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A water-in-oil-in-oil-in-water (W/O/O/W) method for producing drug-releasing, double-walled microspheres

Wang Zheng*

Department of Chemical & Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576, Singapore

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ABSTRACT

A water-in-oil-in-oil-in-water (W/O/O/W) method was developed to fabricate double-walled microspheres for controlled delivery of drugs and therapeutic proteins with reduced initial burst and prolonged release. By using this method, drugs and therapeutic proteins can be loaded into microspheres in solution form as those used in medical treatments. Proteins can be loaded in solutions together with excipients, thereby reducing the risk of losing stability in the process of protein drying and dispersing. This also benefits uniform distribution of drugs inside polymer matrix in comparison to the case with solid drug particles. These microspheres were characterized to have double-walled structure, with a cavity in the centre. The hydrophilic drugs were encapsulated in the inner polymer layer, while the non-drug-loaded outer layer served as a rate-limiting barrier. Drug release profiles for 5-fluorouracil showed low initial burst and prolonged release, which is substantiated by degradation studies.

1. Introduction

Controlled drug release using biodegradable polymers such as poly(lactide-*co*-glycolide) (PLGA), has been shown to hold great promise for implanted therapy. The advantages of such a system would be (i) controllable protein release kinetics over periods of days to months (Freiberg and Zhu, 1984); (ii) complete biodegradability and good biocompatibility of PLGA (Anderson and Shive, 1997); (iii) easy administration of microspheres using standard syringes.

Many groups have developed methods for producing PLGA microspheres by dissolving polymers in a solvent and precipitating it into a sphere, e.g., using solvent evaporation (Vrancken, 1970; Morishita, 1976; Mathiowitz et al., 1990a,b), solvent removal (Mathiowitz et al., 1988; Mathiowitz et al., 1990a,b), spray-drying (Mathiowitz et al., 1992) or coacervation processes (Madan, 1978; Heistand et al., 1960). The double-emulsion (water-in-oil-in-water, or W/O/W), solvent evaporation/extraction method is one typical method widely used for the preparation of PLGA microspheres loaded with hydrophilic drugs such as therapeutic proteins (Nihant et al., 1995; Yeh et al., 1995; Blanco and Alonso, 1997). Typically, these microspheres will give out a very large burst of drug release upon immersion into the release medium. This initial burst release, referred to as the percentage/amount of drug released after 24 h, depends on the immediate diffusion of hydrophilic drugs from polymer matrix (Mehta et al., 1996), and is complicated by its correlation with the effective drug loading (Yeo and Park, 2004). Too high a burst would reduce the effective lifetime of the drug delivery device, reducing its effectiveness both therapeutically and economically (Yeo and Park, 2004). And even worse, excessive initial release rates could result in drug levels close to or exceeding toxic threshold levels. Other problems associated with microspheres made of a single polymer include low encapsulation efficiency for highly water soluble drugs (Bodmeier and McGinity, 1987) and lack of sustained release for periods suitable for periodic therapy especially with hydrophilic drugs (Pekarek et al., 1994a,b).

To overcome the limitation of microspheres made of a single polymer encapsulating hydrophilic drugs, Parrot developed a method for making shell–core structure in microspheres by coating processes involving the use of fluidized beds (Parrot, 1970). The microspheres produced had a uniform coating, but the drawback is that fluidized beds are difficult to design for particle sizes of less than 100 μm. Therefore, Mathiowitz et al. developed a one-step preparation method for fabricating double-walled microspheres, which relies on the spreading equilibria between two fluids suspended as emulsified droplets in a solvent (Pekarek et al., 1994a,b). In this method, two polymer solutions were mixed, with drugs or proteins dispersed into the appropriate polymer. These mixed polymer solutions were then added to the non-solvent, continuous phase to form microspheres. Later, other groups also investigated drug release properties of double-walled microspheres produced from the same concept (Lee et al., 2002; Rahman and Mathiowitz, 2004; Tan et al., 2005; Leach et al., 1999; Leach and Mathiowitz, 1998). Kim et al. reported another method to fabricate

* Tel.: +65 65137991; fax: +65 67900920.
E-mail address: wangzheng@ntu.edu.sg.

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Table 1
Polymer information.

Polymer	Company	Lactide ratio (%)	End group	Intrinsic viscosity (dl g^{-1})[a]	*Mw* (g mol^{-1})[b]
Resomer RG502	Boehringer Ingelheim Company, Germany	50	Ester	0.16–0.24	1.53×10^4
PLGA 53/47	Purac Far East, Singapore	53	Ester	1.05	1.37×10^5
PLGA 75/25	Purac Far East, Singapore	75	Ester	0.93	1.18×10^5
PLGA 80/20	Boehringer Ingelheim Company, Germany	80	Ester	1.7–2.6	2.01×10^5

[a] Intrinsic viscosity of as-received raw polymer, in chloroform, 25 °C.
[b] Molecular weight as determined by GPC.

double-walled microspheres by using multiple concentric nozzles to produce a smooth coaxial jet comprising an annular shell and core material (Berkand et al., 2004).

In this work, a water-in-oil-in-oil-in-water (W/O/OW) method was developed to produce double-walled microspheres for controlled release of hydrophilic drugs and proteins. In this method, aqueous solutions of hydrophilic drugs or proteins were first emulsified with one appropriate polymer solution, which were subsequently emulsified with another polymer solution. Then this emulsion was dripped into the non-solvent bath containing a surfactant to form microspheres. The hydrophilic model drug used in this work was 5-fluorouracil (5-FU) that is widely used in the treatment of ocular cancers. Highly water soluble protein, bovine serum albumin (BSA), was also used as a comparison to 5-FU. The main advantages of this method include: (1) drugs and therapeutic proteins can be loaded into microspheres in solution form as those for injection treatments, therefore no further drying and dispersion work for drugs are needed. This also benefits uniform distribution of drugs inside polymer matrix in comparison to dispersion of solid drug particles in polymers, and thus improving drug release profiles. On the other hand, proteins can thus be loaded together with excipients in solutions, thereby reducing the risk of losing protein stability in the process of protein drying and dispersing; (2) the initial burst release of double-walled PLGA microspheres prepared in this way is very low, e.g., $4.2 \pm 0.9\%$ for 5-FU and $3.3 \pm 0.6\%$ for BSA, suitable for medical applications; (3) drug encapsulation efficiency by using hydrophilic drugs is high, e.g., $86.5 \pm 3.3\%$ for 5-FU; (4) the cumulative release profiles showed reduced initial burst and prolonged release of 5-FU over 70 days.

2. Experimental

Polymer information is given in Table 1. 5-FU was obtained from Pharmachemie BV Company. BSA (Fraction V, minimum 98%) was purchased from Sigma Company. PVA (polyvinylalcohol) hydrolyzed 87–89% with a *Mw* range of 13,000–23,000 was obtained from Aldrich Company. 0.3% (w/v) aqueous PVA solution was obtained by dissolving PVA powder in water at 70 °C with magnetic stirring at 100 rpm and subsequently cooled down to room temperature. Dichloromethane (DCM) of liquid chromatography grade was purchased from TEDIA. All of other reagents were of reagent grade and used as received.

For fabrication of double-walled microspheres from W/O/O/W method, 3 ml DCM solution of PLGA 75/25, or PLGA 53/47, or RG 502 (166.7 mg/ml) was emulsified with 1 ml (or specified otherwise in the text) 5-FU or BSA aqueous solution (50 mg/ml) using a homogenizer (Ultra Turrax T8, IKA®-WERKE, Germany). The resultant emulsion was then emulsified with 3 ml (or specified otherwise in the text) DCM solution of PLGA 80/20 or PLLA (166.7 mg/ml) using the same homogenizer. This emulsion was subsequently injected into a 100-ml aqueous solution of 0.3% (w/v) PVA, which was continuously stirred using a mechanical stirrer (BDC 1850-220, Caframo®) or a homogenizer (L4R, Silverson, USA) for 6 h at 22 °C, to allow solvent evaporation. The microspheres were collected by centrifuging and washed three times with de-ionized water. Then 5-FU loaded microspheres were lyophilized and stored at room temperature.

An Agilent 1100 Series HPLC instrument was used in quantification of 5-FU. The HPLC instrument was equipped with a UV detector set at 264 nm, and connected to a computer with the software (ChemStation for LC 3D). The column used was an Agilent Eclipse XDB-C18 column. The mobile phase was a 90:10 mixture of 0.05 M phosphate buffer (pH 7.0) and methanol. Quantification was carried out by integration of the peak areas at retention times of 5.1 min. Calibration was carried out by diluting 5-FU stock solution (50 mg/ml) to obtain five standards.

For determining drug loading of microspheres, 20 mg lyophilized microspheres were added into 4.0 ml of 0.1 M NaOH solution containing 5% (w/v) SDS and incubated for 24 h at 37 °C. The mixture was then centrifuged and the supernatant was drawn to measure 5-FU loading using HPLC, or determine BSA loading using a bicinchoninic acid kit (BCA). The encapsulation efficiency was expressed as the ratio of actual-to-theoretical drug content. The drug loading was expressed as

$$\%\,\text{drug loading} = \frac{\text{amount of loaded drug}}{\text{amount of polymer} + \text{amount of loaded drug}} \times 100$$

For obtaining drug release profiles of microspheres, 100 mg dried microspheres were dispersed in 4 ml PBS buffer (pH 7.0). The tubes containing microspheres were placed in a 37 °C incubator with shaking three times per day. The supernatant from the tube was collected at prescribed time and analyzed for 5-FU or BSA content. Then same amount of fresh PBS buffer (pH 7.0) was replenished into the tubes.

The surface morphology and internal structure of microspheres were examined by SEM (Model JSM 6360A, JEOL, Japan) at 5 kV or 10 kV. In this case, lyophilized microspheres were previously mounted onto metal stubs using double-sided tapes and then vacuum-coated with gold.

The size of microspheres was examined using Axiotron high performance microscope (Image & Microscope Technology, Korea). Dried microspheres were dispersed in de-ionized water and then placed onto a glass slide. The images were analyzed with a built-in software (i-solution®) to calculate the individual particle size. The mean particle size was referred as the number average diameter.

FTIR spectra were obtained using FTIR microscope (Bio-Rad UMA 500) connected to FTIR spectrophotometer mainframe (Bio-Rad FTS-3500 ARX) and analyzed using Bio-Rad analysis software in the mid IR range (wave number 400–4000 cm^{-1}, resolution 2 cm^{-1}). Standard microspheres of a single polymer and double-walled microspheres were cross-sectioned into halves and mounted on a gold slide for examination. Ten points were randomly selected on the external and the internal walls for obtaining the transmission spectra using the software.

Thermal analysis of the microspheres was performed with a differential scanning calorimeter (DSC Q10, TA instruments) equipped with a cooling system. Approximately 6.0 mg samples were sealed in aluminum pans and were subjected to a heating program from

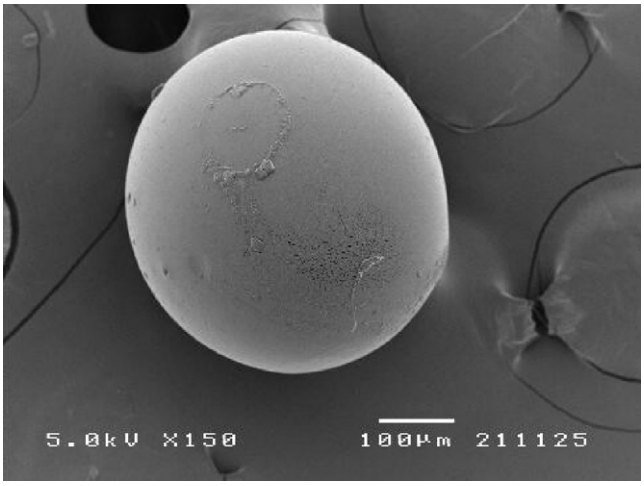

Fig. 1. SEM picture of surface morphology of 5-FU (1 ml) loaded microspheres fabricated with PLGA 80/20 and PLGA 75/25 in the mass ratio of 1:1.

−20 °C to 100 °C for the first heating ramp, then cooled to −10 °C, and reheated on the second ramp to 100 °C at a rate of 10 °C/min. Data obtained were processed on TA universal analyzer software and were identified for glass transition temperature (T_g).

3. Results and discussion

3.1. Preparation of double-walled microspheres using W/O/O/W method

Some groups reported previously fabrication of double-walled microspheres from PLLA and PLGA in DCM by using O/O/W emulsion technique (Lee et al., 2002; Tan et al., 2005). In this method, drug particles were dispersed in PLGA polymeric solution and sonicated. Then this mixture was emulsified with PLLA solution, and subsequently injected into the non-solvent bath containing PVA as the surfactant. In comparison to this method, here we used W/O/O/W technique to produce double-walled microspheres, where aqueous solutions of hydrophilic drugs or proteins were emulsified with one appropriate polymer solution (core material) in the first emulsification step. Thus the use of original drug solutions such as 5-FU solution in medical treatment becomes possible. Proteins can also be loaded with excipients in solutions. In the next step, this mixture was further emulsified with another polymer solution (shell material) to form W/O/O emulsion, which was evident from the change of the clear polymeric solution to a translucent and milky solution after this emulsification. This solution was subsequently injected into the non-solvent bath containing PVA, leading to DCM evaporation and an increase in polymer concentration. As the polymer concentration reaches and exceeds the critical concentration, phase separation between two polymers will occur (Pekarek et al., 1994b; Rahman and Mathiowitz, 2004), and double-walled structure will be formed. In this case, drugs were well distributed within the core material, and the shell acts as rate-limiting barrier to drug release.

Fig. 1 shows surface morphology of microspheres produced from W/O/O/W method, typically using PLGA 80/20 and PLGA 75/25 in mass the ratio of 1:1. It is seen that these microspheres have spherical, smooth and non-porous morphology, distinctly different from the porous morphology of those microspheres prepared with traditional W/O/W method (Ehtezazi et al., 1999). Similar morphology has also been observed with microspheres produced from other polymer pairs. The typical mean particle diameter of 5-FU-loaded (1 ml 5-FU) microspheres, prepared from PLGA 80/20 and PLGA 75/25 in the mass ratio of 1:1 at mechanical stirring speed of 900 rpm, is 515.3 ± 129.1 μm. Increase of mass ratio of PLGA 80/20 to PLGA 75/25 from 1:1 to 2:1 resulted in larger mean particle diameter of 775.0 ± 156.6 μm. Variation of internal water volume from 0.5 ml to 1.5 ml didnot give rise to significant change of particle size. Using homogenizer with high stirring speed in the last emulsification step can effectively reduce the particle size to lower than 10 μm, suitable for injection with a standard needle. As it is difficult to study the internal structure of small microspheres, larger microspheres were involved in this work for further investigation.

Fig. 2 shows the cross-section picture of microspheres produced from PLGA 80/20 and PLGA 75/25 in mass ratio of 1:1. Instead of a solid core observed in microspheres produced with O/O/W method (Lee et al., 2002), a cavity was clearly seen in the centre of the microspheres in this case. Same phenomenon was also observed in other microspheres that were randomly selected for cutting. In comparison to the porous inner structure of microspheres fabricated from traditional W/O/W method (Ehtezazi et al., 1999), the walls of these hollow microspheres are very dense. It is postulated that the internal water fraction resulted in enhanced emulsion viscosity of W/O/O emulsion (Becher, 1983), and thus leading to quick solvent removal upon dispersion of oil phase into the non-solvent bath, and also the formation of a dense and non-porous polymer layer. Later, the coalescence of the inner water droplets within unsolidified oil phase and slow DCM evaporation through the pre-solidified outer polymer layer lead to the formation of a hollow inner structure encased by a dense wall of PLGA.

3.2. Identification of double-walled structure of microspheres

As these double-walled microspheres are actually hollow in the center as evidenced with cross-section pictures, FTIR-microscope spectra thus can be taken on the external and the internal walls of cross-sectioned microspheres separately, which are supposed to represent different polymer compositions for two polymer layers via identification of known characteristic wave numbers of the polymers (Matsumoto et al., 1997). In this case, PLLA was chosen as the shell material, while PLGA 75/25 as the core material, for clearly distinguishing the difference between two spectra.

FTIR-microscope spectra (Fig. 3) of PLLA showed a C–H bending vibration of methyl group at 1390 cm^{-1} and 1462 cm^{-1}, while PLGA 75/25 showed a C–H bending vibration of methyl group at 1408 cm^{-1} and 1465 cm^{-1}, and an C–H vibration of methylene group at 1435 cm^{-1}. By comparison of both spectra with FTIR spectra of standard PLLA and PLGA 75/25 microspheres, we can identify

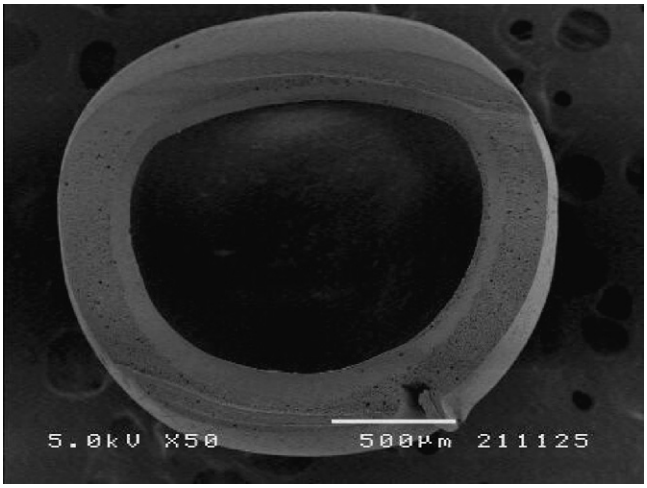

Fig. 2. SEM picture of the cross-section of 5-FU (1 ml) loaded microspheres fabricated with PLGA 80/20 and PLGA 75/25 in the mass ratio of 1:1.

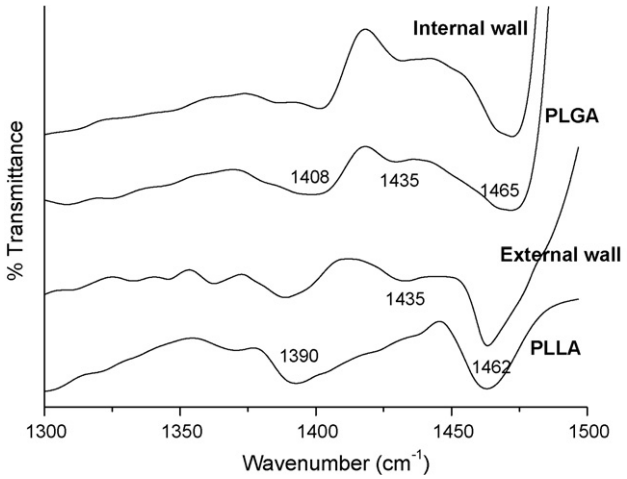

Fig. 3. FTIR-microscope spectra identifying the polymers in the external and the internal walls of microspheres. The external wall is made of PLLA, and the internal wall made of PLGA 75/25.

that the spectra of the internal wall thus correspond to that of PLGA 75/25 while the outer wall to PLLA except for an additional peak at 1435 cm^{-1} (Naraharisetti et al., 2005). However, this peak is relatively smaller in comparison to the other two characteristic peaks of PLLA and could probably be induced by small amount of PLGA entrapped within the outer layer during emulsification of two polymer solutions.

In the fabrication of double-walled microspheres, theoretically it is known that when the emulsion of two polymer solutions is added into the non-solvent bath, the oil phase becomes more concentrated due to solvent evaporation. Two polymers begin to phase separate, and if given sufficient time, will configure themselves in their most thermodynamically stable configuration as dictated by the spreading coefficient theory (Pekarek et al., 1994a,b). In this sense, completing phase separation is crucial for the formation of double-walled structure. This can be identified from DSC thermograms, as one or two discontinuities in the heat capacity can reveal whether or not phase separation has taken place (Bosma et al., 1988).

From DSC thermogram of hollow double-walled microspheres made of PLGA 80/20 and PLGA 75/25 (Fig. 4), it is seen that two T_g can be clearly identified, indicating phase separation has proceeded between this polymer pair. It is supposed that phase separation

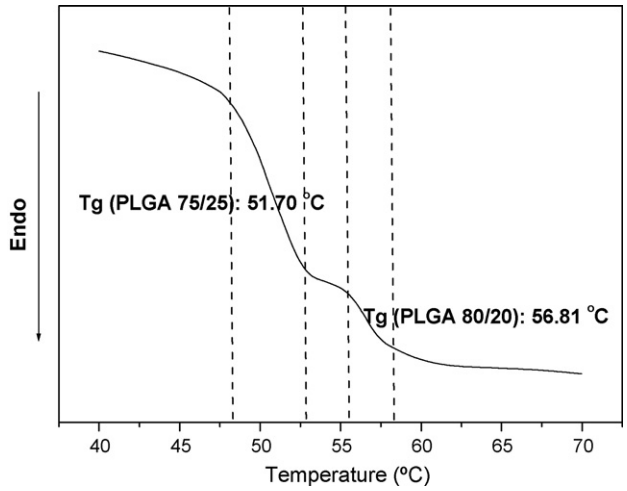

Fig. 4. The DSC thermogram of double-walled microspheres made of PLGA 80/20 (shell) and PLGA 75/25 (core).

Table 2
Drug encapsulation efficiency and drug loading for 5-FU loaded, double-walled microspheres made of two polymers in mass ratio of 1:1 or 2:1.

Microspheres	Drug encapsulation efficiency (%)	Drug loading (%)
PLGA 80/20:RG 502 = 1:1	81.3 ± 3.2	3.9 ± 0.2
PLGA 80/20:PLGA 53/47 = 1:1	82.6 ± 3.5	4.0 ± 0.2
PLGA 80/20:PLGA 75/25 = 1:1	82.3 ± 2.1	4.0 ± 0.1
PLGA 80/20:PLGA 75/25 = 2:1	86.5 ± 3.3	4.1 ± 0.2

between these two polymers could be more difficult as compared with another pair of PLLA/PLGA, since solubility parameters of the former two polymers are more close to each other.

3.3. Drug loading and in vitro release

Some groups investigated in vitro release of hydrophilic drugs from double-walled microspheres made of PLLA and PLGA with O/O/W method (Lee et al., 2002; Rahman and Mathiowitz, 2004; Tan et al., 2005; Leach et al., 1999; Leach and Mathiowitz, 1998). Because usually PLLA degrade more slowly than PLGA, due to more hydrophobic moieties in the former polymer (Wu, 1995), we selected PLGA 80/20 as the shell material instead to achieve better sustained release of 5-FU for 2 months.

Table 2 shows that 5-FU encapsulation efficiency of hollow double-layered microspheres is typically 86.5 ± 3.3% with those microspheres made of PLGA 80/20 and PLGA 75/25 in mass ratio of 2:1. The encapsulation efficiencies for those made of other polymer combinations are also above 80%. Similarly, by using highly hydrophilic protein BSA, we also achieved high encapsulation efficiency up to 84.8 ± 2.3% (mass ratio of PLGA 80/20 to PLGA 75/25 equal to 2:1). These values are much higher than that obtained with monolithic microspheres loaded with 5-FU (Hussain et al., 2002).

The in vitro cumulative release profiles of hollow double-walled microspheres showed reduced initial burst and prolonged sustained release of 5-FU over 70 days (Figs. 5 and 6). The initial burst release of double-walled microspheres made of two polymers in mass ratio of 1:1 was typically 16.7 ± 2.1%, for PLGA 80/20 as the shell material and PLGA 75/25 as the core material (Table 3). Increasing the mass ratio of PLGA 80/20 to PLGA 75/25 up to 2:1 further reduced the initial burst release to 4.2 ± 0.9%. Changing of core materials affected little on the initial burst release as seen from

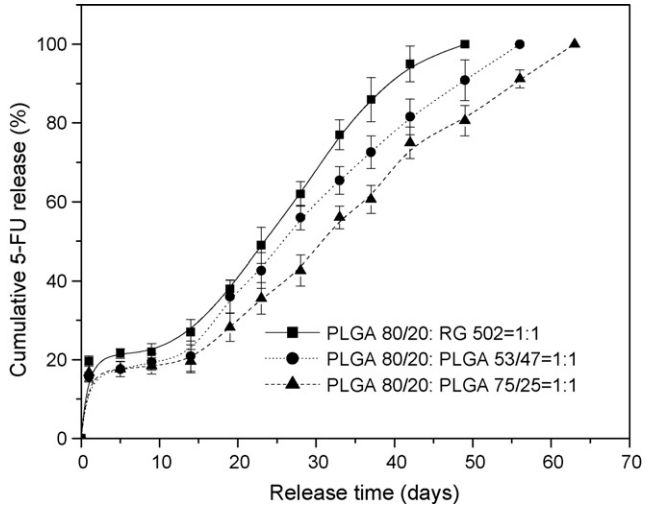

Fig. 5. Cumulative 5-FU release profiles with double-walled microspheres made of PLGA 80/20, PLGA 75/25, PLGA 53/47, and PLGA RG 502 in the mass ratio of 1:1, expressed as the percentage of released 5-FU over totally loaded drug.

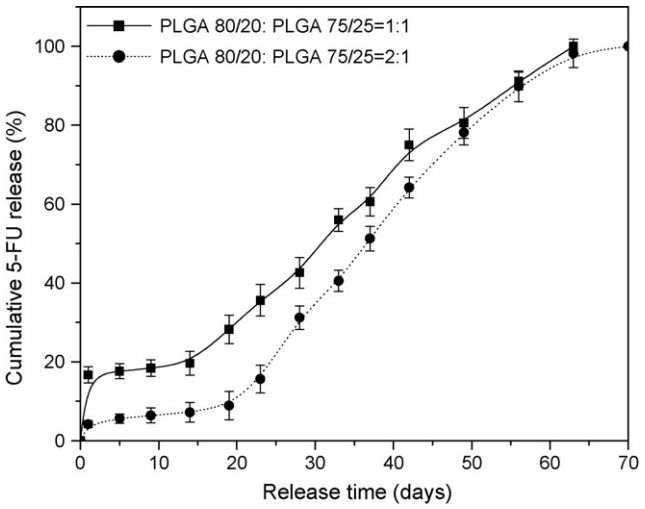

Fig. 6. Cumulative 5-FU release profiles with double-walled microspheres made of PLGA 80/20 and PLGA 75/25, in the mass ratio of 1:1 and 2:1, respectively expressed as the percentage of released 5-FU over totally loaded drug.

Table 3
Initial burst release of 5-FU loaded, double-walled microspheres made of two polymers in mass ratio of 1:1 or 2:1.

Microspheres	Initial burst release (%)
PLGA 80/20:RG 502 = 1:1	19.6 ± 1.3
PLGA 80/20:PLGA 53/47 = 1:1	15.6 ± 1.3
PLGA 80/20:PLGA 75/25 = 1:1	16.7 ± 2.1
PLGA 80/20:PLGA 75/25 = 2:1	4.2 ± 0.9

Table 3. With another model drug of BSA, we also obtained a low initial burst of 3.3 ± 0.6% (mass ratio of 2:1 for PLGA 80/20 to PLGA 75/25). These burst release values are much lower than that up to ~60% as obtained with 5FU-loaded monolithic microspheres (Zhu et al., 2003), again supporting that PLGA 80/20 acts as a rate-limiting barrier that impedes diffusion of hydrophilic drugs from the drug-loaded inner layer. Similar phenomenon was observed before with those double-walled microspheres fabricated from O/O/W method (Lee et al., 2002; Rahman and Mathiowitz, 2004; Tan et al., 2005). As shown in Table 3, further suppression of initial burst release by increasing the mass ratio PLGA 80/20 to PLGA 75/25 proves that immediate diffusion of hydrophilic 5-FU from drug-loaded inner

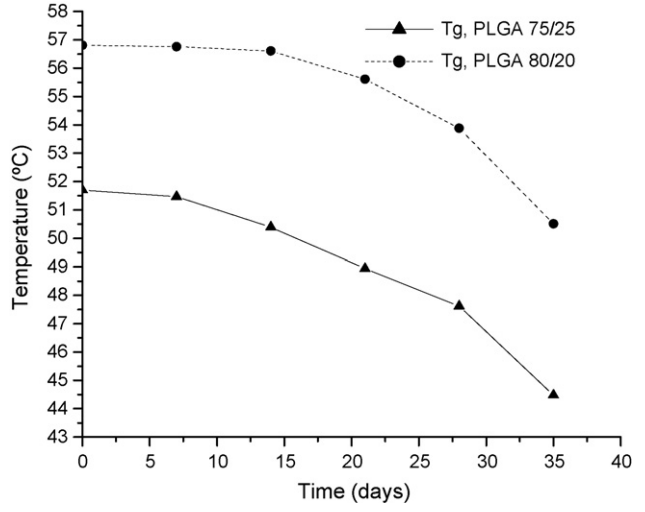

Fig. 7. Plot of glass transition temperature of PLGA 80/20 and PLGA 75/25 (in the mass ratio of 1:1) in double-walled microspheres versus time.

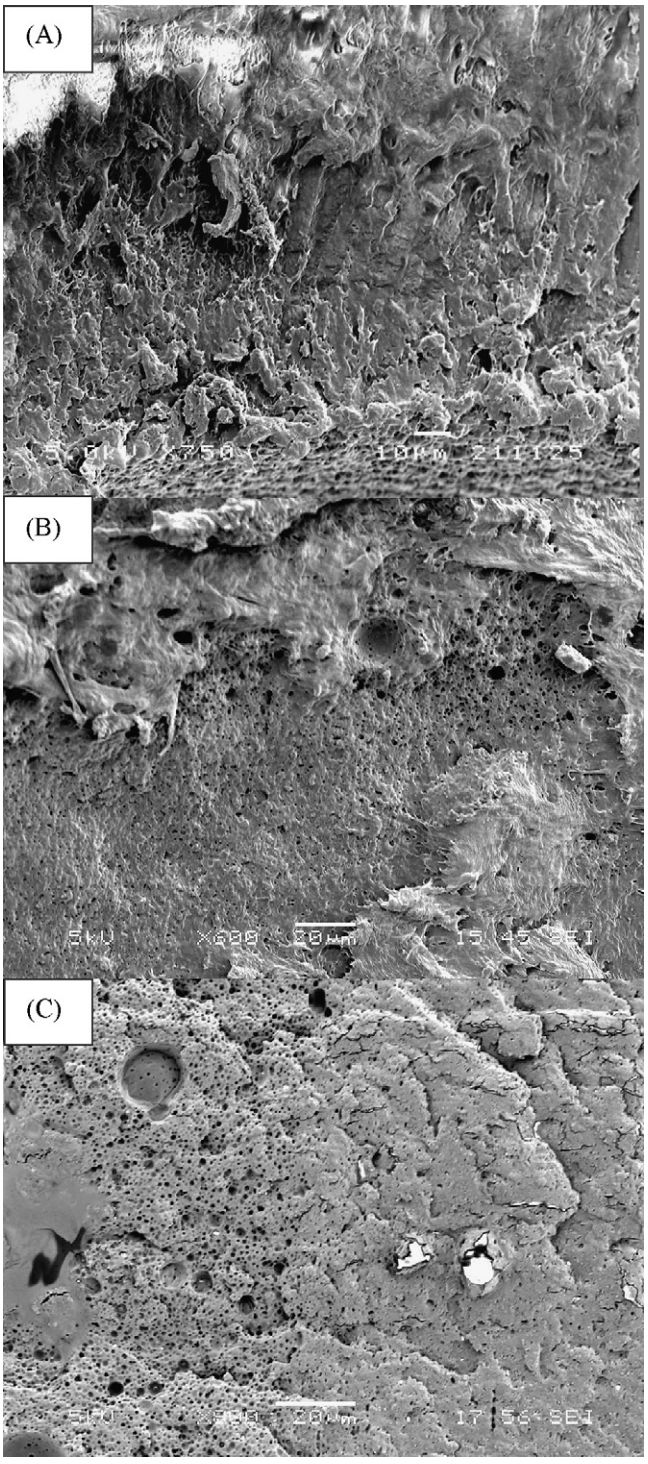

Fig. 8. Cross-section SEM pictures for the walls of double-walled microspheres made of PLGA 80/20 and PLGA 75/25 (in the mass ratio of 1:1) after in vitro degradation for (A) 1 day, (B) 14 days and (C) 28 days.

polymer layer can be retarded by an enhanced non-drug-loaded outer layer.

Cumulative release profiles of 5-FU show a low initial burst release, followed by a lag phase around 15–20 days, and then sustained release up to 70 days (Figs. 5 and 6). Fig. 5 shows that the lag time of microspheres made of PLGA 80/20 and RG 502 is relatively shorter, followed by a smoother gradient to prolonged release. This may be due to the autocatalytic degradation of PLGA 80/20 brought about by carboxylic acids generated during faster degradation of

RG 502 as the lactide ratio and molecular weight of the latter polymer are low (Table 1) (Anderson and Shive, 1997; Alexis, 2005). The release rate of 5-FU is lowest with microspheres made of PLGA 80/20 and PLGA 75/25 (Fig. 5), also due to the slow degradation rate of these two polymers that have high lactide ratio and molecular weight (Table 1).

3.4. Degradation of microspheres

Double-walled microspheres made of PLGA 80/20 and PLGA 75/25 were selected for degradation studies by using DSC and SEM, in order to determine the polymer degradation effects on drug release properties of double-walled microspheres.

Fig. 7 shows the changes of glass transition temperature as a function of time in in vitro degradation study, which reflects changes in polymer molecular weight. This can help to identify the onset of fast polymer degradation, as the steepest gradient of decrease in T_g indicates the highest rate of polymer degradation. As a result, the polymer molecular weight will rapidly decrease, and porosity of microspheres will be drastically enlarged, leading to fast diffusion of drug molecules out of polymer matrix.

DSC plot shows a relatively flat and gentle gradient for changes of T_g up to 15–20 days with PLGA 80/20 as the shell material (Fig. 7). This substantiated our observation of low initial burst release of double-walled microspheres and the time lag phase in the in vitro release profiles, as drug molecules are supposed to release mainly by diffusion through pores on microsphere walls during this period. From SEM picture (Fig. 8), we can see that walls of microspheres are relatively dense in this phase, so the release of hydrophilic drugs is retarded by the non-drug-loaded outer polymer layer of PLGA 80/20. Later, a steeper gradient in T_g decrease indicates accelerated polymer degradation, in accordance with a rapid linear release of drugs from polymer matrix from the onset of 20 days. SEM picture (Fig. 8) also evidences that pores and porosity of polymer walls are highly enhanced in this faster degradation phase.

4. Conclusions

A water-in-oil-in-oil-in-water method was successfully developed to fabricate double-walled microspheres for controlled delivery of hydrophilic drugs and therapeutic proteins with low initial burst and prolonged release. In this method, aqueous solutions of hydrophilic drugs or proteins were first emulsified with one appropriate polymer solution, which was subsequently emulsified with another polymer solution. Then this mixture was dripped into the non-solvent bath containing a surfactant to form microspheres. These microspheres were characterized to have double-walled structure, with a cavity in the centre. Hydrophilic drugs were encapsulated in the inner polymer layer, while the non-drug-loaded outer layer served as a rate-limiting barrier. Drug release profiles for 5-fluorouracil showed reduced initial burst and prolonged release, which is substantiated by degradation studies.

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