Synthesis and characterization of novel poly (sebacic anhydride-*co*-Pluronic F68/F127) biopolymeric microspheres for the controlled release of nifedipine ☆

Namdev B. Shelke, Tejraj M. Aminabhavi*

Drug Delivery Division, Center of Excellence in Polymer Science, Karnatak University, Dharwad 580003, India

Abstract

Amphiphilic block copolymers composed of prepoly(sebacic anhydride) and Pluronic-F68/F127 have been synthesized in different molar compositions via melt-polycondensation reaction. Poly(sebacic anhydride-*co*-PLF68/PLF127) thus formed was characterized by Fourier transform infrared spectroscopy (FTIR), gel permeation chromatography (GPC) and nuclear magnetic resonance spectroscopic (NMR) techniques. The amphiphilic block copolymers were used to prepare microspheres and to encapsulate nifedipine (NFD) by the solvent evaporation technique. Differential scanning calorimetry (DSC) was used to confirm the incorporation of Pluronic into polyanhydrides, while X-ray diffraction (XRD) was performed on the drug-loaded microspheres to investigate the crystalline nature of the drug after encapsulation. Scanning electron micrograph (SEM) pictures indicated spherical nature of the microspheres. Microspheres obtained were in the size range of 10–50 μm as measured by the laser particle size analyzer. *In vitro* release studies of NFD from poly(sebacic anhydride-*co*-Pluronic-F68/F127) microspheres performed in pH 7.4 phosphate buffer indicated sustained release rates of NFD at higher amounts of Pluronic in polyanhydride copolymers; there was no significant difference obtained between the release patterns of NFD from Pluronic-F68 and Pluronic-F127 copolyanhydride microspheres when same amount of Pluronics were used.

1. Introduction

Polyanhydrides are a class of biodegradable and biocompatible polymers that received considerable importance in recent years in biomedical applications. These hydrophobic polymers can be used as controlled release (CR) devices for short-lived drugs by the surface erosion phenomenon and thereby, provide a sustained release effect for the drug over an extended period of time (Peppas and Langer, 1993; Hollinger, 1995; Domb and Langer, 1987). It has been shown earlier that such materials are biodegradable as well as highly biocompatible because their degradation products are nontoxic (Peppas and Langer, 1993).

The properties of polyanhydride can be altered by simple modifications of polymer backbone. In the literature, biomaterials derived from block and graft copolymers have attracted much attention because of their potential use as biocompatible and biodegradable systems (Gan et al., 1996; Chen et al., 1997; Huh and Bae, 1999; Kim et al., 1999). Polyanhydrides are generally pre-polymers or copolymers of poly(amino acids) (Uhrich et al., 1995; Hanes et al., 1996), and poly(ethylene glycol) (Jiang and Zhu, 1999) can be used to modify the structure of polyanhydride.

In the present research, we have employed the tri-block copolymers viz., poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO), a commercially available amphiphilic block copolymer (Pluronics, BASF), which exhibits thermo-responsive properties due to the presence of hydrophobic propylene oxide block.

These triblock copolymers have been used earlier to prepare micelles that are known to increase the bioavailability of drugs (Rosler et al., 2001); these are also approved by the U.S. Food and Drug Administration for use as food additives and pharmaceutical ingredients (Alexandridis and Hatton, 1995).

Earlier, Pluronic/polycaprolactone (PCL) block copolymeric nanospheres have been prepared (Kim et al., 2000) for the CR of indomethacin, wherein it was observed that solubility and hydrophilic nature of PPO block was decreased with an increase in temperature, resulting in increased interactions of PPO and PCL blocks. The i*n vitro* release experiments showed that by increasing the Pluronic content of the block copolymers, drug release rates decreased due to increased intermolecular and intramolecular interactions between PPO and PCL moieties with respect to temperature.

Nifedipine, a calcium channel blocker, has been widely used in the treatment of hypertension, angina and myocardial infarction. It has a plasma lifetime of 2 h. In the earlier literature, many efforts have been made to increase its release characteristics using a variety of synthetic and natural polymers like poly(DL-lactide-*co*-glycolide) (Soppimath and Aminabhavi, 2002), ethyl cellulose (Soppimath et al., 2001b) and cellulose acetate (Soppimath et al., 2001a).

In continuation of these studies and as a part of our ongoing studies on the development of novel delivery systems, we now present a detailed procedure for the synthesis of amphiphilic block copolymers of polyanhydride and Pluronics, and to study the effect of Pluronics on drug (NFD) release patterns. Polyanhydride prepared in this study, using Pluronics, could successfully encapsulate NFD, a water-insoluble drug. It is further demonstrated that the initial burst effect and release rates of NFD can be decreased or controlled by increasing the concentration of Pluronic chains in poly(sebacic anhydride-*co*-Pluronic). The polymers prepared have been characterized by FTIR, NMR, GPC and DSC techniques. Size of the microspheres was measured using laser light scattering technique. Drug-loaded microspheres have been characterized by XRD and SEM techniques. Release kinetics of NFD from poly(sebacic anhydride-*co*-Pluronic) microspheres has been analyzed by Higuchi and Power law equations to confirm the predicted patterns of release trends.
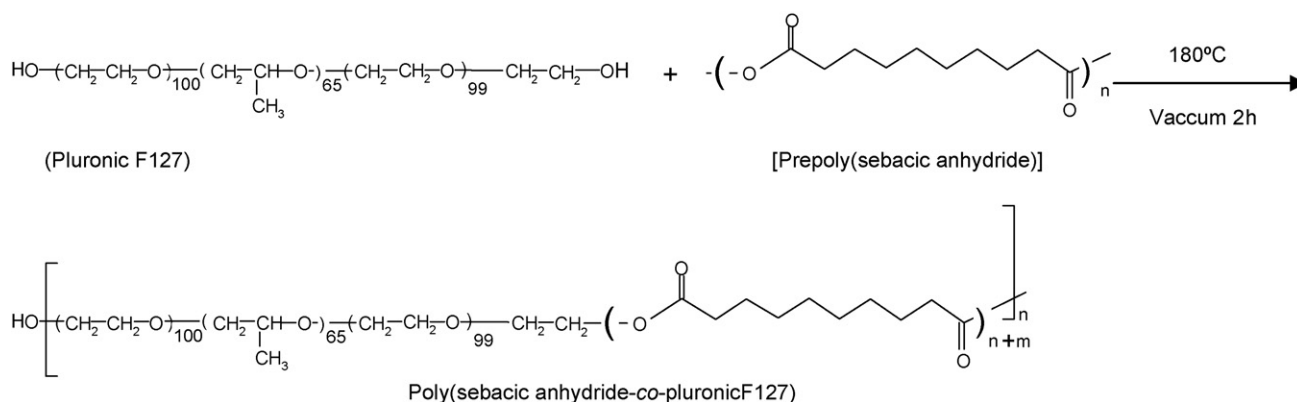
2. Materials and methods

2.1. Materials

Pluronic F68 (PLF68, $M_w = 8400$) and Pluronic F127 (PLF127, $M_w = 12600$) were obtained from Aldrich Chemicals, Milwaukee, WI, USA and dried under high vacuum for 24 h. Analar grade sebacic acid, petroleum ether, toluene, acetic anhydride, dichloromethane (DCM) and diethyl ether were all purchased from s.d. fine Chemicals, Mumbai, India. Sebacic acid was recrystallized thrice from ethanol prior to use. Petroleum ether and diethyl ether were dried over sodium wire; NFD was obtained from Loba Chemical Co. Mumbai, India. All other chemicals were used as received.

2.2. Synthesis of amphiphilic block copolymer composed of poly(sebacic anhydride) and pluronic

The synthesis of prepolysebacic anhydride and amphiphilic block copolymers was carried out by the method suggested in the literature (Leong et al., 1987; Domb and Langer, 1987). A 24 g of sebacic acid and 250 g of acetic anhydride were charged into dry nitrogen purged round bottom flask. The reaction was carried out at 140 °C under rigorous stirring for 30 min. The mixture was then placed in a rotary evaporator to remove acetic acid as well as unreacted acetic anhydride. The crude pre-polymer was recrystallized from dry toluene. The solid crystals were subsequently immersed in the solvent mixture (1:1 dry petroleum ether to ethyl ether) to extract the trace amount of acetic anhydride and toluene. The polymer formed was dried under vacuum. A desired quantity of the refined pre-polymer ($\bar{M}_W = 1580$) and Pluronic were then placed into the reactor in a silicone oil bath at 180 °C under vacuum for 120 min to perform the melt-polycondensation reaction. The final product was first dissolved into dichloromethane and then purified by precipitation with dry petroleum ether. The precipitate was further extracted using the anhydrous ethyl ether to give the purified polymer. The polymers obtained were stored at −20 °C. Accompanying reactions are outlined in Scheme 1.

Scheme 1. Synthesis of poly(sebacic anhydride-*co*-PluronicF127).

2.3. Preparation of polyanhydride/PLF68 and PLF127 block copolymeric microspheres

Microspheres of poly(sebacic anhydride-*co*-PLF68) block copolymer containing the hydrophobic NFD drug were prepared by solvent evaporation technique. Poly(sebacic anhydride-*co*-PLF68/PLF127) block copolymer (100 mg) was dissolved in dichloromethane (4 mL) followed by adding NFD to the polymer (1:0.1) by the weight ratio and stirred at the ambient temperature (30 °C). The polymer drug solution was added dropwise to 100 mL of 2.5% PVA solution under constant stirring using a mechanical stirrer (IKA Labortechnik, Germany) at the rotation speed of 800 rpm. It was further stirred for about 20–30 min to complete evaporation of DCM and then diluted with distilled water. The microspheres formed were isolated using a tabletop centrifuge (Jouan, MR 23i, France) and redispersed into deionized water, and further lyophilized by a freeze-drier (Jouan, LP3, France) to obtain dry microparticles.

2.4. Drug loading efficiency

*Microsp*heres were dissolved in DCM and the amount of NFD encapsulated was determined by a UV spectrophotometer (Secomam, Anthelie, France) at the λ_{max} value of 238 nm. These data were collected in triplicate, but the average values were used in calculating the % drug loading and encapsulation efficiency. Nifedipine content entrapped into the microspheres was calculated from the weight of the initial drug-loaded microspheres and the amount of drug incorporated using the following equations:

$$\text{actual drug loading (\%)} = \left(\frac{\text{weight of drug in microspheres}}{\text{weight of microspheres}} \right) \times 100 \quad (1)$$

$$\text{drug encapsulation efficiency (DE\%)} = \left(\frac{\text{actual drug loading}}{\text{\%theoretical drug loading}} \right) \times 100 \quad (2)$$

Table 2 displays the results of extent of NFD loading and drug loading efficiency of the microspheres.

2.5. Characterization of polymers

2.5.1. Gel permeation chromatography (GPC)

Molecular weights of the synthesized copolymers were determined by gel permeation chromatography (GPC) (Viscotek, Houston, Texas, USA) attached to the differential refractive index detector (Viscotek, VE 3580) by employing two columns (Viscotek gel, GMHH R-H). Flow rate of the mobile phase (THF) was set to 1 mL/min; polystyrene standards were used for calibration runs. Subsequently, the molecular weight of polyanhydrides was reported as the polystyrene equivalent molecular weight. Results of molecular weight distribution and polydispersity index are shown in Table 1.

Table 1
Compositions and molecular weights of the synthesized polymers

Polymer codes	Monomer weight ratios in copolymers (%)		$\overline{M}_w$	$(\overline{M}_w/\overline{M}_n)$ (PDI)
	Sebacic anhydride (mol%)	Pluronic (mol%)		
PP	100	0	9700	3.5
P681	99	1	21280	2.4
P682	98	2	17350	2.1
P683	97	3	16110	2.0
P1271	99	1	28430	3.2
P1272	98	2	24755	3.0
P1273	97	3	21300	2.8

PDI = polydispersity index.

2.5.2. Nuclear magnetic resonance (NMR)

Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 500 MHz instrument (Varian, Unity INOVA 500NMR spectrometer) using CDCl$_3$ as the solvent and tetramethylsilane as an internal standard. ^{1}H NMR spectra of pure polysebacic anhydride and polyanhydride containing Pluronic F68 are displayed in Fig. 1.

2.5.3. Fourier transform infrared spectra (FTIR)

FTIR spectra of the polymers were taken using a Nicolet Avatar 320 spectrophotometer at 2 cm^{-1} resolutions with 64 scans over the spectral range from 4000 to 400 cm^{-1}. Samples were crushed with KBr to get pellets by applying a pressure of 600 kg/cm^2. FTIR spectra of the pure polyanhydride and polyanhydride containing Pluronic F68 are shown in Fig. 2.

2.5.4. Differential scanning colourimetry (DSC)

DSC thermograms of pure poly(sebacic anhydride) and poly(sebacic anhydride-*co*-Pluronic) were recorded using Rheometric Scientific (Model-DSC SP, UK). DSC curves were recorded between 25 and 400 °C under dry nitrogen atmosphere at a flow rate of 20 mL/min. DSC tracings are displayed in Fig. 3(A) and (B), respectively, for different copolymers.

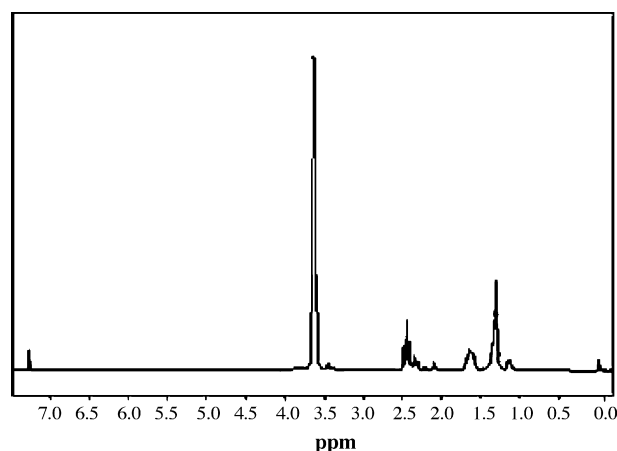Fig. 1. Typical ^{1}H NMR spectrum of poly(sebacicanhydride-*co*-PLF68) block copolymer.
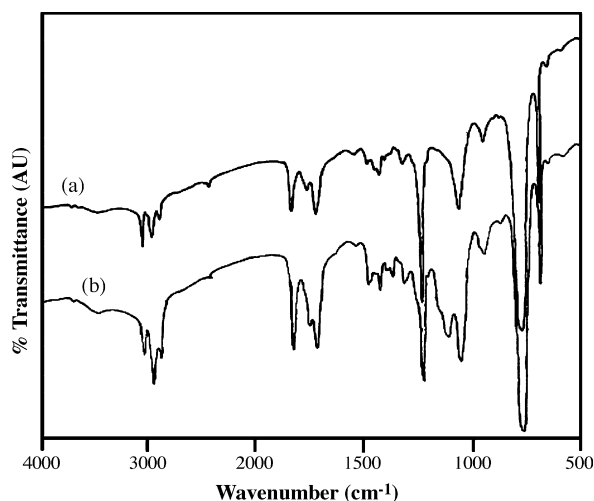
Fig. 2. Typical FTIR spectrum of (a) poly(sebacicanhydride) block copolymer and (b) poly(sebacic anhydride-*co*-PLF68) block copolymer.

2.5.5. X-ray diffraction (XRD)

XRD spectra of pure drug and drug-loaded microspheres are shown in Fig. 4(a) and (b), respectively. Spectra were recorded using an X-ray diffractometer (X-Pert, Philips, UK) and scanning was done in the 2θ angle range of 2–50°. These data were obtained from Shivaji University, Kolhapur, India.

2.5.6. Scanning electron micrograph (SEM)

SEM images of poly(sebacic anhydride-*co*-Pluronic) microspheres were recorded using Leica 400, Cambridge, UK, instrument and are displayed in Fig. 5(a) and (b), respectively, for single microsphere and group of microspheres. These data were obtained from Metallurgy Department, Indian Institute of Science, Bangalore, India.

2.5.7. Particle size analysis

Particle size was measured by a laser light scattering technique (Mastersizer 2000, Malvern, UK). Sizes of the completely dried microspheres of different formulations were measured using the dry sample adopter. The volume-mean diameter (*Vd*) was recorded and these results are given in Table 2.

2.6. In vitro drug release

Weighed amounts of drug-loaded microspheres (10 mg) were placed in 100 mL phosphate buffer of pH 7.4 and 0.1% (w/v)
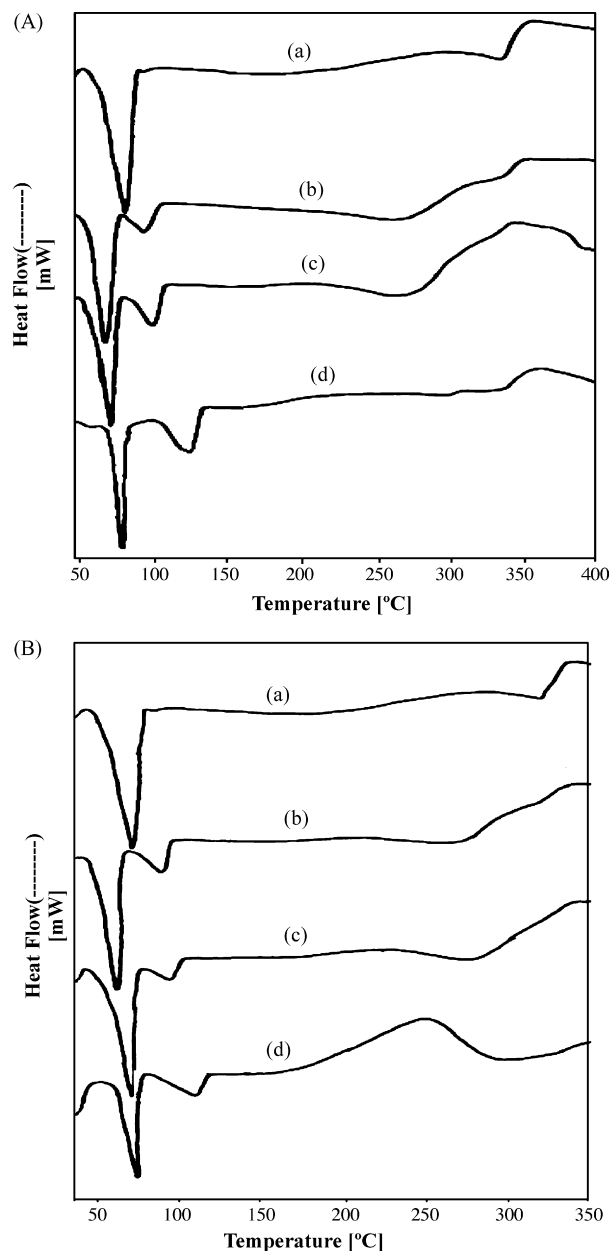

Fig. 3. (A) DSC spectra of (a) pure polysebacicanhydride, (b) poly(sebacic-*co*-1% P68) anhydride, (c) poly(sebacic-*co*-2% P68) anhydride and (d) poly(sebacic-*co*-3% P68) anhydride. (B) DSC thermograms of (a) pure poly(sebacicanhydride), (b) poly(sebacic-*co*-1% P127) anhydride, (c) poly(sebacic-*co*-2% P127) anhydride and (d) poly(sebacic-*co*-3% P127) anhydride.

polysorbate-80 surfactant. The dissolution medium was stirred at 100-rpm speed using the water bath with a shaker (Grant OLS200, Grant Instruments, Cambridge Ltd, UK) and experiments were carried out at 37 °C. Aliquots of dissolution medium (3 mL) were withdrawn and filtered through a 0.45 mm Millipore filter at the predetermined time intervals. After appropriate dilution, drug concentrations were analyzed by UV spectrophotometer at the $\lambda_{max} = 238$ nm. Dissolution medium was maintained at a constant volume by replacing the samples with a fresh dissolution medium.

Table 2
Particle size and % drug encapsulation efficiency of NFD-loaded amphiphilic microspheres at 10 wt.% of constant NFD loading

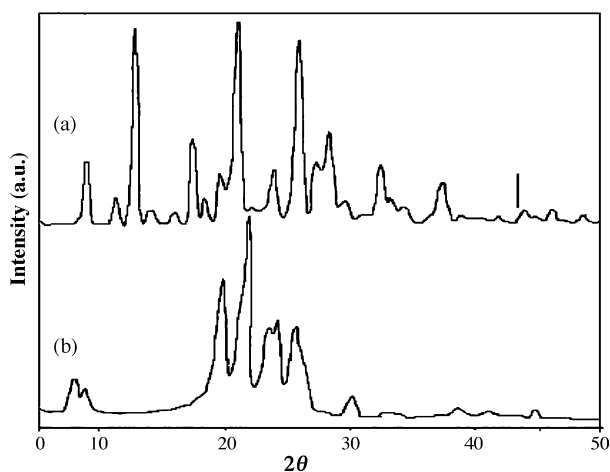| Polymer codes	Microsphere size (μm)	Encapsulation efficiency (%)
PP	10–15	61.5
P681	20	66.9
P682	20–30	79.3
P683	30	87.4
P1271	30	69.0
P1272	30–40	89.6
P1273	40–50	92.6

Fig. 4. XRD spectrum (a) pure nifedipine drug and (b) NFD-loaded poly(sebacic-*co*-Pluronic F68).
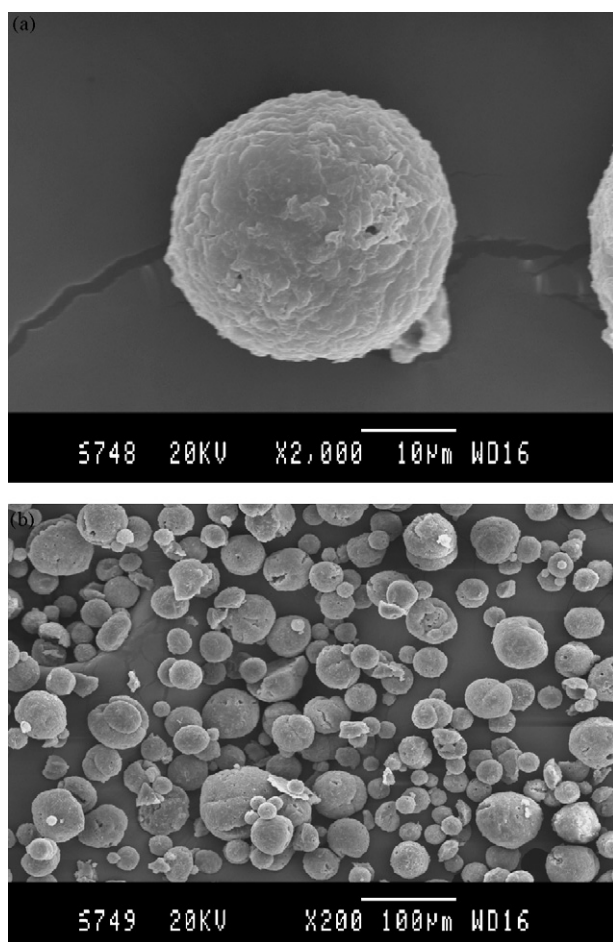

Fig. 5. (a) Scanning electron micrograph of poly(sebacicanhydride-*co*-PLF68) single microsphere. (b) Scanning electron micrograph of poly(sebacicanhydride-*co*-PLF68) group of microsphere.

3. Results and discussion

3.1. Gel permeation chromatography

GPC of the polymers revealed that molecular weight and polydispersity of polyanhydrides decreased with increasing Pluronics content of the prepared polymers (see Table 1). Notice that polydispersity index (PDI) of the polyanhydrides synthesized from Pluronic F68 decreased from 2.4 to 2.0, whereas those prepared with Pluronic F127 decreased from 3.2 to 2.8 with increasing Pluronic content from 1 to 3%. The molecular weight data of pure poly(sebacic anhydride) are in good agreement with the reported data of Zang et al. (2004). No increase in molecular weight of the copolymer was observed with increasing amount of Pluronic content of polyanhydrides; also, PDI values of the synthesized polymers declined as the Pluronic content increased. This could be due to the introduction of Pluronic moiety that might constrain the growth of the polymer chains with higher molecular weights when polymers were prepared by melt-polycondensation reaction. This could also be due to melt condensation of carboxyl anhydride and hydroxyl groups of Pluronic (de-acetic acid reaction), which have higher activation energies than de-acetic anhydride reaction during melt-polycondensation of neat polyanhydrides (Cheng and Chu, 2003).

3.2. Nuclear magnetic resonance (NMR)

^{1}H NMR spectra (Fig. 1) revealed that chemical shift δ observed at 1.3, 1.6, 2.2, and 2.4 ppm are well resolved, which belong to hydrogen atoms of the individual functional groups on poly(sebacic anhydride). However, introducing Pluronics into the polymer would cause another chemical shift for methyl protons of Pluronic block ($-O-CH_2-CH_2-$) and $-(O-CH_2-CH(CH_3)-)$ at $\delta = 3.65$ ppm, which confirms the existence of Pluronics F68 in the polymer chain segments.

3.3. Fourier transform infrared spectra (FTIR)

FTIR spectra of block copolymers show typical double anhydride carbonyl peaks at 1817 and 1745 cm^{-1}, the carboxylic acid peak at 1708 cm^{-1}, and carboxylate (–COO) peak at 1465 cm^{-1} (see Fig. 2). The related absorptions at 952 cm^{-1} (C–O symmetrical structure for the segments containing Pluronic F68) and 1098 cm^{-1} (C–O asymmetrical stretching vibrations for segments containing Pluronic F68) and 1041 cm^{-1} (C–O symmetric stretching vibrations for anhydride segments) are prevalent.

3.4. Differential scanning calorimetry (DSC)

DSC analysis performed on pure polyanhydride and the copolymer are, respectively, presented in Fig. 3(A) and (B). These results were obtained from the first ramp of the thermogram to quantify the best existing morphology of the copolymers. DSC thermograms support the FTIR as well as ^{1}H NMR data, indicating the incorporation of Pluronics into polyan-

hydrides. The melt temperature of pure poly(sebacic anhydride) appeared around 79 °C. In case of poly(sebacic anhydride-*co*-Pluronic), two endotherms were obtained; one for poly(sebacic anhydride) and another for Pluronic segments. The melt temperature of pure poly(sebacic anhydride) segment decreased when Pluronic was incorporated into pure poly(sebacic anhydride). Melt temperatures of the copolymers when incorporated with 1, 2 and 3% of Pluronic F68 were 67.9, 71 and 77.6 °C, respectively. When incorporated with 1, 2 and 3% of Pluronic 127, the melt temperatures were shifted to 68.3, 72.1 and 74.5 °C, respectively. Melting temperatures of the copolymer segments increased with increasing segments of the polymer chains, but these were less than those observed for pure poly(sebacic anhydride).

3.5. X-ray diffraction (XRD)

XRD spectra suggest the nature of NFD present in poly(sebacic anhydride-*co*-Pluronic) microspheres. Crystalline nature is observed from the sharp peaks shown in Fig. 4(a), but there is a decrease in crystallinity when drug is loaded into polymers as shown in Fig. 4(b). XRD spectra reveal the masking of crystalline peaks of NFD after loading into poly(sebacic anhydride). These results are in agreement with the published reports (Cheng and Chu, 2003).

3.6. Particle size analysis

Size distribution of the microspheres was determined using the particle size analyzer and these data are compiled in Table 2. The size of microspheres varied between 10 and 50 μm for different formulations. The increase in size of the microspheres was obtained with an increase in Pluronic content of the copolymers. Comparatively, large size microspheres were obtained in case of poly(sebacic anhydride-*co*-PLF127) polymer microspheres as compared to poly(sebacic anhydride-*co*-PLF68). This is due to the bulk structure of PLF127 as compared to PLF 68.

3.7. Scanning electron micrograph (SEM)

Scanning electron micrograph of the group of microspheres and single microspheres prepared from poly(sebacic anhydride-*co*-Pluronic F68) anhydrides presented in Fig. 5 suggest that microspheres are spherical in nature with smooth surfaces.

3.8. Drug loading efficiency

The amount of NFD encapsulated into the developed poly(sebacic anhydride-*co*-Pluronic) microspheres was calculated using Eq. (2). It was found that drug loading as well as % drug loading efficiency increased with increasing Pluronic concentration of the block copolymer. The % encapsulation efficiency of NFD in pure polyanhydride was lower than observed for the block copolymers. NFD encapsulation efficiency in pure polyanhydride was around 61.5%, whereas efficiencies of 66.9, 79.3 and 87.4%, respectively, were observed for polyanhydrides prepared with 1, 2 and 3% of Pluronic F68. NFD loading efficiencies in poly(sebacic anhydride-*co*-Pluronic F127) polymers increased to 69.0, 89.6, and 92.6%, respectively, with increasing Pluronic F127 contents of the block copolymer from 1 to 3%. This type of increase in NFD loading efficiencies of the microspheres may be due to an increase in PPO segments of the block copolymers, the presence of which would increase the hydrophobic nature of the microspheres. Also, sizes of the microspheres were increased with increasing amounts of Pluronics of the copolymers. For instance, size of the microspheres varied from 10 to 50 μm, depending upon the nature of the copolymer prepared. The size of microspheres followed the same trend as those of % encapsulation efficiency with varying Pluronic contents of the polymers.

3.9. In vitro drug release

In an effort to enhance the release rates of NFD, various types of polymeric matrices have been studied as carriers in the previous literature. For instance, Soppimath and Aminabhavi (2002) used poly(DL-lactide-*co*-glycolide) (PLGA), cellulose acetate (Soppimath et al., 2001a) and ethyl cellulose with cellulose acetate microspheres (Soppimath et al., 2001a,b) to study the CR characteristics of NFD. It was found that release of NFD was extended up to 7 days with PLGA microspheres. The encapsulation efficiency of NFD, which varied between 83 and 98%, was dependent upon the method of preparation of microspheres. It was observed that release of NFD was extended up to 15 h with cellulose acetate hollow floating microspheres (Soppimath et al., 2001a). The release of NFD from the tableted cellulose acetate and ethyl cellulose microspheres were also studied. It was found that faster release rates were observed from cellulose acetate as compared to microspheres of ethyl cellulose (Soppimath et al., 2001b).

In the present investigation, NFD was loaded into poly(sebacic anhydride-*co*-Pluronic) microspheres prepared using different concentrations of Pluronic F68 and F127 with respect to poly(sebacic anhydride) pre-polymer. The *in vitro* release of NFD was investigated in pH 7.4 buffer solution at 37 °C.

The % cumulative release data versus time is displayed in Fig. 6(a) for microspheres prepared using poly(sebacic anhydride). An initial release rate of about 40% was observed within 4 h from the microspheres prepared with plain polyanhydride, probably due to the release of surface adhered NFD particles during drying of microspheres (Cleland et al., 1997; Gabor et al., 1999). The % cumulative release data versus time are compared in Fig. 6(a) and (b), respectively, for microspheres prepared with poly(sebacic anhydride-*co*-Pluronic F68) and poly(sebacic anhydride-*co*-Pluronic F127). From these results, it is obvious that the release of NFD from poly(sebacic anhydride-*co*-Pluronic) microspheres occurs with an initial burst effect, that got minimized with the increasing Pluronic content of the polyanhydride copolymer. After the initial burst effect, subsequent release rates of the drug were found to be very slow. Comparatively, slower release rates were observed from the microspheres prepared with poly(sebacic anhydride-*co*-Pluronic) compared to those prepared from pure poly(sebacic
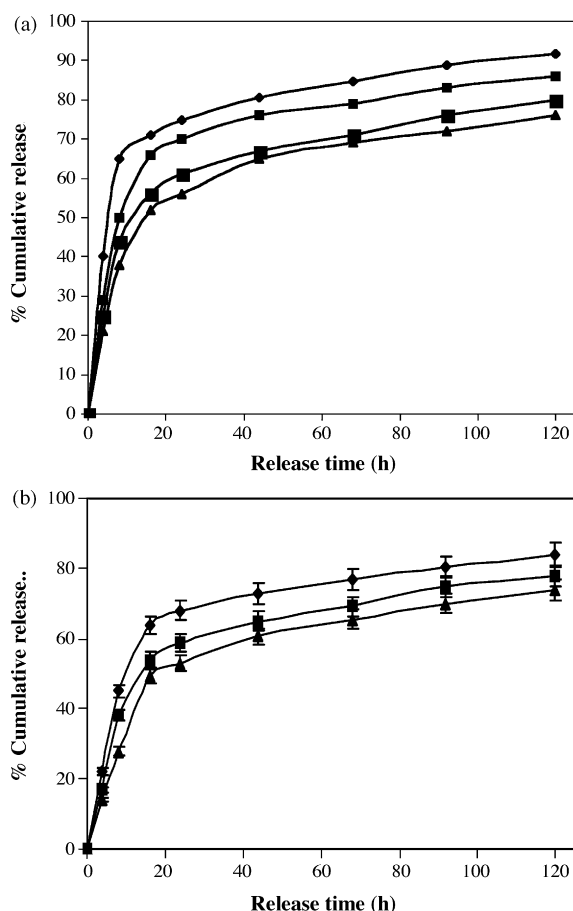
Fig. 6. (a) *In vitro* release profiles of NFD from poly(sebacic anhydride-*co*-PLF68) microspheres: poly(sebacic anhydride) (♦); poly(sebacic anhydride) containing 1% PLF68 (■); poly(sebacic anhydride) containing 2% PLF68 (■) and polysebacic anhydride containing 3% PLF68 (▲). (b) *In vitro* release profiles of NFD from poly(sebacicanhydride-*co*-PLF127) microspheres: poly(sebacic anhydride) containing 1% PLF127 (♦); poly(sebacic anhydride) containing 2% PLF127 (■) and poly(sebacic anhydride) containing 3% PLF127 (▲).

anhydride) polymer. Notice that significant differences in release rates were not observed between the microspheres prepared from poly(sebacic anhydride-*co*-Pluronic F68) and poly(sebacic anhydride-*co*-Pluronic F127). The % cumulative release data observed for 4 h dissolution time were 33, 28 and 22%, while the amounts of drug released at the end of 5 days were 86, 80 and 76%, respectively, for polyanhydrides prepared by taking 1, 2 and 3% of Pluronic F68; notice that these formulations are coded, respectively, as P681, P682 and P683 (see also data in Table 1 and Fig. 6(a)).

The % cumulative release data observed at the end of 4 h of dissolution time were 31, 24 and 18%, while the extent of NFD released after 5 days was 84, 78, and 74%, respectively, for polyanhydrides prepared with 1, 2 and 3% of Pluronic F127, which are coded as P1271, P1272 and P1273 (see data in Table 1 and Fig. 6(b)). The % of PPO is higher in Pluronic F127 (i.e., ≈33%) when compared to PPO in Pluronic F68 (i.e., ≈20%) due to which Pluronic F127 becomes more hydrophobic above the ambient temperature. Also, molecular weights of the block copolymers and sizes of the microspheres were higher than pure polysebacic anhydride.

Table 3
Release kinetics data[a] for poly(sebacicanhydride-*co*-PLF68/PLF127) drug-loaded microspheres

Polymer codes	Higuchi equation		Power law equation	
	K	R^2	n	R^2
PP	0.035	0.98	0.13	0.99
P681	0.044	0.87	0.18	0.92
P682	0.050	0.94	0.21	0.97
P683	0.055	0.92	0.24	0.95
P1271	0.048	0.85	0.20	0.88
P1272	0.056	0.91	0.24	0.93
P1273	0.066	0.87	0.32	0.88

[a]Results were estimated at 95% confidence limit using the statistical error analysis package.

3.10. Drug release kinetics

In order to quantify the drug release rates through polymeric matrices, we have analyzed the release kinetics data using the diffusion equation: $M_t/M_\infty = Kt^{0.5}$ proposed by Higuchi (Roseman and Higuchi, 1970) to evaluate the values of K, the kinetic rate constant, which is independent of geometrical and structural properties of the polymer. Here, M_t is the amount of drug released at time, t and M_∞ is the amount of drug released after (longer time) infinite time. Ritger and Peppas (1987) proposed the power law equation: $M_t/M_\infty = Kt^n$ to analyze the kinetics of drug release rates through polymeric matrices. The values of exponent, n, have been calculated by the least squares method from the slope of the plot of $\ln(M_t/M_\infty)$ versus $\ln t$. These results are presented in Table 3. In general, if $n = 0.5$, the release follows Fickian trends and if $0.5 < n < 1$, release follows an anomalous transport. In the present work, analysis of release kinetics data showed that values of $n < 0.5$ indicate the anomalous nature of NFD release from the matrices.

4. Conclusions

In recent years, biodegradable polymers are found to be useful in drug delivery applications. A class of polymers termed polyanhydrides for biomedical applications has received considerable interest in recent decades. The greatest advantage of such polymers is that their degradation products are highly biocompatible. Realizing, this we have synthesized novel polyanhydrides by invoking different amounts of pre-poly(sebacic anhydride) with respect to Pluronics to form block copolymers, from which microspheres were prepared by the solvent evaporation technique. Nifedipine, chosen as a model antihypertensive drug, was encapsulated into the microspheres. A decrease in % cumulative release rate with an initial burst effect was observed by increasing the concentration of Pluronic content in the polyanhydrides. Also, the % drug loading and % encapsulation efficiency have increased with increasing Pluronic content of the polyanhydride, indicating the effect of hydrophobic segments present in Pluronics on the release rates of NFD through the matrices.

Acknowledgement

References

Alexandridis, P., Hatton, T.A., 1995. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) structure, dynamics, and modeling. Colloid Surf. A. 96, 1.

Cheng, K.C., Chu, I.M., 2003. Crystalline and dynamic mechanical behaviors of synthesized poly(sebacic anhydride-*co*-ethylene glycol). Biomaterials 24, 47–54.

Cleland, J.L., Lim, A., Barron, L., Duenas, E.T., Powell, M.F., 1997. Development of a single-shot subunit vaccine for HIV-1. Part 4. Optimizing microencapsulation and pulsatile release of MN rgp120 from biodegradable microspheres. J. Control Release 47, 135–150.

Chen, X., McCarthy, S.P., Gross, R.A., 1997. Synthesis and characterization on [L]-lactide-ethylene oxide multiblock copolymers. Macromolecules 30, 4295–4301.

Domb, A.J., Langer, R., 1987. Preparation of high-molecular weight polyanhydrides. J. Poly. Sci. Part A Polym. Chem. 25, 3373–3386.

Gabor, F., Ertal, B., Wirth, M., Mallinger, R., 1999. Ketoprofen-poly(D,L-lactic-co-glycolic acid) microspheres: influence of manufacturing parameters and type of polymer on the release characteristics. J. Microencapsulation 16, 1–12.

Gan, Z., Jiang, B., Zhangn, J., 1996. Poly(ε-caprolactone)/poly(ethylene oxide) diblock copolymer. I. Isothermal crystallization and melting behavior. J. Appl. Polym. Sci. 59, 961–967.

Hollinger, J.O., 1995. Biomedical Application of Synthetic Biodegradable Polymers. CRC Press, Boca Raton, FL, USA.

Hanes, J., Chiba, M., Langer, R., 1996. Synthesis and characterization of degradable anhydride-*co*-imide terpolymers containing trimellitylimido-L-tyrosine: novel polymers for drug delivery. Macromolecules 29, 5279–5287.

Huh, K.M., Bae, Y.H., 1999. Synthesis and characterization of poly(ethylene glycol)/poly(L-lactic acid) alternating multiblock copolymers. Polymer 40, 6147–6155.

Jiang, H.L., Zhu, K.J., 1999. Preparation, characterization and degradation characteristics of polyanhydrides containing poly(ethylene glycol). Polym. Int. 48, 47–52.

Kim, K.S., Chung, S., Chin, I.J., Kim, M.N., Yoon, J.S., 1999. Crystallization behavior of biodegradable amphiphilic poly(ethylene glycol)-poly(L-lactide) block copolymers. J. Appl. Polym. Sci. 72, 341–348.

Kim, S.Y., Ha, J.C., Lee, Y.M., 2000. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)/poly(ε-caprolactone) (PCL) amphiphilic block copolymeric nanospheres. II. Thermo-responsive drug release behaviors. J. Control Release 65, 345–358.

Leong, K.W., Simonte, V., Langer, R., 1987. Synthesis of polyanhydrides: meltpolycondensation, dehydrochlorination, and dehydrative coupling. Macromolecules 20, 705–712.

Peppas, N.A., Langer, R., 1993. Advances in Polymer Science: Biopolymers I. Springer, Heidelberg, p. 107.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release. I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Control Release 5, 23–36.

Roseman, T.J., Higuchi, W.I., 1970. Release of medroxyprogesterone acetate from a silicone polymer. J. Pharm. Sci. 59, 353–357.

Rosler, A., Vandermeulen, G.W.M., Klok, H.A., 2001. Advanced drug delivery devices via self-assembly of amphiphilic block copolymers. Adv. Drug Deliv. Rev. 53, 95–108.

Soppimath, K.S., Aminabhavi, T.M., 2002. Ethyl acetate as a dispersing solvent in the production of poly(DL-lactide-*co*-glycolide) microspheres: effect of process parameters and polymer type. J. Microencapsul. 19, 281–292.

Soppimath, K.S., Kulkarni, A.R., Aminabhavi, T.M., 2001a. Development of hollow microspheres as floating controlled release systems for cardiovascular drugs: preparation and release characteristics. Drug Dev. Ind. Pharm. 27, 507–517.

Soppimath, K.S., Kulkarni, A.R., Aminabhavi, T.M., 2001b. Encapsulation of antihypertensive drugs in cellulose based matrix microspheres: characterization and release kinetics of microspheres and tableted microspheres. J. Microencapsul. 18, 397–409.

Uhrich, K.E., Gupta, A., Thomas, T.T., Laurencin, C.T., Langer, R., 1995. Synthesis and characterization of degradable poly(anhydride-co-imides) and their blends with polylactide. Macromolecules 28, 2184–2193.

Zang, Z.Q., Su, X.M., He, H.P., Qu, F.Q., 2004. Synthesis, characterization and degradation of poly(anhydride-*co*-amide)s and their blends with polylactide. J. Polym. Sci. Part A: Polym. Chem. 42, 4311–4317.