Spray Drying Technique to Produce Controlled Release Formulations of Zidovudine—an Anti-HIV Drug

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ABSTRACT: This article explores the application of spray drying technique to produce microparticles of poly(D,L-lactide-*co*-glycolic acid) (PLGA), as well as di-block copolymer of polylactic acid (PLA) and polyethylene glycol (PEG) (PLA-PEG), containing zidovudine (AZT), an anti-HIV drug, to achieve its controlled release over an extended period of time. Of the two polymers studied, PLGA is hydrophobic, whereas PLA-PEG is hydrophilic and the drug, AZT is water-soluble. Formulations were developed containing 10 and 25 wt % of AZT giving encapsulation efficiencies (EE) of 66 to 86% for PLGA and 90 to 94% for PLA-PEG di-block copolymer. All the formulations were characterized by Fourier transform spectroscopy (FTIR) to investigate the interaction of AZT with polymers and to characterize PLA-PEG. NMR was also employed to confirm the formation of PLA-PEG. X-ray diffraction was used to understand the molecular level dispersion of AZT within the polymeric matrices, while differential scanning calorimetry was employed to assess thermal properties. Scanning electron microscopy was employed to understand the surface morphology of AZT-loaded microparticles. *In vitro* release experiments performed in pH 7.4 buffer media extended the release of AZT up to 125 h with PLGA, whereas 30 h were required for releasing AZT through PLA-PEG microparticles. Cumulative release data were fitted to an empirical equation to understand the nature of release characteristics. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 122: 2244–2251, 2011

Key words: poly(lactide-*co*-glycolide); zidovudine; PLA-PEG di-block copolymers; controlled release

INTRODUCTION

Since its first recognition in 1981, Acquired Immunodeficiency Syndrome is a major health threat. To alleviate this problem, one of the earliest anti-HIV drugs viz., zidovudine (3′-azido-3′-deoxythymidine) (AZT) was approved for clinical use. During antiretroviral therapy, it is crucial to maintain systemic drug concentration(s) within therapeutic level(s) of the treatment.[1] AZT has short elimination half-life of 1 h with a low bioavailability and hence, its frequent high doses (200 mg every 4–6 h) are required to maintain therapeutic level.[2,3] AZT, being hydrophilic, has low bioavailability (60%) due to its considerable first pass metabolism with a high clearance rate. Patients receiving AZT will frequently develop anemia and leucopenia.[4] Side effects of AZT are dose-dependent and any reduction in the total administered drug would reduce the severity of its toxicity.[5] Thus, short half-life of 1 h and frequent dosing of large doses of AZT due to low oral bioavailability makes it a good candidate for developing controlled release (CR) formulations.

Several articles[6–9] dealt with transdermal formulations of AZT, but limited data are available on the microparticles of AZT-loaded formulations. For instance, Mandal et al.[10] reported the w/o/w double emulsion solvent evaporation method to produce AZT-loaded poly(D,L-lactide-*co*-glycolic acid) (PLGA) microparticles to achieve an encapsulation efficiency (EE) up to 5%, whereas a maximum EE of 17% was achieved by modifying the secondary aqueous phase.[11] The low EE values were attributed to hydrophilic nature of AZT that would preferentially partition into aqueous media. On the other hand, micro-encapsulation of AZT by double emulsion solvent diffusion technique[12,13] using ethyl cellulose gave EE up to 53%. In any case, for good bioavailability of AZT, there is a need to prepare AZT-loaded microparticles with high EE, which was achieved by spray drying technique using PLGA (80 : 20) and di-block copolymers of polylactic acid (PLA) with polyethylene glycol (PEG).

Spray drying is a well-known technique used to produce continuously the microparticles containing drugs of interest,[14–16] which consists of feeding the polymer solution loaded with an active ingredient into atomizer and spray dried to collect the particles.

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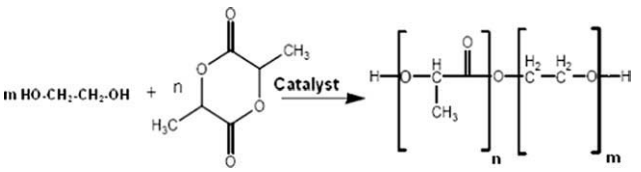

Figure 1 Synthetic scheme for the preparation of PLA-PEG di-block copolymer.

The method is reproducible, rapid and easy to scale-up; however, the disadvantages are that hydrophilic microparticles, which are unusually porous and water-swellable, would quickly release the encapsulated drug.[17] In the literature, PLGA and PLA have been widely used[18–20] in CR applications because of their biodegradability and biocompatibility. Their hydrophobic nature makes them attractive during spray drying to produce drug-loaded microparticles.

In continuation of our earlier research using lactide-based polymers,[16] we now consider using PLGA (80 : 20) of molecular weight 138,500 and PLA-PEG di-block polymer of molecular weight of 45,000 as determined by gel permeation chromatography (GPC) to develop 10 and 25 wt % AZT-loaded formulations. Even though PLA is hydrophobic, PLA-PEG is hydrophilic, which might reduce the time to cumulative release of AZT compared with PLGA. The formation of PLA-PEG was confirmed by NMR. The AZT-loaded microparticles were characterized for particle size by particle size analyzer, morphology using scanning electron microscopy (SEM) and polymorphism of AZT by x-ray diffraction (X-RD). Differential scanning calorimetry (DSC) was used to understand their thermal properties. The *in vitro* drug release experiments were performed in pH 7.4 buffer. These results were analyzed by an empirical equation to assess the nature of the transport mechanism.[21,22]

EXPERIMENTAL

Materials and methods

Poly(ethylene glycol) (PEG 1000) was procured from Aldrich Co., St. Louis, MO. Both PLGA and PLA-PEG polymers were prepared in-house. Zidovudine was received as a gift sample from Cipla Pvt. Ltd., Mumbai; reagent grade dichloromethane (DCM) and methanol solvents were purchased from Ranbaxy Fine Chemicals, New Delhi. All other reagents and solvents used were of analytical grade samples satisfying the pharmacopeia standards. Double distilled Milli Q water was used throughout the study.

Preparation of poly(DL-lactide-*co*-glycolide)

PLGA copolymer of DL-lactide (80%) and glycolide (20%) was prepared under identical conditions as described before[16] using tin-octoate (0.05%) as a catalyst, and polymerization was carried out at 180°C for 1 h. Polymerized yellow colored solid was purified by dissolving in acetone and re-precipitated in excess water. Resulting polymer was vacuum-dried in oven at 60°C for 12 h and stored in an inert atmosphere.

Synthesis of PLA -PEG di-block copolymers

To prepare PLA-PEG di-block copolymer, DL-lactide (molecular weight 144) and PEG (molecular weight 400) were taken in a single-necked flask containing 0.05% of tin-octoate catalyst, and polymerization was carried out at 165°C for 2 h. The polymer obtained was purified by dissolving in DCM and re-precipitated in excess methanol (nonsolvent). The resulting polymer was vacuum-dried in oven at 60°C for 12 h and stored in an inert atmosphere. The reaction scheme of the formation of the polymer is shown in Figure 1.

Both PLGA and PLA-PEG polymers were characterized for molecular weight using GPC available at SICART, Anand, Gujarat, India. The Perkin-Elmer, Series-200 system was used with RI detector and THF solvent at 30°C. The results of molecular weight along with polydispersity index values are given in Table I.

Preparation of AZT-loaded PLGA/PLA-PEG microparticles

Spray-dry experiments

Since both the polymers and AZT are soluble in DCM, microparticles were produced by spraying AZT-containing polymer solutions prepared in DCM through the nozzle of a spray drier (LU-222 Advance Spray Drier, Labultima, Mumbai, India) under co-current flow type condition. The instrument was equipped with a standard 0.7-mm, two fluid spray Teflon-coated spray nozzle. The inlet air temperature of 70°C and outlet air temperature of 50°C were used. The drug-loaded solution 100 mL was sprayed through the nozzle using a peristaltic pump maintained at a pressure at 203 kPa. The solution spray rate was maintained at 15 mL/min and the atomized liquid drops were dried by a coaxial flow of air maintained at a flow rate of 1 m^3/min.

TABLE I
GPC Data of PLGA Polymers at 25°C

Polymer	$\overline{M}_w$	$\overline{M}_n$	PDI
PLGA	1,38,500	77,800	1.78
PLA-PEG	45,000	25,000	1.8

PDI = Polydispersity index = $\frac{\overline{M}_w}{\overline{M}_n}$.

TABLE II
Size and % Encapsulation Results of the PLGA and PLA-PEG Formulations

Polymer	Loading of AZT (%)	Encapsulation[a] efficiency (%)	Particle size[a] (μm)	Yield (%)
PLGA	10	66 ± 0.5	9 ± 1.5	60
PLGA	25	86 ± 1.5	14 ± 2.1	65
PLA-PEG	10	90 ± 1.0	6 ± 1.5	55
PLA-PEG	25	94 ± 1.2	8 ± 1.0	60

[a] The values of ± indicates standard deviations calculated from three sets of data.

Two batches of the drug-loaded microparticles were prepared by loading 10 and 25 wt % of AZT with respect to weight of polymer(s) prepared as 1% solution in DCM. These results are displayed in Table II.

Fourier transform infrared spectroscopy

FTIR spectra were taken on Spectrum GX, Perkin-Elmer instrument to investigate the interactions of AZT with PLGA and PLA-PEG. Samples were crushed with KBr and pellets were made under a hydraulic pressure of 300 kg/cm^2. FTIR spectra of pure AZT, placebo, and AZT-loaded microparticles were scanned from 4000 to 400 cm^{-1} using a scanning resolution of 4 and number of scans of 10.

NMR spectroscopy

^{1}HNMR was recorded in $CDCl_3$ using 400 MHZ on Varian 400 MHZ FTNMR spectrometer. The chemical shifts are reported in δ ppm relative to tetramethylsilane.

Differential scanning calorimetry

DSC curves of the pure AZT, placebo, and AZT-loaded microparticles were recorded using Perkin-Elmer differential scanning calorimeter (Model-DSC7). The analysis was done by heating the samples at 10°C/min under inert nitrogen atmosphere.

X-ray diffraction

The crystalline nature of pure AZT and AZT-loaded microparticles were evaluated by powder X-RD using a Philips diffractometer (model PW-1710) attached to the digital graphical assembly and a computer with Cu-NF 25 KV/20-mA tube as the Cuα-radiation source in the range of 0°–50° of 2θ.

Particle size

Particle size was measured by laser light scattering technique (Mastersizer 2000, Malvern). Sizes of the completely dried microparticles of different formulations were measured by dry sample technique on a volume basis using a dry sample adapter (supplied with the Malvern 2000 model instrument). Completely dried particles were placed on the sample tray under vacuum and the compressed air system was used to suspend the particles. The laser obscuration range was maintained between 1 and 2% to record the volume-mean diameter (V_d) of the microparticles. After measuring the size of each sample, the dry sample adapter was cleaned thoroughly to avoid cross contamination. Triplicate data were collected for each sample and average values are considered for data analysis.

Scanning electron microscopy

SEM images of the AZT-loaded microparticles were taken on a JEOL model JSM-840A, Japan. Microparticles were sputtered with gold to make them conducting and placed on a copper stub. Thickness of the gold layer accomplished by gold sputtering was about 15 nm. These measurements were done at Indian Institute of Science, Bangalore, India.

Determination of encapsulation efficiency

To determine % drug loading and % EE, drug-loaded (10 mg) microparticles were dissolved in DCM and drug was extracted using phosphate buffer solution (pH 7.4). The solutions were filtered and drug concentration was estimated using HPLC (Shimadzu), on a Spherisorb ODS column (5 μm, 250 × 4.6 mm inner diameter, Waters Corporation, Milford, MA) equilibrated with methanol : water (80 : 20, vol/vol) mixture as the mobile phase at 25°C under a flow rate of 1.0 mL/min using a UV detector at 265 nm. The % drug loading and % EE of drug-loaded microparticles were calculated as:

$$\%\ \text{Drug loading} = \left(\frac{\text{Weight of drug in microparticles}}{\text{Weight of microparticles}}\right) \times 100 \quad (1)$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (2)$$

These data are compiled in Table II.

In vitro drug release

In vitro drug release of the formulations was investigated in phosphate buffer solution (PBS) of pH 7.4 (without enzymes) having molarity of 0.2 *M*. Microparticles (10 mg) were suspended in 1 mL of PBS and placed within the dialysis bag. The sample within the dialysis bag was taken in a conical flask

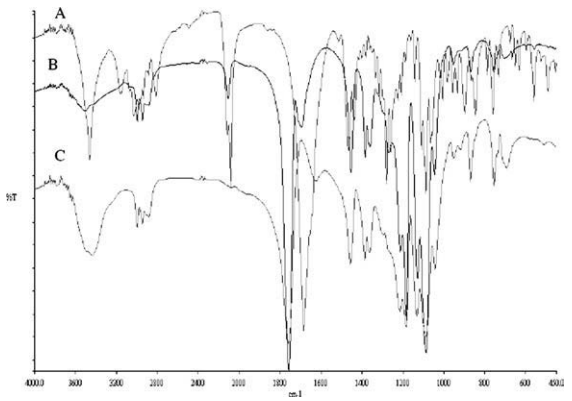

Figure 2 FTIR spectra of (A) pure AZT, (B) AZT-loaded PLA-PEG and (C) placebo PLA-PEG microparticles.

containing 50 mL of PBS as the dissolution medium on a shaker at 100 rpm speed at 37°C (New Brunswick Scientific Innova 4230, Minnesota). The amount of drug released was determined by withdrawing 2 mL aliquots of the sample at the selected specified time intervals. The volume withdrawn was replenished with an equal volume of fresh and prewarmed PBS at 37°C. Samples were analyzed at 25°C using HPLC as described before.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy

FTIR spectra of pure AZT, placebo PLA-PEG, and AZT-loaded PLA-PEG microparticles are displayed in Figure 2, whereas those of PLGA formulations are displayed in Figure 3. As seen in Figure 2, for placebo PLA-PEG, two characteristic absorption bands at 2998 and 2947 cm^{-1} are assigned to —C—H and —CH_2 stretching vibrations, respectively. The characteristic bands of PLA-PEG appearing at 1759 and 1625 cm^{-1} are due to C=O and O—CO stretching vibrations, respectively. The bands at 1458 and 1386 cm^{-1} are assigned to C—C multiple bond stretching and C—H bending vibrations, respectively.

As shown in Figure 3, FTIR of placebo and AZT-loaded PLGA microparticles exhibit bands at 2998 and 2948 cm^{-1}, respectively that are assigned to —C—H and —CH_2 stretching vibrations of PLGA. Another set of bands appearing at 1757 and 1621 $cm^{-1,}$ respectively are due to C=O and O—CO stretching vibrations of PLGA, while the bands at 1456 and 1385 cm^{-1} are due to C—C multiple bond stretching and C—H bending vibrations, respectively. Bands in the region 1090–1187 cm^{-1} are assigned to C—O—C stretching vibrations.

FTIR spectra of the pure AZT drug displayed in both Figures 2 and 3 has characteristic bands at 3462 cm^{-1} due to O—H/N—H stretching vibrations, whereas those observed at 2935 and 2814 cm^{-1} are due to C—H stretching vibrations. Bands at 1685 and 1467 cm^{-1} are attributed to the primary amide (NH) bending and aromatic N—H bending vibrations, respectively. Carbonyl (C=O) stretching vibrations are seen at 1651 cm^{-1}, whereas the bands at 1467 and 1333 cm^{-1} are due to —CH_2 bending and C—H vibrations, respectively. The C—N stretching vibrations are seen at 1280 and 1189 cm^{-1}.

Figures 2 and 3 display no differences in spectra of AZT-loaded PLA-PEG and AZT-loaded PLGA microparticles compared with placebo microparticles. However, with AZT-loaded spray dried PLA-PEG and of PLGA microparticles, even though some additional bands have appeared due to the presence of AZT in the polymers, these bands of AZT were not prominent due to identical stretching in placebo as well as drug-loaded formulations at the same wave number. This suggests no evidence of any chemical interactions of AZT with the spray dried formulations.

NMR spectroscopy

^1H NMR spectrum of the di-block copolymer was done to confirm the formation of the polymer. It is observed that the NMR signal corresponding to —CH_3 (d, $J = 7.5$ Hz) protons appeared at 1.58 ppm. The signal corresponding to —CH proton appeared at 5.17 ppm, whereas that corresponding to —OH proton was observed at 3.6 ppm. A less intense signal appearing at 4.4 ppm is due to protons of O—CH_2 moiety of PEG. Thus, NMR confirms the formation of di-block copolymer.

Differential scanning calorimetry

To investigate the molecular level dispersion of AZT with the polymers, DSC thermograms were produced for pure AZT, placebo, and AZT-loaded

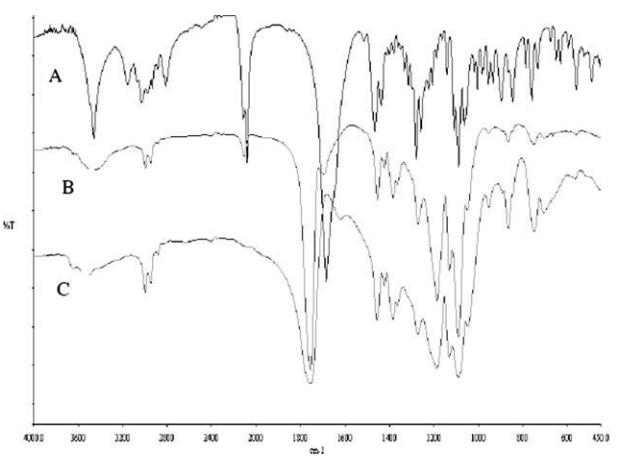

Figure 3 FTIR spectra of (A) pure AZT, (B) AZT-loaded PLGA and (C) placebo PLGA Microparticles.

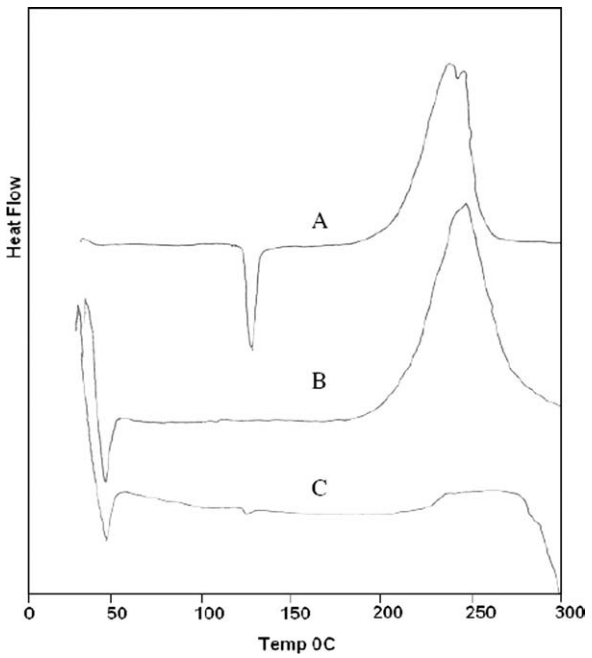

Figure 4 DSC thermograms of (A) pure AZT, (B) placebo PLGA and (C) AZT-loaded PLGA microparticles.

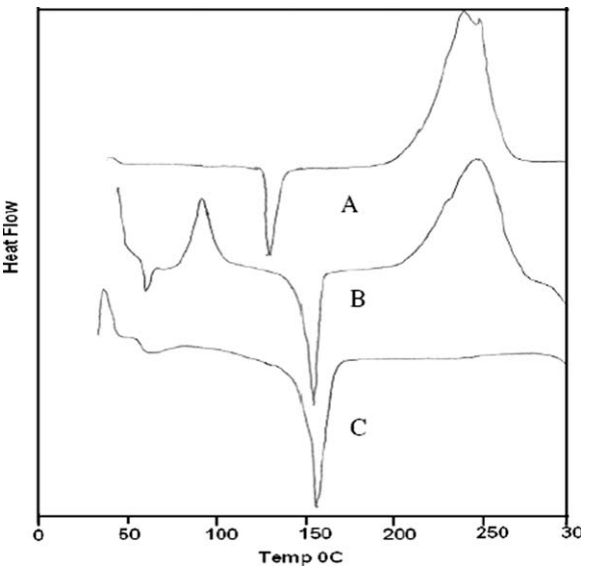

Figure 5 DSC thermograms of (A) pure AZT, (B) AZT-loaded PLA-PEG and (C) placebo PLA-PEG microparticles.

polymers, and these are displayed in Figures 4 and 5, respectively for PLGA and PLA-PEG-based formulations. As shown in Figure 4 (curve A), AZT exhibits a sharp peak at 125°C corresponding to its melting temperature (124°C) as reported in the literature.[23] In case of AZT-loaded PLGA (curve C), the melting temperature peak of AZT has not appeared and was probably masked by the amorphous nature of the PLGA polymer. However, ignoring the appearance of a very small peak at around 125°C and the absence of such a peak in placebo (curve B), we can conclude that drug is molecularly dispersed in the PLGA matrix.

DSC thermogram shown in Figure 5 for pure AZT (curve A) has a sharp melting temperature at 124°C. For the placebo and AZT-loaded PLA-PEG matrices, intense peaks were observed around 150°C (see curves C and B), indicating their melting temperatures. In case of AZT-loaded PLA-PEG (curve B), a sharp exothermic peak observed around 80–100°C might be due to the induced cold crystallization of PLA due to the presence of hydrophilic PEG and AZT. This implies that PLA block of the PLA-PEG polymer would be semi-crystalline, but no such peak was observed in PLA-PEG placebo matrix (curve C).

X-ray diffraction

Typical X-RD profiles of pure AZT, placebo PLGA and AZT-loaded PLGA microparticles are displayed in Figure 6. For pure AZT (curve A), intense peaks were observed at 2θ of 10°, 17°, 21°, 26°, and 30°, suggesting its crystalline nature. In case of placebo PLGA, no intense peaks were observed suggesting its amorphous nature. For AZT-loaded microparticles of PLGA, two small peaks appeared at 2θ = 32° and 48° are possibly due the surface adhered drug molecules; but the absence of characteristics peaks of AZT in the drug-loaded PLGA formulations confirm that AZT is molecularly dispersed in into the PLGA matrix. The X-RD profiles of PLA-PEG matrix was not displayed to avoid redundancy and also due to the fact that no indication of crystalline peaks of AZT were observed in the AZT-loaded PLA-PEG microparticles.

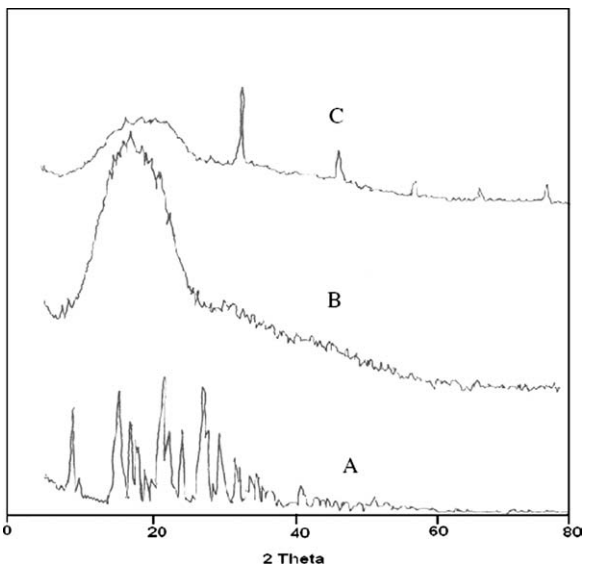

Figure 6 X-RD plots of (A) pure AZT, (B) placebo and (C) AZT-loaded PLGA microparticles.

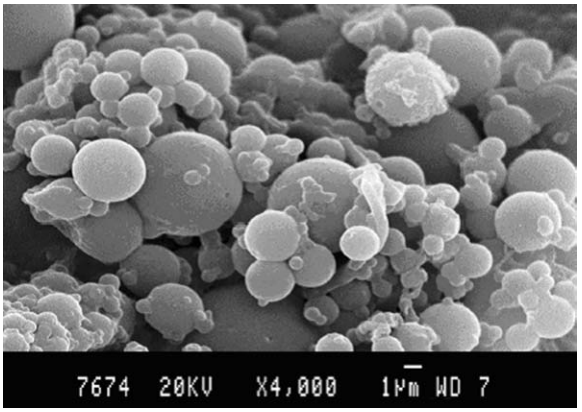

Figure 7 SEM micrographs of AZT-loaded PLGA microparticles.

Particle size analysis and scanning electron microscopy

Mean volume diameter size distribution data given in Table II show systematic variations with the extent of drug loading. For instance, with 10 and 25 wt % AZT-loaded microparticles of PLGA, sizes range from 9 to 14 μm, whereas for microparticles of PLA-PEG, the mean volume diameters range from 6 to 8 μm for 10 and 25 wt % AZT-loaded formulations, respectively. Thus, with the increasing drug loading, the size of the microparticles also increased.

SEM pictures of drug-loaded PLGA and PLA-PEG microparticles are respectively displayed in Figures 7 and 8. In case of PLGA, particle surfaces appear to be smoother than those of PLA-PEG microparticles. The size of PLGA microparticles are somewhat smaller than those of PLA-PEG microparticles and also, the latter exhibited higher levels of agglomeration and more of surface adhered debris compared to AZT-loaded PLGA microparticles.

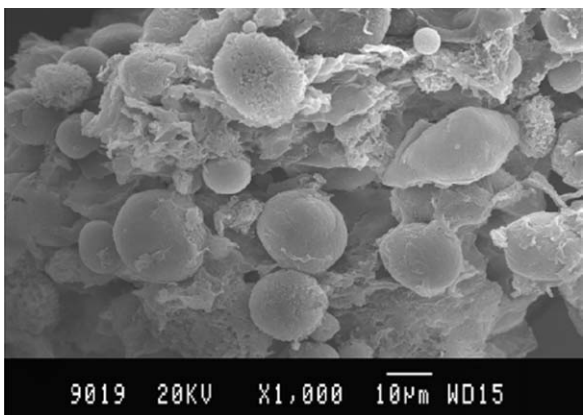

Figure 8 SEM micrographs of AZT-loaded PLA-PEG microparticles.

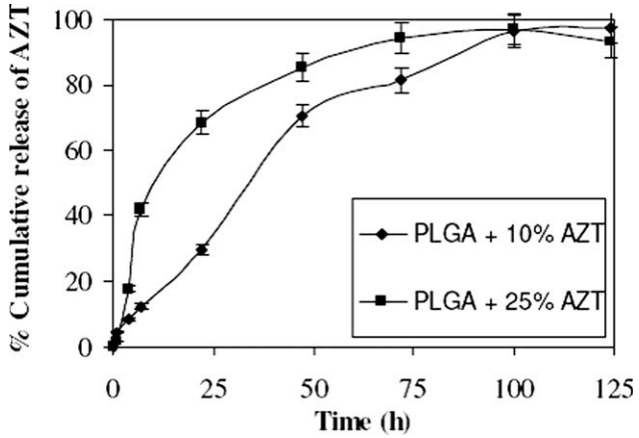

Figure 9 % Cumulative release of AZT-loaded PLGA microparticles. Symbols: (■) 25% and (◆) 10%.

Encapsulation efficiency

Encapsulation efficiency (Table II) increased with increasing drug loading. For instance, EE values of 66 and 86% were observed for 10 and 25% AZT-loaded PLGA compared with 90 and 94% for PLA-PEG matrix containing, respectively 10 and 25% AZT. The higher EE values observed for PLA-PEG than PLGA matrices is attributed to more hydrophilic nature of PLA-PEG than PLGA in the presence of another hydrophilic AZT molecule.

In vitro drug release

Cumulative drug release profiles of 10 and 25 wt % AZT-loaded PLGA and PLA-PEG microparticles versus time are respectively displayed in Figures 9 and 10. Dissolution experiments were carried out at 37°C, and triplicate data collected for each system were averaged out for data display that are presented with error bars. For both the systems, the

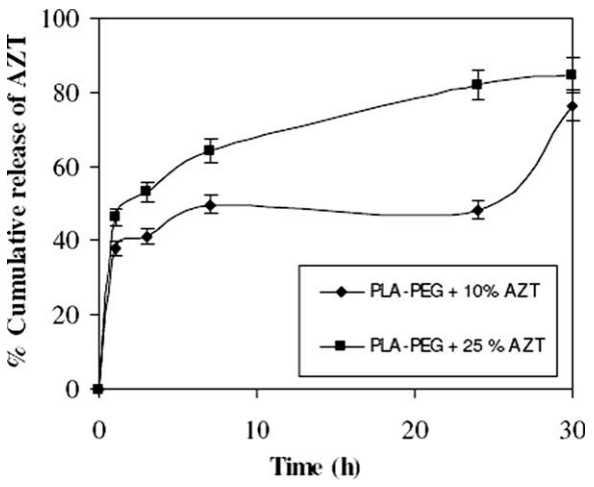

Figure 10 % Cumulative release of AZT-loaded PLA-PEG microparticles. Symbols: (■) 25%, (◆) 10%.

TABLE III
Analysis of Cumulative Release Data Using eq. 3 for Different Formulations

Formulation	k	n	Correlation[a] coefficient, r
PLGA -10 % AZT	0.038	0.682	0.981
PLGA -25 % AZT	0.038	0.682	0.981
PLA-PEG-10 % AZT	0.352	0.209	0.934
PLA-PEG-25 % AZT	0.452	0.184	0.989

[a] Computations were done by least-squares method at 95% confidence level.

release of AZT from 25% loaded microparticles was higher than those of 10% loaded formulations. Moreover, for 10 wt % AZT-loaded formulations the release curves exhibited inflexion points. Nearly 96% of AZT was released from PLGA, whereas only 82% of AZT was released from PLA-PEG matrix. This effect can be explained as due to higher solubility of hydrophilic AZT in the hydrophilic PLA-PEG matrix than hydrophobic PLGA. As regards the time of release, most of the drug was released from PLA-PEG (Fig. 10) in about 30 h, whereas with PLGA (Fig. 9), the release of AZT occurred in 125 h. Such wide variations are attributed to the differences in the nature of the two polymers used.

Drug release kinetics

The cumulative drug release results were analyzed by fitting to an exponential equation of the type.[21,22]

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \tag{3}$$

Here, M_t/M_∞ represents fractional drug release at time, t, k is a constant, characteristic of drug-polymer system, and n is an empirical parameter characterizing the release mechanism. Using least-squares procedure, we have estimated the values of n and k for all formulations, and these data are given in Table III. For values of $n = 0.5$, drug diffuses and releases from the polymer matrix following Fickian diffusion. For $n > 0.5$, anomalous or non-Fickian transport occurs. If $n = 1$, completely non-Fickian or Case II release kinetics is operative. Intermediary values ranging between 0.5 and 1.0 can be attributed to anomalous type transport.

In this study, the values of k and n showed a clear-cut dependence on the extent of drug loading as well the nature of the carrier polymer. Values of n for AZT-loaded PLA-PEG (10 and 25%) vary from 0.18 to 0.20, while n value was 0.68 for PLGA microparticles loaded with either 10 or 25 wt % of AZT. These data suggest the shift of transport from Fickian to anomalous type, which could occur because of the reduction in the regions of low microviscosity and closure of microcavities in the matrix. The lower exponent values of n for PLA-PEG matrix suggest the anomalous transport and such smaller values are due to higher swelling of PLA-PEG matrix than PLGA. This fact is further confirmed by smaller values of the parameter, k in case of PLGA than PLA-PEG matrix, suggesting lower interactions of the drug with PLGA than with PLA-PEG. Similar findings have been observed elsewhere, wherein the effect of different polymer ratios on dissolution kinetics was studied.[24–26]

CONCLUSIONS

CR formulations containing AZT, an anti-HIV drug, have been developed by choosing two different types of carrier systems viz., hydrophobic PLGA and hydrophilic PLA-PEG for the hydrophilic AZT drug using spray drying technique. The formulations were characterized for drug-polymer interaction, microparticle size, morphology, uniform drug dispersion, and thermal properties using, respectively, FTIR, particle size analyzer, SEM, X-RD, and DSC. Higher EE of PLA-PEG matrices is attributed to its more hydrophilic nature than PLGA. It was observed that AZT did not show any chemical interactions with both the polymers. Nearly 96% of AZT was released from PLGA with the release time of 125 h, whereas for PLA-PEG-based formulation, nearly 82% of AZT was released in about 30 h. While we cannot offer any explanations for these varied behaviors of the two matrices, based on our data, PLGA microparticles can be the better alternatives for delivering AZT. The kinetics of drug release followed the anomalous type transport.

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