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Effect of different ratios of high and low molecular weight PLGA blend on the characteristics of pentamidine microcapsules

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Abstract

Two different PLGA samples (Resomer 502 and Resomer 506), either alone or in combinations, were used to prepare microcapsules. Microcapsules were prepared using a double emulsion solvent evaporation technique. The efficiency of encapsulation increased significantly when a mixture of 1 part Resomer 506 and 7 parts Resomer 502 was used to prepare the microcapsules. The efficiency of encapsulation of this batch was 23.7%, whereas the efficiency of encapsulations was only 13.9 and 9.8%, respectively, when the microcapsules were prepared with 100% Resomer 502 or 100% Resomer 506. In contrast, irrespective of the relative ratio of Resomer 502/Resomer 506, the median particle size of the microcapsules showed similar distribution pattern with the median size lies between 49 and 83 μm. The glass transition temperature (T_g) decreased significantly (44.6–25.5 °C) as the amount of Resomer 502 was increased in the formulation. The presence of Resomer 502 at lower concentration, along with Resomer 506, initially reduced the "burst effect." However, incorporation of a higher amount of Resomer 502 increased the "burst effect." Drug release from these microcapsules continued over 80 days. In conclusion, efficiency of encapsulation increased significantly when Resomer 506 was mixed with Resomer 502 at a ratio of 1:7. Blending of Resomer 502 with Resomer 506 reduced the glass transition temperature, which resulted in higher amount of drug release throughout the dissolution study.

Keywords: PLGA; Pentamidine; Formulation; Microcapsules; Solvent evaporation; Dissolution

1. Introduction

Microencapsulation of therapeutically active compounds in envelopes of biodegradable polymer has become a well-established technology for controlled release drug delivery (Lewis, 1990). Controlled release microcapsules of numerous therapeutic agents have been developed during the last three decades and several of these formulations have received worldwide marketing approval (Ogawa et al., 1989; Okada et al., 1991; Okada, 1997). Most of these formulations are developed using aliphatic polyesters based on lactic acid and glycolic acid, poly(lactide-co-glycolide) (PLGA). These copolymers have attracted much attention because the biodegradation rate of the copolymer is easily controlled by altering its composition. As for example, biodegradation rate of lactide/glycolide 50/50 (PLGA 50:50) is approximately 2 months,

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whereas, the biodegradation rate of lactide/glycolide 85/15 (PLGA 85:15) is approximately 5 months (Lewis, 1990).

Besides composition, biodegradation rate also depends on several formulation and processing factors (Mi et al., 2002; Freier et al., 2002; Birnbaum and Brannon-Peppas, 2003). Biodegradation rate controls the drug release from a PLGA microcapsule formulation towards the latter part of the dissolution, whereas, the initial drug release from the formulation is governed by diffusion of drug through the polymer (O'Donnell and McGinity, 1997). Both biodegradation and diffusion also depend on the molecular weight of PLGA (Cha and Pitt, 1990). Blending of different molecular weight PLGA also provides the opportunity for a more controlled drug release (Ravivarapu et al., 2000a; Kenawy et al., 2002), initially and throughout the dissolution process (Shen et al., 2000; Wolfgang and Monika, 2002). Several investigators have also reported advantages of blending PLGA and/or other biodegradable polymers (Huatan et al., 1995; Yeh et al., 1996; Jiang and Schwendeman, 2001; Ambrosio et al., 2002; Chandy et al., 2002; Tsuji, 2003).

The primary objective of this study was to evaluate the effect of blending of low molecular weight (M_w) and high M_w PLGA on the characteristics of microcapsules prepared by double emulsion solvent evaporation technique. Pentamidine was used in this study as a model drug.

2. Materials and methods

2.1. Materials

The high M_w copolymer poly(D,L-lactic/glycolic acid), PLGA 50:50 (RG 506; inherent viscosity 0.8 dl/g; M_w 100,000) and low M_w copolymer poly(D,L-lactic/glycolic acid), PLGA 50:50 (RG 502; inherent viscosity 0.2 dl/g; M_w 14,000) were obtained from Boehringer Ingelheim (Germany). The surfactant L-α phosphatidylcholine was obtained from Avanti Polar-lipids, Inc. (Albaster, AL, USA). Pentamidine, polyvinyl alcohol (PVA; M_w 30,000–70,000; 98–99% hydrolyzed), and dichloromethane (spectrophotometric grade), were obtained from Sigma Chemical Co. (St. Louis, MO, USA).

Table 1
Description of formulations

Formulation	Amount of PLGA (g) in 5 ml DCM		Amount of pentamidine (mg)
	RG 506	RG 502	
A	1.00	–	100
B	0.75	0.75	150
C	0.50	1.00	150
D	0.50	1.25	175
E	0.25	1.50	175
F	0.25	1.75	200
G	–	2.50	250

Relative proportion of pentamidine/PLGA was maintained constant at 1:10.

2.2. Experimental methods

Seven different formulations were prepared using two different PLGA samples (Resomer 502 and Resomer 506), either alone or in combinations (as listed in Table 1). Microcapsules were prepared by double emulsion solvent evaporation technique. Following the preparation, the freeze-dried microcapsules were sieved using a 425 μm screen to remove large agglomerated particles. The samples were analyzed for efficiency of encapsulation, particle size distribution, thermal characterization, weight loss and in vitro drug release. The relative proportion of the amount of drug and total amount of PLGA was maintained constant.

2.3. Viscosity of PLGA solutions

A specific amount of PLGA or a mixture of PLGA was dissolved in 5 ml of dichloromethane. The viscosity of the polymer solution was measured by a Brookfield Synchro Lectric Viscometer (Brookfield Engineering Laboratories, Stoughton, MA, USA) at room temperature, using a number 4 spindle and a rpm setting of 20. The viscosity was calculated in centipoise (cP) by measuring the force to turn the spindle in the solution and using the standard Brookfield Factor Finder chart. Each measurement was done in triplicate.

2.4. Preparation of microcapsules

Microcapsules were prepared using double emulsion solvent evaporation technique (O'Donnell and McGinity, 1997). Seven formulations, labeled A–G,

were prepared by dissolving a specific amount of pentamidine powder in 1 ml of deionized water followed by emulsification in 5 ml of dichloromethane containing a specific amount of PLGA (Table 1). The polymer solution was previously mixed with 250 μl of lipophilic surfactant L-α-phosphatidylcholine in chloroform (8 mg/ml). The emulsification was carried out by sonication at output 4 (50 W) for 30 s (ultrasonic probe, Sonic & Materials Inc., Danbury, CT, USA). The resulting emulsion was further emulsified in 2 ml of an aqueous solution of polyvinyl alcohol (PVA; 1%) by vortexing for 15 s and then diluted in 100 ml of PVA aqueous solution (0.3%). The mixture was stirred magnetically at 500 rpm for 3 h at room temperature to allow complete evaporation of the solvent. Pentamidine microcapsules were finally collected by centrifugation at 3000 rpm and washed four times with deionized water to remove any residual PVA on the surface of the microcapsules. The microcapsules were later freeze-dried ($-70\,^{\circ}C$; 6×10^{-4} mbar) (Labconco, Kansas City, KS, USA) to obtain a free-flowing powder. Each formulation was prepared in triplicate.

2.5. Particle size and morphology

Particle size and distribution was determined by a Mastersizer 2000 laser scattering device (Malvern Instruments Ltd., Malvern, UK). This technique measures the size of particles dispersed in a medium by the scattering pattern of a laser light shown through the medium. The size calculations assume the presence of spherical particles. The samples were analyzed in a water medium and the Frauenhofer method was utilized to calculate the size distributions. For each sample, a background run of deionized water was performed. A sample of microcapsules (5 mg) was added to the deionized water in a small volume sample dispersion unit. After subtraction of the background, the particle size distribution calculation was performed. Each measurement was performed in triplicate.

The surface and internal morphology of the microcapsules were examined by scanning electron microscopy (SEM) (Hitachi S570, Gaithersburg, MD, USA), fitted with an energy dispersive X-ray analyzer (EDXA). Samples for SEM were mounted on metal stubs and coated with gold to a thickness of 200–500 Å.

2.6. Thermal analysis

Differential scanning calorimetry of pentamidine, RG 502, RG 506, and pentamidine-loaded microcapsules (Formulations A–G) was performed using a DSC 2920 (TA Instruments, New Castle, DE, USA) in order to characterize their physical state after encapsulation. About 5 mg of a sample was weighed, crimped into an aluminum pan and analyzed at a scanning rate of $3\,^{\circ}C$/min. The glass transition temperature (T_g) was calculated using TA universal analysis software by extrapolating the linear portion of the thermograms above and below the glass transition point and determining the midpoint.

2.7. Determination of total content

For each formulation, a 30 mg sample was dissolved in 1 ml of dichloromethane. Forty milliliters of 0.15% Tween 20 was added to the solution followed by ultracentrifugation (35,000 rpm at $15\,^{\circ}C$) to completely separate the precipitated copolymer. The efficiency of extraction and recovery of pentamidine was measured independently with five different samples. The efficiency of extraction was at least 99%.

2.8. Analysis

The amount of pentamidine in each sample was determined by measuring the absorbance spectrophotometrically (Beckman DU 640, Fullerton, CA) at 262 nm and intrapolating the data to the pentamidine standard curve. Each experiment was performed in triplicate.

2.9. Mass loss study

In an effort to monitor the mass loss or degradation of the microcapsules, fifteen samples from each of the seven formulations (A–G), of 20 mg each were weighed individually, and each sample was placed in a 50 ml polypropylene tube and incubated in 40 ml of phosphate buffer (pH 7.4) with constant shaking (20 rpm) at $37\,^{\circ}C$. At each of the preset sampling time, three samples were filtered through Millipore filter (0.2 μm) and washed with 15 ml deionized water. Each of the filtered samples was weighed accurately after drying.

2.10. In vitro dissolution studies

For each formulation, a 20 mg sample of the microcapsules was transferred in a 5 cm long dialysis tube (5.7 mm diameter; M_w cut off 15,000) (Spectrum Laboratories, Rancho Dominiguez, CA). The tube was filled with 1.5 ml of phosphate buffer (pH 7.4) and sealed. The sealed tube was immersed in a polypropylene tube containing 40 ml of phosphate buffer as the dissolution medium. The polypropylene tubes were incubated in a water bath at 37 °C with constant shaking at 20 rpm. The total amount of the dissolution medium (40 ml) was replaced with fresh phosphate buffer at preset time intervals. The amount of pentamidine in the dissolution medium was analyzed spetrophotometrically at 262 nm. After completion of the dissolution study, any residue of microcapsules in the dialysis tube was removed and analyzed for the presence of residual pentamidine. Dissolution studies of each formulation were repeated three times.

2.11. Curve fitting

Curve fitting was performed using SigmaPlot graphic software package, version 7.0 (SPSS Inc., Chicago, IL, USA). The dissolution data obtained between 5 h and 35 days were fitted to the equation and the best fit parameters (k and n) were calculated.

2.12. Statistical analysis

The efficiency of encapsulation of pentamidine, amount of drug released from the different formulations of microcapsules during the in vitro study, and percent weight remaining at different time intervals were compared by Proc GLM using SAS software package. In the presence of significant difference, a comparison of the pairwise means was performed using Student–Newman–Keul's (SNK) multiple range test. A P value of <0.05 was considered as evidence of a significant difference.

3. Results and discussion

The double emulsion solvent evaporation technique is one of the most commonly used methods for microencapsulation of drugs. These microcapsules are generally smooth, spherical and provide sustained drug release. However, the properties of these microcapsules are greatly influenced by the physicochemical characteristics of the drug, the polymer, the organic solvent used in their preparation, and the emulsification process (Alex and Bodmeier, 1990). Aqueous solubility of a drug is one of the most important physicochemical characteristics, which influences the efficiency of encapsulation in PLGA. Efficiency of encapsulation of water soluble drug is often low (Mandal, 1999) and several attempts have, therefore, been made to increase the efficiency of encapsulation by changing processing parameters such as inner aqueous phase/polymer phase volume ratio and the polymer phase viscosity (O'Donnell and McGinity, 1997; Pean et al., 1998; Ravivarapu et al., 2000b). In the present study, an attempt was made to improve the efficiency of encapsulation of a model water soluble drug, pentamidine, by blending a low M_w (RG 502) and a high M_w (RG 506) PLGA. Besides the efficiency of encapsulation, the effect of blending was also measured by evaluating the particle size distribution, particle morphology, DSC thermograms, dissolution, and weight loss.

3.1. Particle size and morphology

The results of the particle size analysis are listed in Table 2. The sizes of the microcapsules were not significantly different from one formulation to the other. The median particle size, based on vol.% of the microcapsules, from different batches was between 49 and 83 μm. The particles were all smaller than 165 μm. The distribution of particles within each formulation

Table 2
Effect of PLGA blending on the particle size and glass transition temperature (T_g)

Formulation	Median size (μm)	80% confidence (μm)	T_g (°C)
A	69	37–124	46.05
B	49	23–90	44.07
C	70	35–131	37.59
D	68	34–127	35.36
E	70	31–141	35.48
F	83	32–163	35.39
G	66	24–152	25.44

T_g for RG 506: 42.17 °C and RG 502: 34.95 °C.

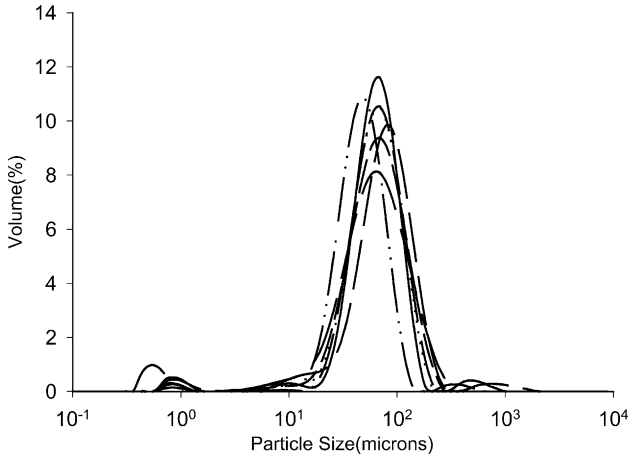

Fig. 1. Particle size distribution of the microcapsules (Formulations A–G). (A) ———; (B) — —; (C) — — —; (D) - - - -; (E) ……; (F) —·—·—; (G) —··—··—.

showed similar distribution pattern (Fig. 1). In general, blending of PLGA did not influence the size and distribution of microcapsules.

Fig. 2 shows the SEM pictures of the microcapsules. The shape of the microcapsules from different formulations was spherical but the surface morphology was different. The surface of the microcapsules containing only the high M_w PLGA (RG 506) appeared to be rugged and porous. However, incorporation of low M_w PLGA (RG 502) reduced the ruggedness. The microcapsules containing 1:2.5 or higher proportion of low M_w PLGA appeared to be smooth and spherical with relatively fewer pores. During the microencapsulation of drugs using solvent evaporation technique (w/o/w), the polymers precipitate on the surface of the liquid emulsion followed by evaporation and/or extraction of the organic solvent. In the present study, the PLGA solution precipitated on the liquid droplets and produced a thin coating due to evaporation of dichloromethane. One would expect a smooth surface when the viscosity of the solution is relatively low and facilitates uniform distribution throughout the surface. In our study, the viscosities of the first three formulations (A–C) were 740 cP or higher, which made the uniform spreading difficult and resulted in a rugged surface. The presence of relatively larger pores in these three formulations also indicates a rapid evaporation of dichloromethane. A cross-sectional view of the microcapsules from different formulations was studied and no significant differences were observed. The difference in internal morphology, observed between the microcapsules from a particular formulation was comparable to the difference observed between the microcapsules from different formulations. Fig. 2(H) shows the internal morphology of Formulation F. This SEM micrograph revealed a porous internal morphology including a relatively large pore near the center of the microcapsule. The porous internal structure is the characteristic of in-water solvent evaporation method. During the polymer precipitation, the organic solvent evaporates and the aqueous phase containing the drug traps into the matrix. Once the microcapsules are dried, the aqueous pocket becomes a pore. During the process of polymer precipitation, more aqueous phase from the external environment diffuses in and results in a larger pore. The relatively larger pore inside the matrix may also result from the coalescence of the aqueous droplets inside the matrix.

3.2. Thermal analysis

DSC thermograms in Fig. 3 show that the characteristic peak for the melting of pentamidine at 192 °C was absent in the microcapsules with less than 14% efficiency of encapsulation, and started to appear in samples with higher drug loading. In the process of preparation of microcapsules, the polymer is loaded with drug in solution. Upon evaporation of the solvent, the drug can either crystallize or remain in a dissolved state in the polymer. If the drug remains in

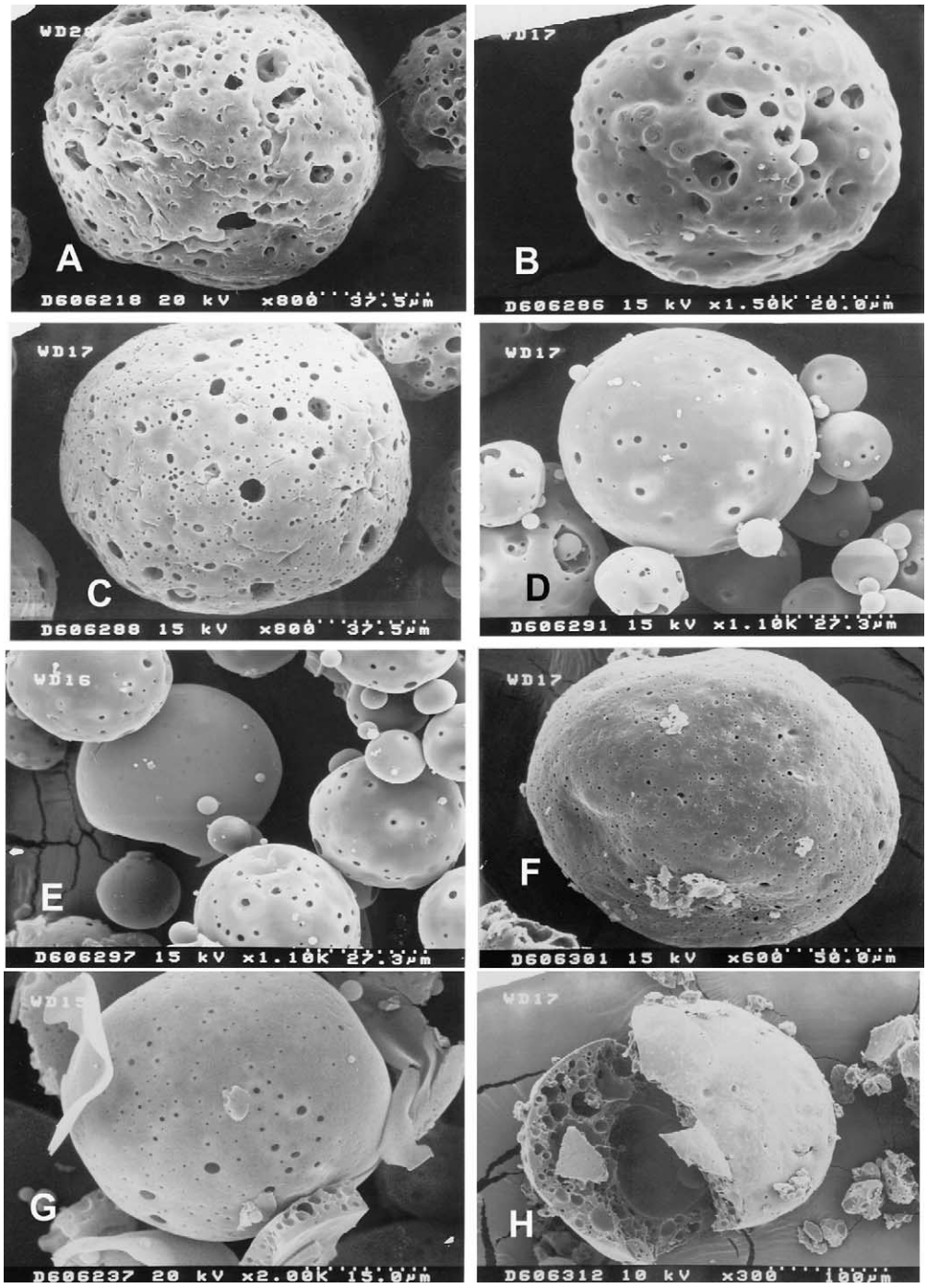

Fig. 2. Typical SEM photographs of the microcapsules. Formulations A–G; (H) cross-sectional view of the microcapsules (Formulation F).

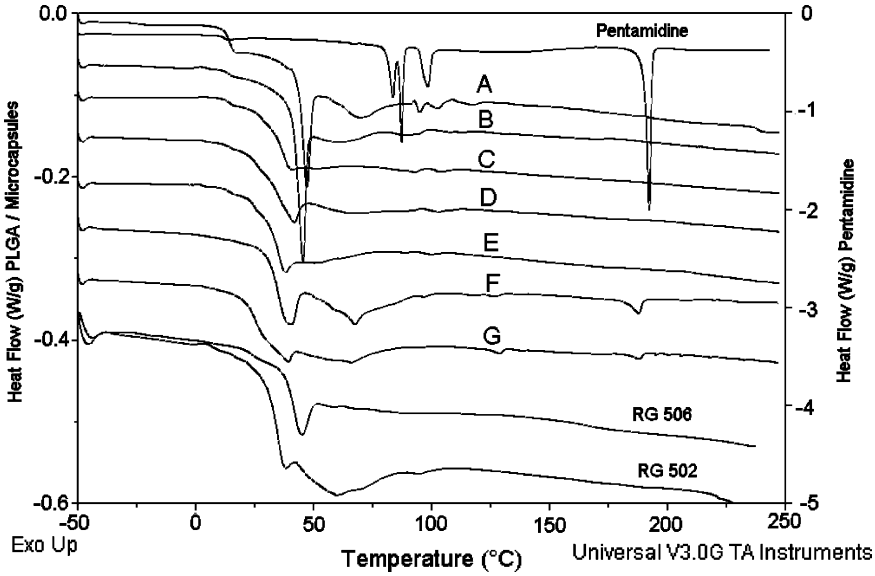

Fig. 3. DSC thermograms of pentamidine: Formulations A–G, Resomer 502, and Resomer 506.

a dissolved state in the polymer, the peak for melting of the drug will be absent. This appears to be the case for the microcapsules with efficiency of encapsulation less than 14%. If the drug crystallizes during the preparation of the microcapsules, the melting peak of the drug will appear in the DSC thermogram of the microcapsules. This is observed in Formulations F and G. The smaller melting peak observed in these microcapsules can be explained as follows: when the efficiency of encapsulation is 14% or higher, the polymer becomes saturated with the drug, and the remainder of the drug crystallizes out. This is further confirmed by the relative size of the peaks in Formulations F and G. Formulation F, which has a higher efficiency of encapsulation, shows also a larger peak for the melting of pentamidine. There was a change in the glass transition temperature of PLGA in the microcapsules compared to the pure PLGA (RG 506: 42 °C; RG 502: 35 °C). The T_g for Formulation A, which contains only the high M_w PLGA increased slightly compared with the pure PLGA. On the other hand, the processing conditions and excipients drastically reduced the T_g for the Formulation G, which contains only the low M_w PLGA. Blending of PLGA also shifted the T_g of the formulations towards the T_g of the low M_w PLGA.

3.3. Efficiency of encapsulation

Efficiency of encapsulation of pentamidine was determined by measuring the total amount of pentamidine present in each 30 mg sample (i.e. core loading experimental), and comparing this value with the expected amount of pentamidine in each of the samples based on the drug loading during the preparation (i.e. core loading theoretical). Blending of PLGA showed a significant ($P < 0.05$) effect on the efficiency of encapsulation. The efficiency of encapsulation varied from 7 to 24%. The sample prepared with a 20% solution of RG 506 PLGA in DCM showed the highest viscosity (900 cP). The efficiency of encapsulation in these microcapsules was 9.8% (Formulation A). Blending of RG 502 with RG 506 reduced the overall viscosity of the PLGA solutions and also the efficiency of encapsulation (but the difference was not statistically significant) until the total PLGA concentration increased to 40% and the RG 506:RG 502 ratio to 1:7 (Formulation F). The efficiency of encapsulation of this Formulation F was 23.7%. Formulation G prepared with only low M_w PLGA (50% solution of RG 502 in DCM) showed the lowest viscosity (100 cP). The efficiency of encapsulation of this batch was also significantly reduced ($P < 0.05$)

Table 3
Effect of PLGA blending on the efficiency of encapsulation

Formulation	RG 506:RG 502 (ratio)	Efficiency of encapsulation (%) (EE) (mean ± S.D.)	Results of SNK[a]	Results of regression model, $EE = C \times \eta$			
				PLGA concentration in DCM (%) (C)	*P* value	Viscosity in cP (η)	*P* value
A	1:0	9.8 ± 0.8	F > G = A = C = E = D = B	20	<0.0001	900	0.218
B	1:1	6.8 ± 0.4		30		740	
C	1:2	8.6 ± 1.3		30		760	
D	1:2.5	6.9 ± 0.9		35		520	
E	1:6	7.9 ± 1.0		35		150	
F	1:7	23.7 ± 2.7		40		200	
G	0:1	13.9 ± 1.4		45		100	

[a] Student–Newman–Keul's multiple range test.

compared with Formulation F. In general, blending of PLGA showed a significant effect on the efficiency of encapsulation. The total concentration of PLGA in these formulations increased from 20 to 50%, but the blending of low M_w PLGA reduced the viscosity of the samples from 900 to 150 cP. In an effort to identify the factor(s) responsible for this change in efficiency of encapsulation, a linear regression analysis was performed using the following model (Eq. (1)):

$$EE = C \times \eta \quad (1)$$

where EE is the efficiency of encapsulation, C is the concentration of PLGA, and η is the viscosity of the solution. The results of the regression analysis are listed in Table 3. Apparently, the effect of viscosity was not statistically significant ($P > 0.05$), whereas, the PLGA concentration showed a significant effect ($P < 0.05$) on the efficiency of encapsulation. However, the microcapsules prepared with 50% PLGA (Formulation G) showed significantly lower efficiency of encapsulation (13.9%) compared with the microcapsules prepared with 40% PLGA (23.7%, Formulation F). This contradiction may be due to a change in the glass transition temperature (T_g) when the microcapsules were prepared with only the low M_w PLGA. The T_g for this formulation was 25.44 °C, which was significantly lower than the other formulations. Several investigators have reported similar observations concluding that efficiency of encapsulation of water soluble drugs during solvent evaporation method is inversely related with the T_g (Chen et al., 1994; Goedemoed et al., 1991).

3.4. Mass loss study

Fig. 4 shows the weight percentage remaining at a specific sampling time. Mass loss during a specified sampling period was determined by measuring the residual weight using the following Eq. (2):

$$\text{Mass loss (\%)} = \frac{\text{initial weight} - \text{residual weight}}{\text{initial weight}} \times 100 \quad (2)$$

The initial mass loss during the first two weeks was between 17 and 23% for the various formulations. However, the differences between the various

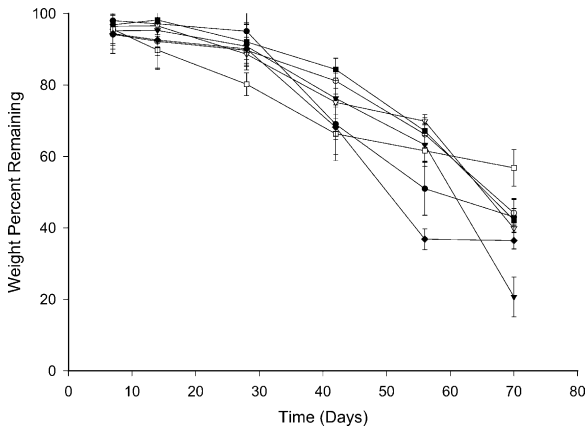

Fig. 4. Degradation profiles of the microcapsules over time: Formulation A (●); Formulation B (○); Formulation C (▼); Formulation D (▽); Formulation E (■); Formulation F (□); Formulation G (◆).

formulations were not statistically significant. The differences in mass loss at the end of four or six weeks were also not statistically significant ($P < 0.05$), despite some differences among formulations. Formulation F, which contains the highest amount of pentamidine, showed the minimum mass loss at the end of eight weeks. This formulation also contains the highest amount of low M_w PLGA (1:7) compared with the other four formulations (B–E) containing PLGA blends. Thus, blending of PLGA did not significantly change the microcapsules' weight loss during our eight weeks study. Otherwise, we may have failed to see the change because of relatively high standard deviation associated with these experiments due to such a small sample size.

3.5. In vitro dissolution studies

Fig. 5 shows the dissolution profiles of pentamidine from the microcapsules up to 80 days. The burst release was measured by determining the initial drug release at 30 min. The last two formulations (F and G) showed significantly high ($P < 0.05$) burst release compared with the other formulations (Table 4). These two formulations showed the highest amount of the incorporated drug, and thus may have a higher amount of pentamidine near the surface. These two formulations also contained a larger amount of polymer. The presence of a larger amount of polymer was expected to reduce the burst release by forming a dense polymer coating on the surface of the microcapsules. However, these formulations contain either a very low amount or none at all, of the high M_w PLGA. Thus, use of low M_w PLGA may have increased the diffusion of pentamidine through the microcapsules' wall. Fifty percent of the drug from these two formulations was released within 1.8 and 13.3 h, respectively. Formulation A showed 50% drug release within 6 days, whereas blending low M_w PLGA, as low as 1:2, reduced the rate of drug release significantly ($P < 0.05$) with 50% drug release shifted to 23 days (Formulation C). Formulation D showed the slowest drug release with fifty percent release at 32 days. Since Formulation A contains only the high M_w PLGA, one would expect slower release from these microcapsules, but other formulations contain an overall higher amount of total PLGA. Overall, higher amounts of total PLGA may have produced a denser polymer wall and reduced drug dissolution from these formulations, except Formulations F and G. The faster drug release from the last two formulations, F and G, may be due to a larger initial burst release which

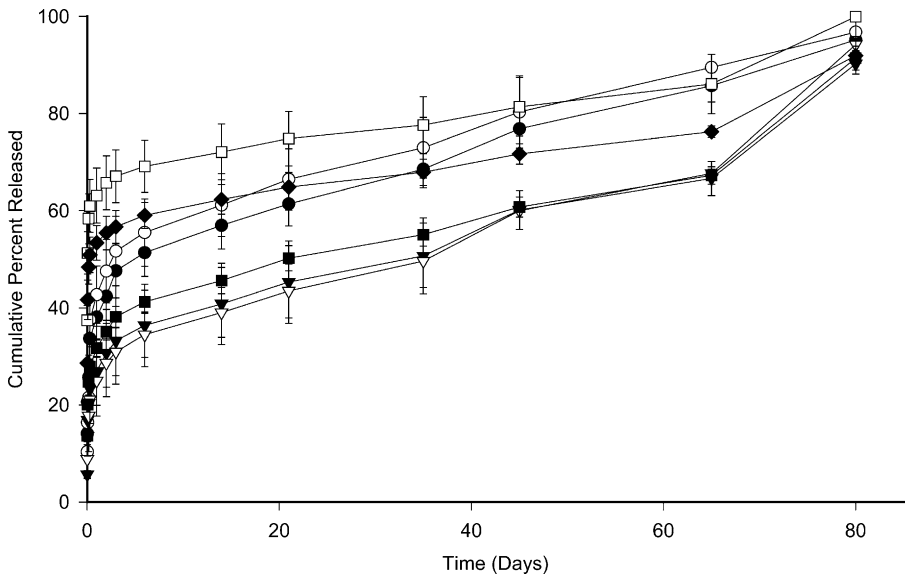

Fig. 5. Dissolution profiles of the microcapsules: Formulation A (●); Formulation B (○); Formulation C (▼); Formulation D (▽); Formulation E (■); Formulation F (□); Formulation G (◆).

Table 4
Effect of PLGA blending on the dissolution

Formulation	Burst release (%)	Results of SNK[a]	$T_{50\%}$ (day)	Results of SNK[a]
A	14.1	F > G> A = E = B = D = C	6.3	D = C = E > A = B = G = F
B	10.3		3.7	
C	5.7		23.1	
D	8.8		31.8	
E	13.7		18.6	
F	36.0		0.1	
G	28.6		0.6	

[a] Student–Newman–Keul's multiple range test.

resulted in a higher cumulative release at any given time.

The effect of blending of PLGA on the diffusion kinetics was evaluated by curve fitting the dissolution data to the Eq. (3):

$$\frac{M_t}{M_\infty} = Kt^n \tag{3}$$

where M_t/M_∞ is the fractional release of the drug in time t, k is the kinetic constant, and n is the diffusional exponent for drug release. The best fit parameters along with the coefficient of determination (R^2) values obtained from the curve fitting are listed in Table 5. The high values of R^2 suggest that this equation provides a good fit for the dissolution data. A comparison of the kinetic constant (k) values revealed that the value for the formulation contain only the high M_w PLGA (Formulation A), is significantly low compared with the formulation contain only the low M_w PLGA (Formulation G). The parameter n indicates the drug release mechanism. The value of n is 0.5 for Fickian diffusion and 1 for Case II diffusion. A value of n greater than 0.5 but less than 1 indicates a non-Fickian or anomalous diffusion, which is a mixture of Fickian and Case II diffusion. When n is greater than 1 the drug release occurs through the super Case II diffusion (Shah et al., 1993; Mandal, 1995). The listed values of n (Table 5) indicate that the release of pentamidine from these formulations did not follow any one of these mechanisms directly. The values of n were all less than 0.2 indicating a failure to follow either the Fickian or Case II diffusion mechanism. The release of drug from a biodegradable matrix greatly depends on the biodegradation rate of the polymer. The PLGA matrix started degrading as early as 7 days and between 17 and 23% of the matrix loss was observed within 14 days (Fig. 4).

Table 5
Effect of PLGA blending on the diffusion kinetics: best-fit parameters, k and n, based on equation $M_t/M_\infty = Kt^n$

Formulation	Kinetic constant (k)	Diffusional exponent (n)	Coefficient of determination (R^2)
A	0.273 (0.003)[a]	0.167 (0.005)[a]	0.997
B	0.375 (0.008)	0.168 (0.008)	0.992
C	0.393 (0.019)	0.180 (0.019)	0.987
D	0.248 (0.004)	0.187 (0.006)	0.996
E	0.319 (0.004)	0.149 (0.005)	0.997
F	0.601 (0.005)	0.056 (0.003)	0.987
G	0.530 (0.005)	0.066 (0.004)	0.987

[a] Standard deviation of three independent reading.

4. Conclusions

PLGA polymer has been used for more than two decades for the development of controlled release microcapsules of drugs. A wide variety of PLGA polymers are currently available commercially to achieve desired physicochemical characteristics of these microcapsules. One of the most important criteria for evaluation of these microcapsules is the efficiency of encapsulation.

In our present study, efficiency of encapsulation increased significantly when Resomer 506 was mixed with Resomer 502 at a ratio of 1:7 (Formulation F). The presence of pentamidine in this formulation (F) was confirmed through DSC. However, this formulation also showed significantly high "burst release,"

which implies that a major portion of the encapsulated pentamidine was deposited near the surface. The surface of the microcapsules containing only the high M_w PLGA (RG 506) appeared to be rugged and porous. When low M_w PLGA (RG 502) was incorporated, the ruggedness was reduced. Microcapsules containing low M_w PLGA in a ratio of 1:2.5 or higher appeared to be smooth, spherical and less porous.

In summary, blending of different ratios of low and high molecular weight PLGA significantly improved some of the desired physicochemical characteristics of the drug-filled microcapsules. Blending of different M_w of PLGA can also produce controlled release microcapsules with desired drug release profiles.

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