a case, the release mechanism should be a two-stage release type. The initial quick release, followed by the slow release of chlorambucil from the chitin/PLGA 50/50 blend microspheres due to the hydration of chitin matrix and the bulk hydrolysis of dispersed PLGA domain can be expected.

In the present study, a two-phase release model is observed from the release of chlorambucil from chitin/PLGA 50/50 blend microspheres (Fig. 11). The initial stage of drug-release rate increases with the increase of chitin content, which is due to the increased hydration ability of chitin/PLGA 50/50 blend microspheres. Over 60% of chlorambucil that is released at the early stage of quick release suggests that chlorambucil is mostly incorporated to the more hydrophilic chitin matrix after phase separation. The following stage of slow release is sustained for over 200 h. Due to the fact that chitin is more hydrophilic than PLGA 50/50, a higher content of chitin in the blended microspheres exposes the dispersed PLGA 50/50 particulates expose to aqueous environment easily, and results in the faster drug release which is contributed by the bulk hydrolysis of PLGA 50/50 particulates. A sudden increase in the release rate of chlorambucil is observed at 150 h post-operation, which suggests that this period of bulk hydrolysis makes PLGA 50/50 particulates less durable for the protection of the drug from dissolution. In conclusion, such a chitin/PLGA 50/50 blend microsphere is novel and interesting, and may be used as a special drug-delivery system.

4. Conclusion

In this study, we prepared a novel microsphere based on chitin/PLGA 50/50 blending, which was developed to be used for the delivery of anti-cancer drug. The microsphere consists of separated PLGA and chitin phase in the chitin/PLGA 50/50 blends. The phase-separated PLGA 50/50 particulates were well dispersed in chitin matrix, and the particle sizes decreased with the increase of chitin content. The hydration and degradation of chitin and PLGA phase in the blend microsphere demonstrate significantly different characteristics, which dominate the drug-release mechanism of the chitin/PLGA 50/50 microspheres. The results indicted that the chitin/PLGA 50/50 blend microspheres might prove useful in a potential polymer carrier for the controlled release of anti-cancer drugs.

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