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Fabrication of double-walled microspheres for the sustained release of doxorubicin

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Abstract

Double-walled microspheres with poly(*L*-lactic acid) shells and poly(*DL*-lactic–co-glycolic acid) cores were fabricated using solvent evaporation technique which involves the phase separation phenomenon of a binary composite of these two polymers. Doxorubicin, a hydrophilic drug, was entrapped within the core of these double-walled microspheres with different core–shell thicknesses and compositions to investigate the in vitro release on this class of microspheres. Microspheres of different size ranging from 50 to 300 μm were also fabricated to investigate whether this method is suitable for fabricating small particles for intramuscular injection applications, and their phase separation and surface morphology were examined by differential scanning calorimetry, scanning electron microscopy, and optical microscopy.

Keywords: Double-walled; Microsphere; Doxorubicin; Controlled release

1. Introduction

Doxorubicin (DOX), one of the anthracycline ring antibiotics with great antitumor activity against solid tumors and leukemia, has the ability to interact with DNA and consequently inhibit important cellular functions [1]. However, its therapeutic potential has been restricted by its dose-limited cardiotoxicity and by the resistance developed by the tumor cells to this molecule after some time of treatment [2]. In view of that, traditional single-polymer microspheres with a high initial burst caused by drug trapped on the surface have their limitations in clinical applications [3]. To eliminate the initial burst and better control the release of this highly water-soluble cardiotoxic drug, double-walled microspheres with drug encapsulated in the inner core are fabricated using several methods. One method is solvent evaporation, which involves a single-step phase separation of composite binary polymer solutions [4–7]. This method has proven advantageous over other early attempts to simply coat existing microspheres using pan coating, fluidized beds or spray drying in eliminating initial bursts and obtaining sustained controlled release [8,9]. The uniform shell layer prevents diffusion of the hydrophilic drug located in the inner core. By careful selection of the mass ratio of the two polymers used, the thickness of shell of the double-walled configuration can be controlled. That, in turn, gives us more degrees of freedom in designing the desired release profile of drugs suitable for various treatments.

Double-walled microspheres have also been investigated extensively as drug carriers for sustained and controlled release. Mathiowitz et al. reported on a double-walled microspheres system consisting of a core of poly(1,3-bis-(*p*-carboxyphenoxypropane)–co-(sebacic anhydride)) 20:80 coated with layer of poly(*L*-lactide) (PLLA) [11–14]. Five process variables were studied to optimize manufacturing conditions: polymer solution concentration, polymer weight ratio, polymer solution volume ratios, encapsulation temperature, and airflow rate across the top of the encapsulation vessel [11].

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Lee et al. [7] demonstrated the fabrication of composite double-walled microspheres with PLLA shells and poly(*DL*-lactic–co-glycolic acid) (PLGA) cores, within which highly water soluble etanidazole was entrapped using solvent evaporation. Rahman et al. [15] also successfully encapsulated fluorescein isothiocyanate (FITC)-labeled bovine serum albumin (FITC-BSA) using this method. A technique for identifying the composition of the core and shell polymer has been devised by Lee et al. [7]. With this dissolution technique, we investigated the critical PLLA:PLGA mass ratio that results in core–shell inversion. Henceforth, based on knowledge of the solubility parameter, which predicts the polymer phase into which the drug will preferentially partition, we developed a formulation to help localize different drugs in the core of such a double-walled system. In our study, in vitro release of doxorubicin was also performed to confirm the double-walled configuration with the hydrophilic drug encapsulated within the core.

2. Materials and methods

2.1. Materials

Poly(*L*-lactic acid) (PLLA, MW (weight-average molecular weight), 85,000–160,000), poly(*DL*-lactic–co-glycolic acid 50:50) (PLGA, MW 40,000–75,000), doxorubicin (MW 214), and poly(vinyl alcohol) (PVA) (MW 31,000–50,000) were all purchased from Sigma–Aldrich, USA, and used without modification. HPLC-grade acetonitrile was purchased from Fisher (Fair Lawn, NJ, USA). Phosphate-buffered saline (PBS) used for in vitro release was obtained from Pierce (Rockford, IL, USA) containing 0.1 M sodium phosphate, 0.15 M sodium chloride, pH 7.2. All other materials or solvents used were of analytical grade.

2.2. Fabrication of double-walled microspheres

Doxorubicin-loaded double-walled microspheres were prepared using a modified oil–oil–water (o/o/w) emulsion solvent evaporation technique developed by Mathiowitz et al. [4] and using the polymer incompatibility between PLLA and PLGA 50:50 (the ratio 50:50 refers to the lactide/glycolide ratio) which results in their complete phase separation.

PLLA and PLGA 50:50 were separately dissolved in 1 ml of dichloromethane (DCM) (overall concentration 20%, w/v). The drug containing particles, doxorubicin (5%, w/w), was added to PLGA 50:50 polymeric solution only and sonicated using an ultrasonic probe (Model XL2000, Misonix, NY, USA) at 2-W output for 30 s to break down the drug crystals. Then the two polymeric solutions were mixed and sonicated for 20 s to form a homogeneous solution. The mixture was injected dropwise into the nonsolvent bath containing 200 ml of polyvinyl alcohol (PVA) solution (0.5%, w/v) which was dissolved with 0.25 ml DCM, stirring continuously at 500 rpm to create the o/o/w emulsion. Continuous stirring for 4 h allows for the extraction and evaporation of DCM which allowed phase separation of PLLA and PLGA before hardening of the microspheres. Next, the microspheres were filtered and rinsed with distilled water to remove residual PVA, and then dried under vacuum in the desiccator. Fabricated microspheres were stored in a desiccator to prevent hydrolytic degradation of the biodegradable polymer under humidity.

Microspheres having different core–shell configurations of PLLA/PLGA and varying shell thickness and core diameter were prepared in the same manner by altering the polymer mass ratio (w/w) of PLLA to PLGA ranging from 1:1 to 1:3. Single-polymer (PLLA and PLGA) microspheres without drug loading intended for characterization and reference comparison were also prepared using the well-established single emulsion method [3,17].

2.3. Characterization

2.3.1. Morphology and composition studies

The morphology of microspheres in in vitro and degradation studies was observed by scanning electron microscopy (SEM, JSM-5600LV, Jeol, Tokyo, Japan) at an accelerating voltage of 15 kV. Microspheres were cross sectioned using a razor blade, mounted on metal stubs, and coated with a layer of platinum using an auto fine coater (JFC-1300, Joel), which allowed us to view the surface morphology and internal structure of the microspheres. Studies were carried out to analyze changes in surface morphology and internal structure of microspheres at various stages of degradation.

For identification of the composition of the core and shell polymer, we used the dissolution method devised by Lee et al. [7] based on the different solubility of the polymer pair PLLA and PLGA in ethyl acetate. Briefly, a cross-sectioned double-walled particle was first immersed in ethyl acetate for 10 min. The remnant was then collected for SEM observation. Knowing that although PLGA 50:50 is soluble in ethyl acetate while PLLA is not, we can determine the core–shell composition by examining whether the remnant has a solid core or hollow shell structure. (Note: the solubility of PLGA and PLLA in ethyl acetate at room temperature (25 °C) is 580 and 0.1 mg/ml, respectively.) The former would mean a double-walled microsphere with PLGA shell, and the latter would be derived from a microsphere with a PLGA core.

The drug distribution was identified by observing the distinct red crystalline drug filaments within the loaded microspheres with an optical microscope (Olympus Vanox Model BX60, Japan). Different polymer layers in double-walled microspheres can be identified based on the difference in crystalline structures as well. In preparation for optical microscopy, the microspheres were sectioned using a microtome blade and mounted onto glass slides for viewing under cross Polaroid. Further, doxorubicin is slightly fluorescent, unlike the polymeric materials used (PLLA and

PLGA), and hence, it can be easily identifiable using an optical microscope with a fluorescent screen.

2.3.2. Thermal analysis using the differential scanning calorimeter

Thermal analysis of the microspheres was performed using a modulated differential scanning calorimeter (DSC) (DSC 2920 modulated DSC, TA instruments) equipped with controller (TAC 7/DX, TA instruments) connected to a cooling system. The samples (about 6.5 mg) were placed in sealed aluminum pans and subjected to heating from 20 to 150 °C for the first heating ramp, cooled to 20 °C, and finally reheated on the second ramp to 150 °C, all at a rate of 10 °C/min. All data obtained were processed on TA universal analyzer software and glass transition temperature (T_g) was determined.

2.3.3. In vitro release and degradation study

Encapsulation efficiency (EE) is defined as the percentage of the actual mass of drug encapsulated in the polymeric carrier relative to the initial amount of drug loaded as described in the equation

$$\text{encapsulation efficiency (\%)} = \frac{C_{\text{actual}}}{C_{\text{theoretical}}} \times 100, \qquad (1)$$

where C_{actual} (mg) is the actual amount of drug contained in microspheres and $C_{\text{theoretical}}$ (mg) the theoretical loading which is equal to the total amount of drug used initially. The actual amount of drug encapsulated within the microspheres was determined using an extraction method, in which 5 mg of microspheres was accurately weighed out in triplicate and dissolved in 2 ml of DCM, chloroform, or dimethyl sulfoxide (DMSO) each.

The doxorubicin-containing solution was then extracted using 5 ml of deionized water, into which the water-soluble drug will preferentially partition. Filtration was carried out before the solution was analyzed using reverse-phase HPLC (Agilent HPLC Series 1100, USA) at the wavelength of 480 nm. The mobile phase selected for analyzing doxorubicin was 0.05 M sodium acetate (pH 4) and acetonitrile in a volume ratio of 72:28 (v/v %). For the calibration, free drug dissolved in deionized water was prepared to build up a standard curve.

For release studies, triplicate samples (10 ± 0.5 mg) of microspheres were incubated in 5 ml of PBS (pH 7.4, Pierce, Pockford, IL, USA) in screw-topped centrifuge tubes. The tubes were placed in a horizontal thermal oscillating water bath maintained at 37 °C and 120 rpm. (Cetomat WR, B. Braun Biotech International, Germany). At selected times following the incubation, aliquots were collected after centrifugation (Eppendorf Centrifuge 5810R) at 12,000 rpm for 10 min and PBS was replaced. The aliquots were then filtered and analyzed using the HPLC system as described above.

For degradation study, microsphere samples (20 ± 5 mg) were accurately weighed and placed in vials containing 10 ml of PBS maintained at 37 °C in a thermostated oscillating water bath at 120 rpm (Cetomat WR). The microspheres were removed at predesignated times for extensive study using SEM as described in Section 2.3.1 and differential scanning calorimetry where the thermal DSC study described in Section 2.3.2 was carried out to characterize any change in polymer T_g under degradation.

3. Results and discussion

3.1. Fabrication of double-walled microspheres

Individual polymeric solutions of PLLA and PLGA in DCM (20% w/v) below their critical polymeric concentration, and mass ratio of PLLA/PLGA of 1:1, were mixed to form an o/o emulsion and dispersed into an aqueous nonsolvent PVA, saturated with one or two drops of DCM with mechanical stirring that eventually resulted in the formation of an o/o/w emulsion [7,15]. The DCM from nonsolvent and polymeric solution was lost by evaporation, resulting in an increase in polymer concentration. As the polymer concentration reaches and exceeds the critical concentration inducing phase separation, phase separation occurs and the polymer eventually hardens to form the double-walled configuration structure. Because of the dynamic nature of the solvent evaporation process, the polymer inside the DCM droplets was able to relax by the time the required critical concentration inducing phase separation was reached, and phase separation occurred before the polymer was hardened by solvent extraction. By keeping the fabrication conditions constant, double-walled microspheres of PLLA/PLGA mass ratios 1:2 and 1:3 were also prepared.

The resulting microspheres (Fig. 1A) can be classified as a class of reservoir-dispersed matrix systems in which doxorubicin is dispersed within the core, and the shell acts as a rate-limiting barrier to drug release. Different fabrications of PLLA/PLGA mass ratios 1:1, 1:2, and 1:3 yielded volume mean diameters of 167.34 (±122.77), 167.51 (±103.53), and 171.52 (±118.50) μm, respectively (Table 1). The different fabrications produced double-walled microspheres with the same mode diameter of 228 μm. As polymer PLLA/PLGA mass ratio was altered, shell thickness and core size could be varied. This is evident in Figs. 1A, 1C, and 1D.

3.2. Critical polymer ratio inducing core–shell inversion (CRi)

It was found that core–shell inversion occurred when the total PLLA/PLGA mass ratio increased from 1:1 to 1:2, holding all other fabrication conditions constant. This core–shell composition could be influenced by various physicochemical factors, including solvent species, polymer concentration, molecular weight, drug loading, among which the PLLA/PLGA mass ratio play a critical role.

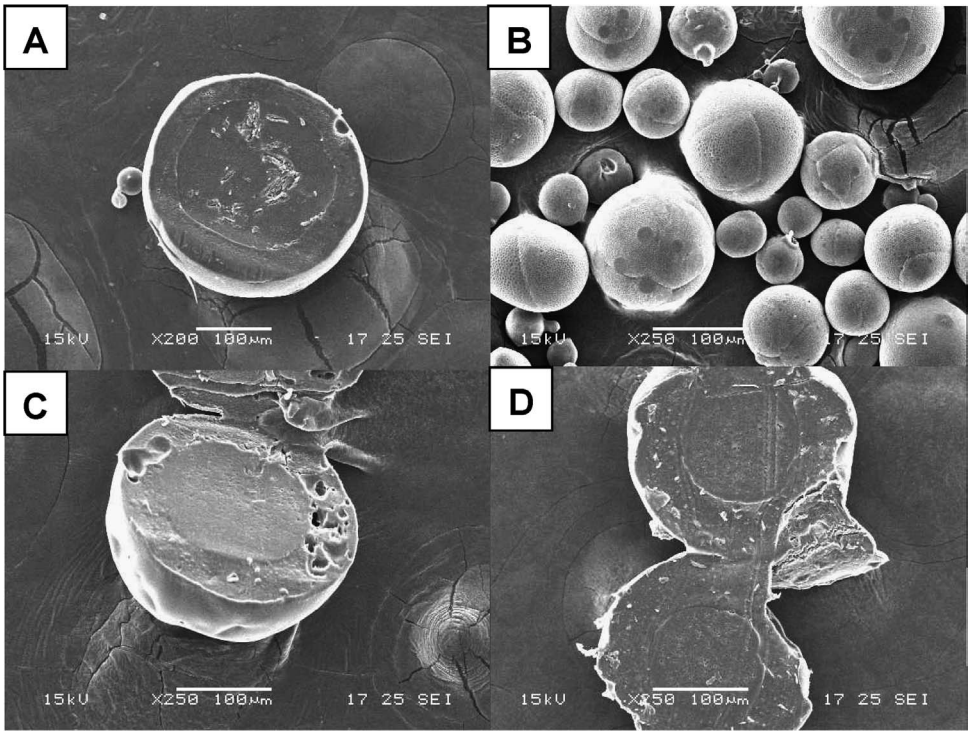

Fig. 1. Scanning electron micrographs of double-walled microsphere prepared using the solvent evaporation method: (A, B) PLLA/PLGA (1:1); (C) PLLA/PLGA (1:2); (D) PLLA/PLGA (1:3).

Table 1
Characterization of PLLA/PLGA double-walled microspheres prepared by solvent evaporation method

Sample	PLLA/PLGA ratio	Yield (%)	Mean diameter (µm)	Drug loading (%)	Encapsulation efficiency (%)
D1	1:1	80.34	167.34 ± 122.77	5	87.42
D2	1:2	75.12	167.511 ± 103.53	5	60.46
D3	1:3	64.10	171.52 ± 118.5	5	71.78
D4	1:2	74.94	–	3	65.42
D5	1:2	66.43	–	8	30.81

Table 2
Comparison of polymer compositions of core and shell

No.	Polymer ratio (PLLA/PLGA)	Core	Shell
1	1:1	PLGA	PLLA
2	1:2	PLLA	PLGA
3	1:3	PLLA	PLGA
4	1:1.25	PLLA	PLGA
5	1:1.5	PLLA	PLGA
6	1:1.75	PLLA	PLGA

At the low PLLA/PLGA mass ratio of 1:1, PLGA was found to be the inner phase with the continuous phase (shell layer) PLLA-rich. As we increased the PLLA/PLGA ratio to 1:2 or 1:3, phase inversion occurred so that the continuous phase became PLGA-rich and subsequently formed the outer shell layer during solvent evaporation. This could be explained by the fact that as the mass ratio of PLGA used increased, there was more PLGA than PLLA after phase separation. As such, during solvent evaporation, the engulfing phase (continuous phase) was naturally composed of the polymer phase with higher volume (or mass). On the other hand, at high PLLA/PLGA mass ratios, the continuous phase is PLLA, which subsequently forms the outer shell that engulfs the inner core after solvent evaporation. Matsumoto et al. [10] and Rahman and Mathiowitz [15] obtained similar results of phase inversion in their studies. Closer investigation revealed that the critical polymer ratio (CRi) lies between PLLA/PLGA 1:1 and 1:1.25, as shown in Table 2.

3.3. *Identification of drug distribution*

The water-soluble drug doxorubicin was found to be located in the PLGA-predominant phase in all these double-walled microspheres. A later experiment showed that doxorubicin selectively localizes within the PLGA-rich phase whether it is initially, placed in the PLLA or PLGA before these two polymers are mixed. Similar selective distribution between these two polymers was observed by Rahman and Mathiowitz [15], as their drug located predominantly in the PLLA-rich phase.

As distribution theory [16] states, the distribution of a drug substance varies according to the solubility parameter of the polymer–DCM solutions, and that of the drug may provide a plausible explanation for our observations, because it has been successfully applied to predict distribution of cisplatin and amino acid within bisphasic polymeric

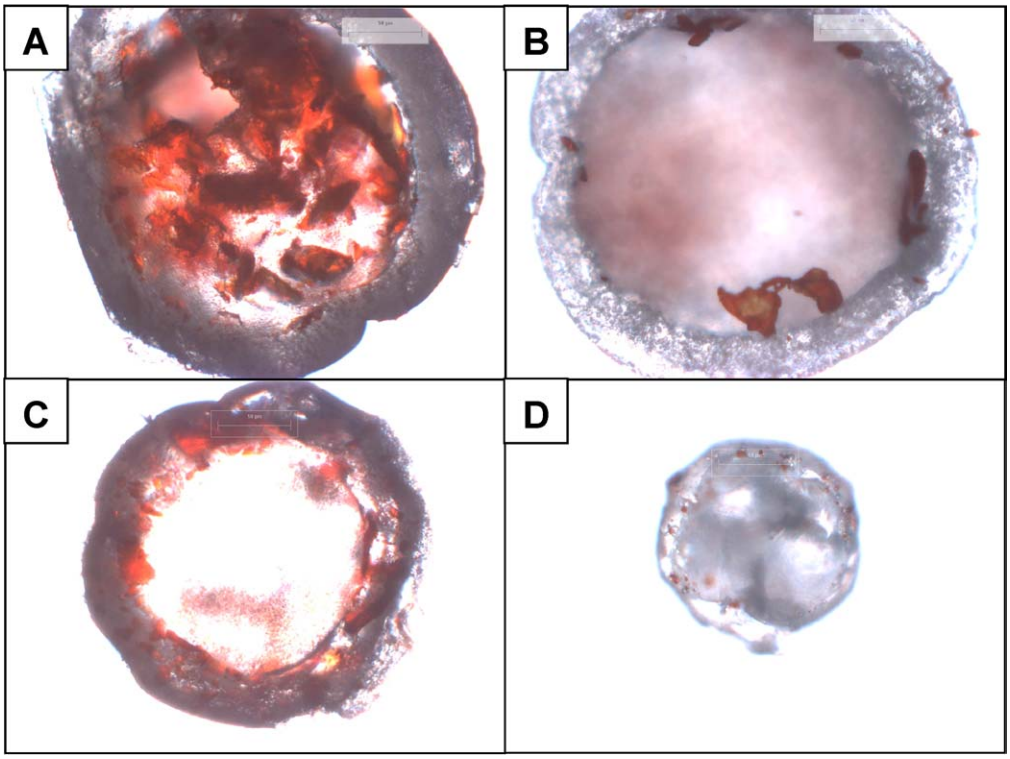

Fig. 2. Optical micrographs of double-walled microspheres before and after dissolution with ethyl acetate: (A) PLLA/PLGA (1:1) before dissolution; (B) PLLA/PLGA (1:1) after dissolution; (C) PLLA/PLGA (1:2) before dissolution; (D) PLLA/PLGA (1:2) after dissolution.

solutions [10]. The theory can be represented as

$$\log \frac{X_{\mathrm{PLGA}}}{X_{\mathrm{PLLA}}} = V_{\mathrm{drug}} \frac{(\delta_{\mathrm{drug}} - \delta_{\mathrm{PLLA/DCM}})^2 - (\delta_{\mathrm{PLGA/DCM}} - \delta_{\mathrm{drug}})^2}{2.3RT}, \quad (2)$$

where X_{PLGA} and X_{PLLA} are the concentrations of drug in the PLGA and PLLA phases, respectively; δ_{drug}, $\delta_{\mathrm{PLGA/DCM}}$, and $\delta_{\mathrm{PLLA/DCM}}$ are solubility parameters of the drug, PLGA phase, and PLLA phase, respectively; V_{drug} is the molecular volume of the drug; R is the gas constant; and T is absolute temperature.

The solubility parameter is a means of predicting whether a substance will dissolve in a given solvent and a quantitative measure of what is commonly known as polarity. As PLGA and doxorubicin are both more hydrophilic (i.e., more polar) than PLLA, we can deduce that their solubilities are more alike than those of PLLA (i.e., less polar) and doxorubicin. Therefore, the difference between the solubility parameters of PLGA and doxorubicin would be smaller than the difference between the solubility parameters of PLLA and doxorubicin, implying that the drug concentration in the PLGA phase would be much higher than that in the PLLA phase. This is consistent with our findings: optical microscopy observations clearly showed the tendency of doxorubicin to localize within the PLGA-predominant phase.

Thus for any given drug, one can use Eq. (2) to predict whether it will preferentially partition to the PLLA or PLGA phase. Then by selecting an optimized PLLA/PLGA mass ratio, one can design double-walled microspheres with drug loaded to core, with a surrounding protective, rate-limiting shell. Fabricated with such a strategy, double-walled microspheres contain high drug-loaded reservoir-like cores, surrounded by a low drug-loaded compact rate-limiting barrier.

3.4. Identification of core–shell polymer composition

Cross-sectional views of double-walled microspheres with different PLLA/PLGA polymer ratios before and after dissolution in ethyl acetate were observed under the optical microscope. Figs. 2A and 2C show a microsphere with PLLA/PLGA mass ratio of 1:1 (D1) before and after dissolution, whereas Figs. 2B and 2D represent PLLA/PLGA mass ratios of 1:2 (D2) and 1:3 (D3). The distinct crystalline red filaments of doxorubicin were found localized in the core with a surrounding clear shell for the D1 sample (Fig. 2A) and in the shell encapsulating a clear core for D2 and D3 (Fig. 2C). When tested using ethyl acetate dissolution, the identical particle from sample D1 (Fig. 2B) showed the configuration of a hollow shell. Based on the known solubility of PLGA and insolubility of PLLA in ethyl acetate, the core and shell were identified as PLGA and PLLA, and doxorubicin was found to be located in the PLGA core. However, after dissolving the same microsphere from samples D2 and D3, the shell containing doxorubicin disappeared and a transparent core remained (Fig. 2D). This gives us the hint

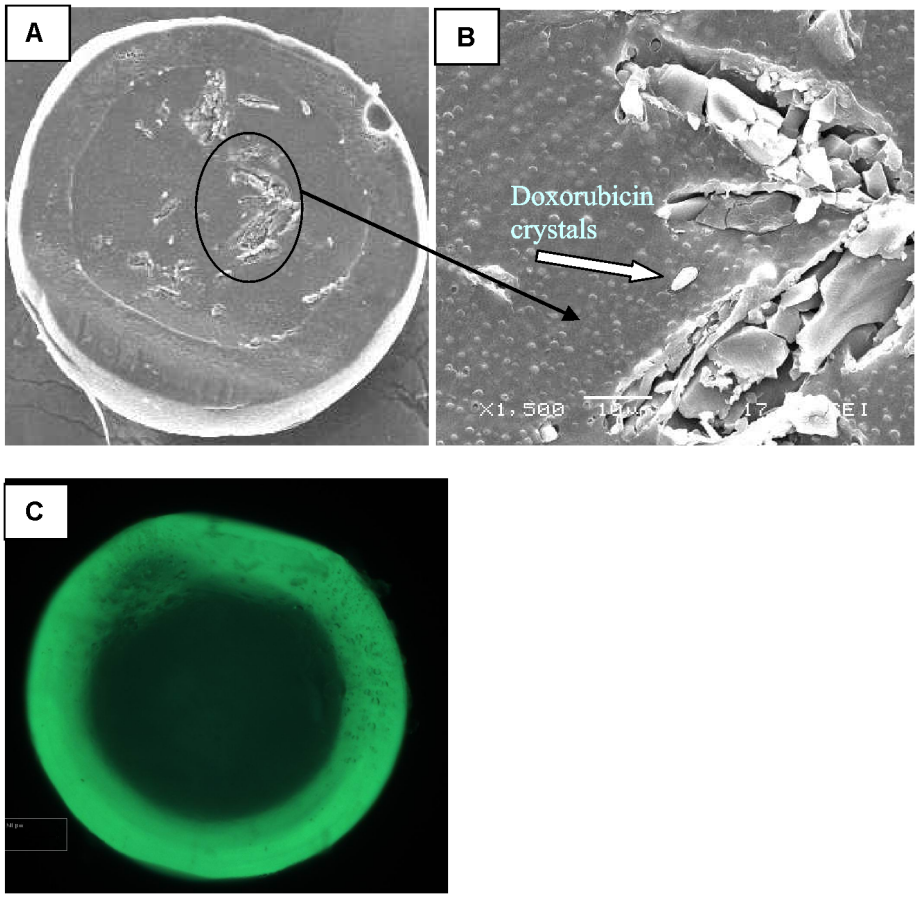

Fig. 3. (A) Doxorubicin entrapped within the core, PLGA/PLLA 1:1. (B) Closeup of the core with crystalline doxorubicin. (C) Fluorescent doxorubicin dispersed in the shell, PLGA/PLLA 3:1.

that samples D2 and D3 have reversed core–shell configurations with the core and shell materials PLLA and PLGA. Therefore by increasing the PLLA/PLGA ratio from 1:1 to 1:2, core–shell inversion occurs.

SEM images (Fig. 3A) and closeups (Fig. 3B) of D1 revealed doxorubicin crystals trapped in the core, which was identified as PLGA by dissolution in ethyl acetate as mentioned earlier. It can be seen that doxorubicin was localized in the shell for D3 and D2, which was identified to be PLGA. As doxorubicin is slightly fluorescent, unlike the PLGA and PLLA used, it can easily be identified using a fluorescent screen, as shown in Fig. 3C.

Close observation revealed the remnant shell for D1 (Fig. 4B) to be porous while numerous tiny spheres were found on the remnant core for D2 and D3 (Fig. 4D). That can be explained by phase separation which was not complete during solvent evaporation and resulted in the formation of two discontinuous layers containing a tiny amount of the other polymer in each phase. During solvent evaporation, the polymer concentration increases and the polymeric phase becomes more viscous and harder to separate. Thus, subsequent hardening of the microspheres led to a tiny amount of the other polymer trapped in each phase.

DSC thermograms of double-walled microspheres of PLLA/PLGA mass ratio 1:1 (D1) samples showed two glass transition temperatures, one each for PLLA and PLGA. The points are identified in DSC thermograms where they were plotted together with the thermograms of the pure PLLA and PLGA polymers used as a control. Their respective T_g values are shown in Table 3.

Table 3
Thermal properties of pure polymers and double-walled microspheres obtained from DSC thermograms

	Literature [7]	PLGA microspheres	PLLA microspheres	Double-walled (1:1) microspheres
$T_{g/PLGA}$ (°C)	45–60	45–47	–	49–50
$T_{g/PLLA}$ (°C)	60–67	–	58–60	59–60

3.5. *In vitro release*

The cumulative in vitro release of double-walled microspheres with 5% drug loading localized in the inner core (D1 sample) showed reduced initial burst and prolonged sustained release over 70 days, as shown in Fig. 5. This profile was compared against that of double-walled microspheres with 5% drug loading in the outer shell (D2 and D3). The release profile for D1 had a suppressed initial burst (<10%, in

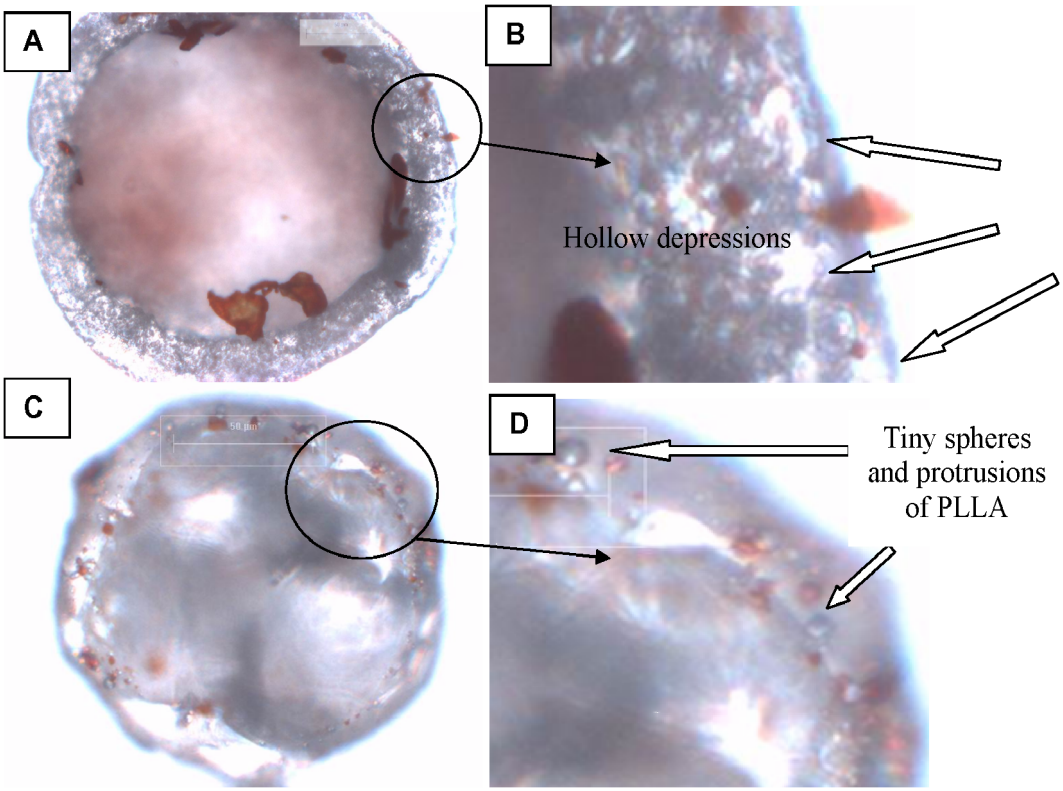

Fig. 4. Optical micrographs of double-walled microspheres: (A) PLGA/PLLA 1:1. (B) Closeup of wall with pores and hollow depression after dissolution (enlarged from (A)) by ethyl acetate. (C) PLGA/PLLA 2:1. (D) Closeup of core with tiny spheres and protrusions (enlarged from (C)) after dissolution by ethyl acetate.

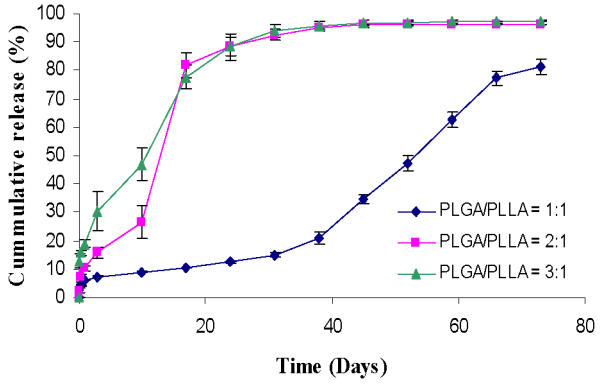

Fig. 5. Cumulative doxorubicin release showing the effects of PLLA/PLGA mass ratios: 1:1; 1:2; and 1:3.

first 6 days), as the initial burst was due to the drug adhering to the surface of the microspheres. After 6 h of in vitro release, the initial burst was 4.24 ± 0.42 for D1, 0.89 ± 0.46 for D2, and 12.89 ± 2.44 for D3. Following the initial burst, the release profile of D1 exhibited a characteristic lag phase and linear sustained release for 25 days leading up to 2 months where it plateaus. The PLLA shell of these microspheres acted as a barrier and effectively retarded the diffusion of drug located in the PLGA core; thus, sustained release was achieved. The release profiles for D2 and D3 are relatively steeper, with high initial bursts, and most of the loaded drug was released within 21 days. Such release profiles resemble those of traditional single-polymer microspheres.

3.6. Degradation study

Degradation studies were conducted using DSC and SEM to determine the effects of polymer in vitro degradation on drug release profile, as well as to elucidate the mechanism behind it. Values of glass transition temperature obtained from DSC analysis were plotted against time to help identify the points where fast degradation occurred (Fig. 6). As changes in thermal parameters of polymers PLLA and PLGA reflect changes in molecular weight, they indicate the extent of degradation of the double-walled microspheres. Points of the steepest gradients, when plotted against time, would indicate the highest rate of degradation, where the most rapid decrease in molecular weight indirectly implied the most drastic change to porosity and permeability of microspheres to external medium and degradation products.

Plots for both D1 and D3 show that the degradation rate of the polymer that formed the inner core was retarded as compared with when it formed the shell. This supported our reasoning that the outer shell served as a barrier protecting the core materials from rapid degradation.

From established literature, it is known that PLGA is much more susceptible to hydrolytic degradation. As a result, the PLGA shell for D3 degraded much faster, leaving

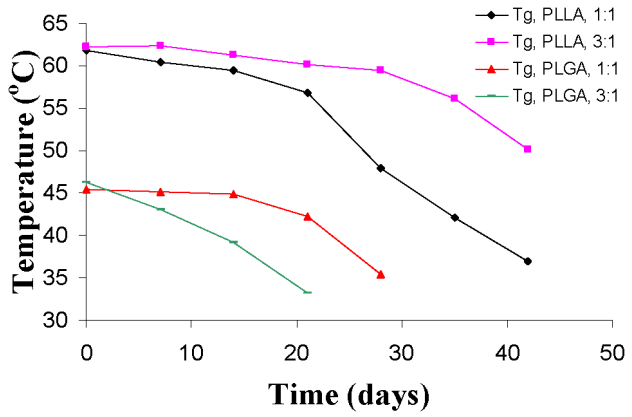

Fig. 6. Plot of glass transition temperature of PLLA and PLGA in double-walled microspheres versus time.

many hollows and depressions within 20 days, as evident from Fig. 7B2. Subsequently, drug trapped in the PLGA shell was released as soon as degradation occurred. However, for D1, DSC plots for the PLLA shell showed a relatively flatter and gentler gradient for glass transition temperature up to and around 20 days, as shown in Fig. 6. This substantiated our observation that degradation was limited during the initial release and time lag phase of the in vitro, release for D1, and that observation agreed with the SEM images obtained (Figs. 7A1 and 7A2), which showed little change in the porosity of the PLLA shell as indicated in the closeup in Fig. 8. Hence, during this period drug would be released via diffusion out of the matrix. That was followed by the steepest gradient corresponding to a sudden acceleration of the degradation mechanism of the PLLA shell (D1) and kinetics along with the fastest decline in molec-

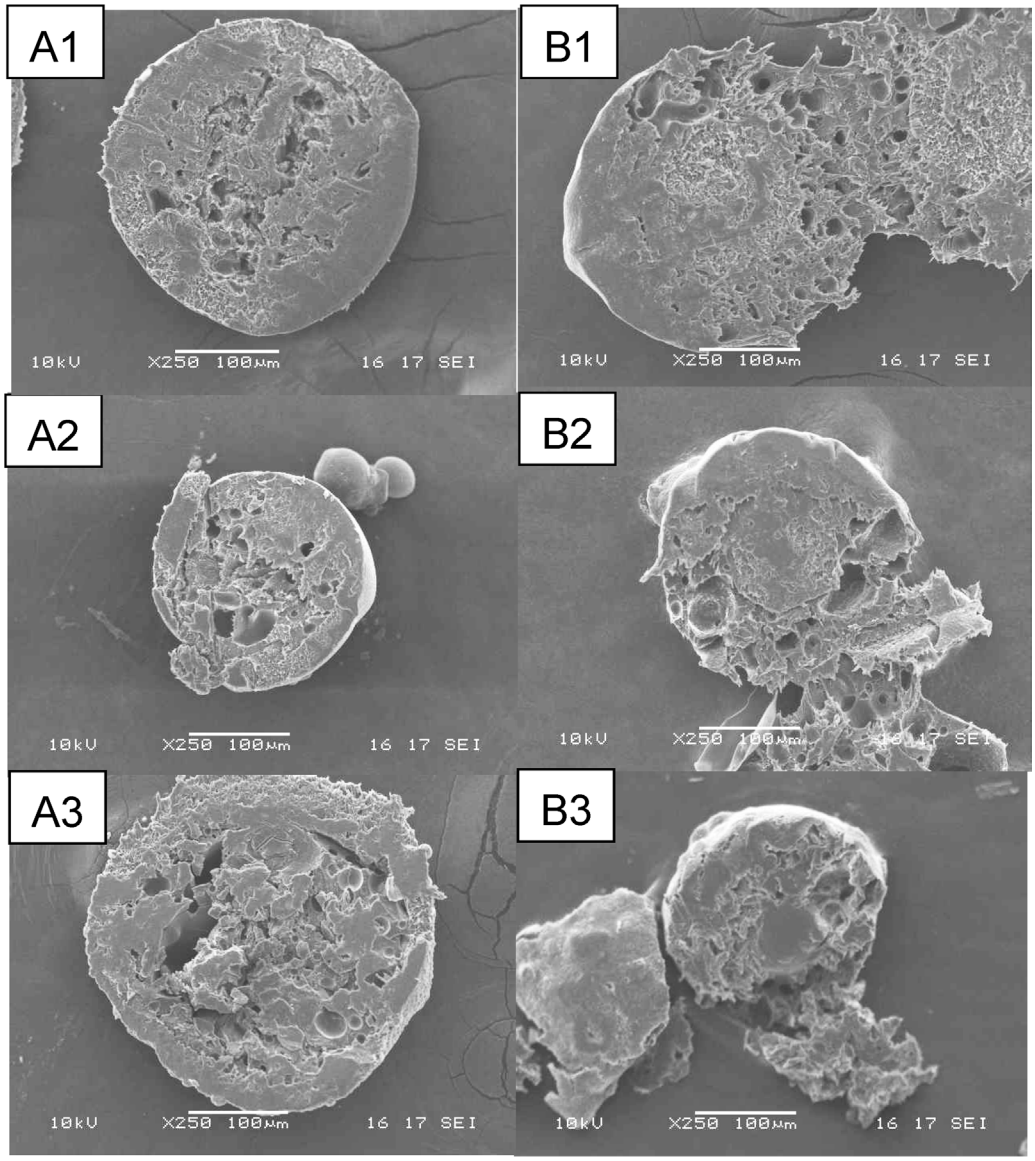

Fig. 7. Scanning electron micrograph of double-walled (A) 1:1 PLGA/PLLA and (B) 1:3 PLGA/PLLA showing surface and cross-sectional views: (1) 14 days; (2) 21 days; (3) 28 days.

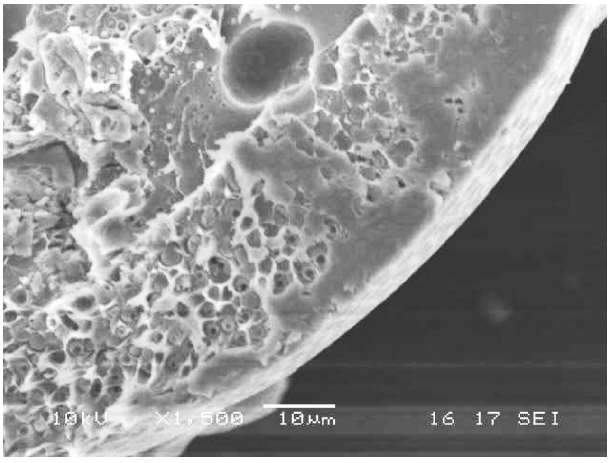

Fig. 8. Closeup scanning electron micrograph of PLLA shell (D1 sample) after 21 days.

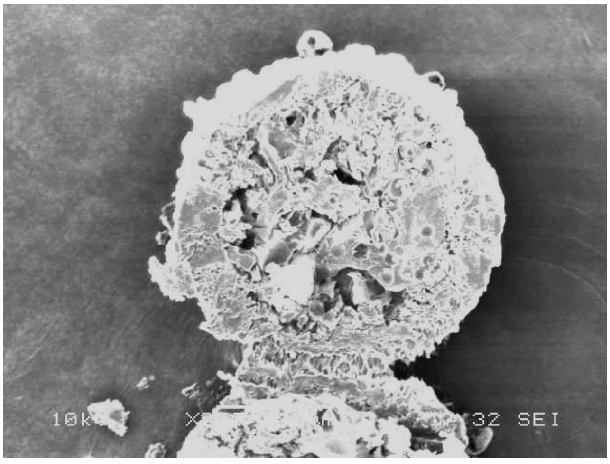

Fig. 9. Scanning electron micrograph of double-walled 1:1 PLGA/PLLA after 35 days of in vitro release.

ular weight and change in permeability and porosity starting at the onset of 35 days of in vitro release, as shown in Fig. 6. The corresponding SEM image in Fig. 9 indicated higher porosity in the more resistant PLLA shell. This gradient was constant from 35 to 65 days of in vitro release, indicating that there were no further alterations to the degradation kinetics for D1. This again agrees with our SEM observation of a rapid increase in the porosity and state of degradation of microspheres from Fig. 7A3 and corresponds to the rapid linear release that occurred as a result of drastic changes in the porosity and permeability of the PLLA shell of D1.

4. Conclusions

Fabrication of microspheres with a unique double-walled configuration consisting of a rate-limiting shell barrier and a drug-dispersed core matrix was successful. Investigational studies into the critical PLLA/PLGA polymer ratio that results in reversed core–shell configuration allowed us to encapsulate hydrophilic drug within the inner core of the double-walled microspheres. Such formulations can be achieved with accurate prediction of the preferential distribution of drug in two different insoluble polymers. Hence, we were given more freedom in manipulating the core–shell composition as well as designing the optimum shell thickness and core diameter. That, in turn, provided the means for fabricating double-walled microspheres with high drug loading within the core, protected by a rate-limiting shell layer. It was found that fabrication of double-walled microspheres using modified solvent evaporation by phase separation can achieve high encapsulation efficiencies. The drug delivery system designed for this work was able to achieve sustained and controlled release for a water-soluble drug with low initial burst. However, the large size of the double-walled microspheres is a hindrance to intravenous injection, and surgical operations become a necessity.

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