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Research paper

The design of flexible ciprofloxacin-loaded PLGA implants using a reversed phase separation/coacervation method

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ABSTRACT

The purpose of this research is to design and characterize flexible PLGA-based implants for the controlled release of ciprofloxacin hydrochloride for up to 6 weeks in vitro. This research uses a reversed phase separation/coacervation method to fabricate flexible PLA and PLGA: excipient implants with dichloromethane/mineral oil as solvent/non-solvent. Physical characterization was performed using thermal and mechanical analyses. Drug loading and release studies were performed with ciprofloxacin HCl as the model drug. Release kinetics was modeled to elucidate possible mechanisms of drug release. Four polymer–excipient combinations with glass transition temperatures less than 20 °C and representing a wide range of Young's moduli were shown to entrap up to 8% of ciprofloxacin HCl that could be released at a controlled rate for 65 days in vitro. The release rate could consistently fit a ternary Gaussian pattern with an $R^2 > 0.99$. It was postulated that these release patterns could be related to ciprofloxacin that was loosely or poorly bound (burst release), trapped within the polymer matrix, or encapsulated by the polymer. These studies show that flexible implants can be fabricated from PLGA-based polymers for the controlled release of ciprofloxacin hydrochloride for up to 6 weeks in vitro.

1. Introduction

Flexible devices with spongy, plastic, or rubbery consistency have numerous applications in drug delivery and tissue engineering. Current biomaterials used for fabricating flexible devices include hydroxyapatite cement [1,2], silicone [3,4], collagen [5–8], gelatin sponges [9,10], and their combination with synthetic or natural polymers such as elastin [11,12], chitosan [13,14], and polytetrafluoroethylene [15–18].

The polylactide (PLA) and polylactide-co-glycolide (PLGA) group of polyesters have been investigated for numerous drug delivery and tissue engineering applications. The wide applicability of these polymers stems from their being biocompatible, biodegradable, and commercially available in a wide range of physicochemical properties. Despite the wide range of physical and chemical properties offered by these polymers, devices and scaffolds fabricated from the PLA and PLGA carriers tend to be rigid and inflexible at physiological temperature. The overall goal of this research is to develop flexible PLA- and PLGA-based biodegradable aggregates with spongy, plastic, or elastic consistency at or below physiological temperature. Such materials offer the potential for filling dead spaces following surgery in osteomyelitis and for filling periodontal pockets to treat chronic destructive periodontitis.

The solvent/non-solvent method for coacervation and phase separation has been widely used to prepare microencapsulated drug formulations [19–22]. In this research, we report a modified phase separation process that will produce PLA and PLGA aggregates with flexible consistency. The process consists of dissolving the polymer solution into dichloromethane followed by a rapid addition of this solution into a large excess of mineral oil to cause phase separation. To further examine the physical properties of these precipitates, excipients that could disperse or dissolve in the polymer solution were included, and the thermal and mechanical properties of the resulting polymer–excipient precipitates were characterized. The excipients included mannitol (disperse in the PLA/PLGA dichloromethane solution) and surfactants spanning a wide range of HLB values, including polyethylene glycol (PEG) 300, Tween 80, and Span 85. Finally, the potential to specific polymer–excipient combinations to entrap and release a model drug (ciprofloxacin HCl) at multiple drug load levels is reported.

2. Materials and methods

2.1. Materials

Polymers: The following polymers were used in this study: PLA100 (inherent viscosity 0.39 dL/g), PLGA copolymers 90:10,

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75:25, 65:35, and 50:50, with inherent viscosities 0.52, 0.17, 0.37, and 0.15 dL/g, respectively. These polymers were obtained from Alkemers, OH. Ciprofloxacin HCl was obtained from a local compounding pharmacy in Omaha, NE. Dichloromethane (DCM), heavy mineral oil, mannitol, Tween 80, Span 85, and PEG 300 were obtained from Sigma Aldrich, St. Louis, MO.

2.2. Methods

2.2.1. Fabrication of PLA and PLGA implants

Control polymeric implants were fabricated by first dissolving 0.5 g of PLA 100, PLGA 90:10, 75:25, 65:35, or 50:50, in 15 mL of DCM. The resulting solution was rapidly added into 100 mL of the non-solvent (mineral oil) to cause phase separation. Excipient-containing polymeric implants were fabricated by first dissolving or dispersing 0.5 g of the excipient (Tween 80, PEG 300, Span 85 or mannitol) in the polymer–DCM mixture, which was subsequently added into 100 mL of mineral oil. The choice of surfactants was intended to represent a wide range of HLB values, as Tween 80, PEG 300, and Span 85 are known to have HLB values of 15, 11.4, and 1.8, respectively.

The precipitates were hardened by incubation in 20 mL n-hexane for 24 h, followed by drying at room temperature for a further 5–7 days. With five types of polymers and four excipients, a total of 20 precipitates were prepared for initial thermal and mechanical characterizations. Based on these properties, only four polymer–excipient combinations were selected for further implant fabrication. Drug loading in the four selected implants was performed by uniformly dispersing powdered ciprofloxacin hydrochloride into the polymer–excipient mixture prior to addition into the non-solvent. Sufficient amount of ciprofloxacin hydrochloride was added to obtain a theoretical drug loading of approximately 2%, 10%, or 18% w/w, respectively.

2.2.2. Thermal and mechanical analyses

DSC thermograms were obtained using a Shimadzu, DSC-60, differential scanning calorimeter, fitted with a Shimadzu TA-60 data processor after calibration with an indium standard of melting point 156 °C. Thermograms were obtained by heating 3–8 mg samples in crimped aluminum pans at 10 °C/min from −20 to 200 °C in a nitrogen atmosphere (flow rate 20 ml/min). All samples were subjected to an initial heating cycle, (first heating), air cooled, and immediately subjected to a second heating cycle (second heating). Changes in the glass transition temperature (T_g), jump in heat capacity (ΔC_p), melting/endothermal peak temperatures (T_m), and enthalpies (ΔH_m) corresponding to the second heating cycle were monitored using TA software. A Shimadzu EZ-test 100 N was used to plot stress–strain curves for the control and excipient-containing polymeric implants. Young's modulus (Y_m) was determined for the implants from the slope of the stress–strain curves.

2.2.3. High-Performance Liquid Chromatography (HPLC) assay of ciprofloxacin

The method was adopted from Dash et al., after modifications [23]. The mobile phase consisted of citrate buffer (pH 3.8), acetonitrile, and methanol (75:20:5 v/v/v). The apparent pH of the mobile phase was adjusted to 2.4 with perchloric acid. The flow rate of the mobile phase was maintained at 1 ml/min. A Spherisorb (C-18) pH stable column of length 15 cm was used for this study, and column effects were monitored at 272 nm. Phenacetin was used as an internal standard. Ciprofloxacin concentration was determined using peak ratios.

2.2.4. Drug loading and in vitro dissolution studies

To determine drug loading, about 2–5 mg of the delivery system containing ciprofloxacin was dissolved in 5 mL of dichloromethane. The ciprofloxacin was extracted into the dissolution medium using 5 × 3 mL of the HPLC mobile phase described above. Cumulative dissolution studies were performed to determine ciprofloxacin release into the dissolution medium.

2.2.5. Release rate modeling

Analysis of best fit was performed using Gaussian release rate modeling with the non-linear curve fitting software, the Scientist 3.0 from Micromath Research®, MO. Scientist employs a least-squares minimization algorithm for non-linear curve fitting. Multiple (binary and ternary) release patterns were investigated and compared with the Modified Akaikean Model selection criterion (MSC) using the Wilcoxon Matched-Pairs Signed-Ranks Test ($p < 0.007812$). The MSC considers the relative information content in the parameters of each model such that the same data set fit to different models will result in different values for the MSC. While a model with more parameters will generally provide a better fit than one with fewer parameters, increasing the complexity of the model without significantly improving the fit would cause loss of information per parameter, resulting in a smaller value for the MSC. MSCs were therefore used in this study to determine the choice of the appropriate model in this study. All the data sets over both models were compared using the Wilcoxon Matched-Pairs Signed-Ranks Test.

3. Results

Implants obtained using PLGAs with higher lactide content (PLGA 90:10 and PLA) had the appearance of a cottony mass as shown in Fig. 1. Those obtained from the lower lactide content, such as PLGA 50:50 and 65:35, showed a transparent gel-like consistency (figure not shown).

3.1. Effect of processing on the glass transition temperatures

Figs. 2a and b are representative thermograms showing the effect of processing and excipients on the glass transition of PLGA 50/50 and 65/35. TGA thermograms showed maximum weight loss of 1–5% by weight for PEG-containing implants, whereas weight loss for all other polymer–excipient combinations ranged from 0% to 2%.

All unprocessed polymers, processed controls, and those fabricated with mannitol as the excipient showed a distinct T_g marked by a clear lowering of C_p. The processed controls showed signifi-

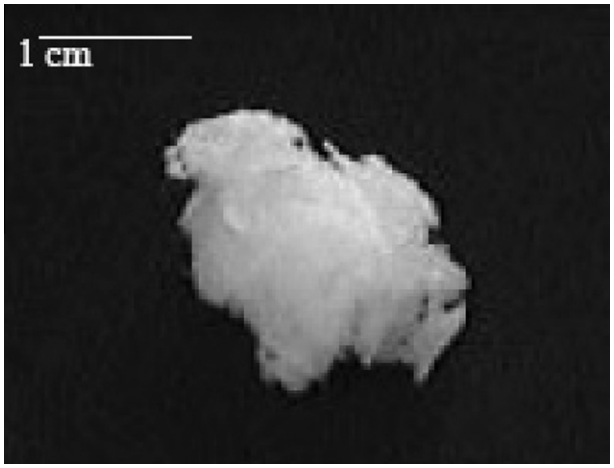

Fig. 1. A representative photograph of a phase-separated implant fabricated with PLA 100.

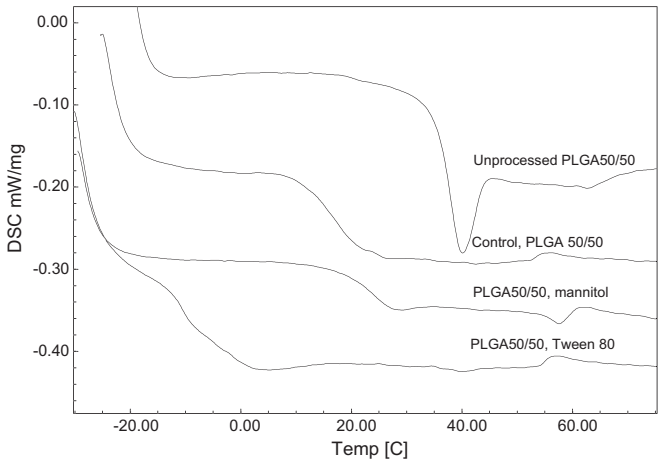

Fig. 2a. Representative DSC thermograms showing the effect of processing and selected excipients on the glass transition of PLGA 50/50.

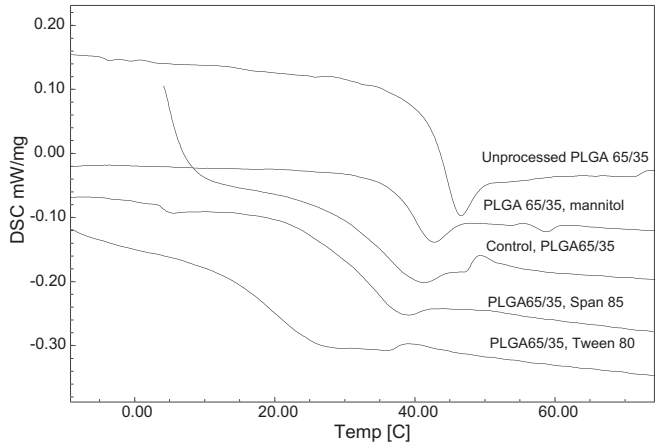

Fig. 2b. DSC thermograms showing the effect of processing and excipients on the glass transition of PLGA 65/35 polymers.

cantly lower T_g values compared to unprocessed polymers, possibly due to plasticization by mineral oil. For polymers containing PEG 300, Span 85, or Tween 80, an accurate value for T_g could not be assigned to certain polymer–excipient combinations due to lack of confidence in the determination of the baseline heat capacity. The glass transitions temperatures that could be measured are reported in Table 1. It was evident that excipient except mannitol caused significant lowering in the glass transition temperature of PLGA.

3.2. Mechanical properties characterization

Table 2 shows the Y_m of processed controls and excipient-containing polymers. Intrinsic viscosities are also shown to enable comparison. Table 2 clearly shows that the Y_m of PLA remained relatively constant at 3.5 ± 0.23 N/mm^2. Similarly, inclusion of mannitol also resulted in a similar Y_m of 3.5 ± 0.26 for all polymers except PLGA 95:25. These results suggest that PLA and mannitol may not be ideal choices if manipulation of thermal and mechanical properties is desired. For the PEG 300-containing implants, Y_m appeared to be a function of intrinsic viscosity, again with the exception of PLGA 50:50. Table 2 also shows that a wide range of Y_m values may be obtained by carefully varying the choice of the polymer/excipient combinations.

Table 2
Effect of excipients on the Young's modulus (Y_m) of PLA and PLGA copolymers.

Polymer	Int. visc. (dL/g)	Y_m in N/mm^2				
		Control	MTL	PEG	Twn	Spn
PLA 100	0.39	3.3	3.3	3.4	3.8	3.7
PLGA 90/10	0.52	2.0	3.3	9.6	3.5	2.1
PLGA 75/25	0.17	11.2	3.7	4.9	11.5	3.8
PLGA 65/35	0.37	8.4	3.8	0.4	3.6	10.9
PLGA 50/50	0.15	12.7	7.1	2.9	–	–

Key: Excipients: PEG = polyethylene glycol 300, Twn = Tween 80, Spn = Span 85. – Not detected.

Based on the thermal and mechanical analyses, four polymer–excipient combinations with T_g values less than 20 °C and representing a wide range of Young's moduli were selected to study ciprofloxacin loading and release. These combinations were PLGA 90/10:Span 85, PLGA 75/25:Tween 80, PLGA 65/35:Tween 80, and PLGA 65/35:PEG 300. The polymer–excipient combinations were designated as P90S, P75T, P65T, and P65P, respectively.

3.3. Ciprofloxacin assay

Fig. 3 shows the HPLC elution profile of ciprofloxacin hydrochloride and phenacetin (internal standard). The standard curves

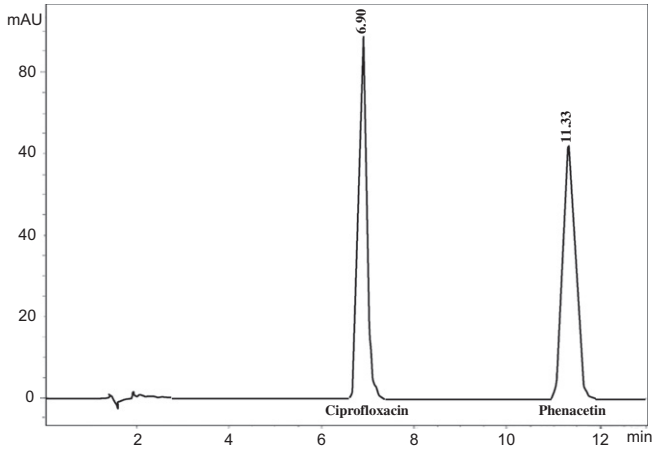

Fig. 3. Representative HPLC chromatograms showing retention times for ciprofloxacin and phenacetin.

Table 1
Effect of processing and excipients on the glass transition temperature (T_g) of PLA and PLGA polymers.

Polymer	Int. visc. (dL/g)	Glass transition temperature (T_g) in °C					
		UPP	CPD	MTL	PEG	Twn	Spn
PLA 100	0.39	45.3	37.2	45.1	–	–	41.5
PLGA 90/10	0.52	48.7	46.4	37.4	–	27.1	1.8
PLGA 75/25	0.17	36.5	30.1	35.5	–	5.3	29.1
PLGA 65/35	0.37	42.8	34.2	37.9	15.4	19.3	29.8
PLGA 50/50	0.15	35.7	16.8	22.0	–	–4.5	12.5

Key: Int. visc.: Intrinsic viscosity, UPP: Unprocessed polymers, CPD: Control polymeric devices. MTL, PEG, Twn, and Spn refer to PLA and PLGA devices fabricated with mannitol, polyethylene glycol 300, Tween 80, and Span 85, respectively. – Not determined.

Table 3
Drug loading and percent encapsulation of ciprofloxacin in the flexible PLGA implants.

S. No	Designation	Implant constitution	Theoretical drug load (%)	Actual drug loading (%)	Percent encapsulation (%)
1A	$P90S_L$	PLGA 90:10/Span 85	2.6	0.7 ± 0.3	28.6
2A	$P90S_M$	PLGA 90:10/Span 85	11.1	2.9 ± 0.6	26.0
3A	$P90S_H$	PLGA 90:10/Span 85	18.2	7.8 ± 1.2	42.7
1B	$P75T_L$	PLGA 75:25/Tween 80	2.5	0.7 ± 0.0	27.1
2B	$P75T_M$	PLGA 75:25/Tween 80	11.4	2.9 ± 0.4	25.1
3B	$P75T_H$	PLGA 75:25/Tween 80	18.5	3.4 ± 0.9	18.3
1C	$P65T_L$	PLGA 65:35/Tween 80	2.6	0.4 ± 0.2	15.0
2C	$P65T_M$	PLGA 65:35/Tween 80	11.8	5.5 ± 1.5	46.6
3C	$P65T_H$	PLGA 65:35/Tween 80	19.1	5.1 ± 0.5	26.5
1D	$P65P_L$	PLGA 65:35/PEG 300	2.6	1.0 ± 0.2	38.3
2D	$P65P_M$	PLGA 65:35/PEG 300	10.9	8.2 ± 2.6	75.4
3D	$P65P_H$	PLGA 65:35/PEG 300	18.6	8.7 ± 0.5	47.0

were constant over the concentration range 0–18 μg/mL. The equation relating the peak height ratio to the ciprofloxacin hydrochloride concentration was $y = 0.3132x + 0.0327$, where y = peak height ratio and x = ciprofloxacin hydrochloride concentration.

3.4. Drug loading

The four polymer–excipient combinations (P90S, P75T, P65T, and P65P) were loaded with ciprofloxacin HCl at a low, medium, and high level in the range of 2.5–19% w/w. The resulting implants were designated with a subscript of L, M, or H to indicate the level of drug load. The theoretical drug load, actual loading (as determined from quantitative assay of ciprofloxacin), and the percent encapsulation are shown in Table 3.

From Table 3, it is evident that percent encapsulation was generally low (35 ± 17%). With the exception of P90S implants, percent encapsulation was maximum at the low or medium level and decreased significantly for implants loaded with the high level of ciprofloxacin HCl. Based on these drug loading studies, implants fabricated with a low or medium drug load were selected for further drug release studies.

Table 4
Release modeling showing ternary and binary Gaussian fits with associated release profile parameters, descriptive statistics, and Modified Akaikean Model selection criterion.

Polymeric release systems	1A		1B		1C		1D	
Implant constitution	PLGA 90:10/Span85		PLGA 75:25/Span85		PLGA 65:35/Tween80		PLGA 65:35/PEG300	
Actual drug load	0.7 ± 0.3		0.7 ± 0.0		0.4 ± 0.2		1.0 ± 0.2	
Percent encapsulation	28.6		27.1		15		38.3	
Gaussian release pattern	Ternary	Binary	Ternary	Binary	Ternary	Binary	Ternary	Binary
Parameters								
$m_1 \pm d_1$	−2.4 ± 1.3	−41.1 ± 19.4	−2.2 ± 1.1	−16.73 ± 8.9	−0.1 ± 0.4	7.5 ± 6.3	0.1 ± 0.6	7.2 ± 1.3
$m_2 \pm d_2$	5.2 ± 2.3	46.4 ± 13.5	4.7 ± 2.6	23.0 ± 22.7	7.0 ± 3.9	10.5 ± 4.6	6.8 ± 3.1	13.5 ± 26.5
$m_3 \pm d_3$	63.0 ± 29.6	NA	26.3 ± 16.0	NA	10.8 ± 3.7	NA	24.8 ± 9.6	NA
K_1	72.0	1092.9	201.6	423.9	2.0	10.7	1.6	5.8
K_2	12.7	24.5	11.8	52.8	9.4	26.1	14.6	72.5
K_3	54.5	NA	40.9	NA	25.4	NA	36.2	NA
Statistical analysis								
R^2	0.99968	0.99554	0.99989	0.99595	0.99907	0.99993	0.99947	0.99817
MSC	6.91	4.57	6.78	3.45	11.72	8.49	6.17	5.23
Serial correlation	2.9825	3.301	−0.40139	2.5789	1.6665	3.4205	1.0307	2.3582
Skewness	−6.6067	−4.3389	0.50625	−8.8398	−3.4554	−8.7483	−16.094	−4.7758
Kurtosis	1.2542	0.62688	0.16315	5.9921	0.15307	3.5299	18.094	0.16177
Polymeric release systems	2A		2B		2C		2D	
Implant constitution	PLGA 90:10/Span85		PLGA 75:25/Span85		PLGA 65:35/Tween80		PLGA 65:35/PEG300	
Actual drug load	2.9 ± 0.6		2.9 ± 0.4		5.5 ± 1.5		8.2 ± 2.6	
Percent encapsulation	26		25.1		46%		75.4	
Gaussian release pattern	Ternary	Binary	Ternary	Binary	Ternary	Binary	Ternary	Binary
Parameters								
$m_1 \pm d_1$	0.2 ± 0.4	2.2 ± 6.7	−3.0 ± 1.8	−26.6 ± 22.1	−0.1 ± 1.0	−2.3 ± 7.3	−1.5 ± 1.2	3.7 ± 4.7
$m_2 \pm d_2$	6.0 ± 3.2	21.2 ± 1.4	5.2 ± 2.1	34.9 ± 11.0	5.2 ± 1.6	11.0 ± 14.2	5.5 ± 2.1	21.2 ± 24.7
$m_3 \pm d_3$	24.7 ± 7.5	NA	25.2 ± 16.7	NA	10.2 ± 13.9	NA	15.4 ± 25.9	NA
K_1	1.5	27.1	63.5	245.4	5.8	33.9	20.2	18.2
K_2	18.3	18.1	9.5	19.8	9.1	12.6	9.3	38.6
K_3	17.7	NA	38.1	NA	14.2	NA	46.8	NA
Statistical analysis								
R^2	0.99925	0.99960	0.99933	0.99883	0.99994	0.99999	0.99991	0.99946
MSC	6.02	5.68	6.74	5.15	7.72	7.53	8.25	6.05
Serial correlation	0.17412	1.8107	−0.06782	1.4678	−0.44655	2.9995	−1.269	1.5655
Skewness	−17.626	−6.4719	−11.874	−5.6493	2.352	−5.1106	−4.1166	−3.7995
Kurtosis	21.457	4.5294	11.499	0.71778	0.27661	2.42	0.75428	1.585

3.5. Release modeling

Cumulative fraction of ciprofloxacin released vs. time was fit to two different Gaussian release rate models: 2G for binary release and 3G for a ternary release pattern. In general terms, the release rate for the ternary release pattern consists of three normally distributed release profiles, each associated with a mean and standard deviation. Since the integral of the Gaussian function yields 1 with the units dy/dx, multiplying the individual releases by a unique coefficient k normalized to the fraction of released yields the contribution of each of the individual releases, which will add up to the total amount released. The resultant parameters

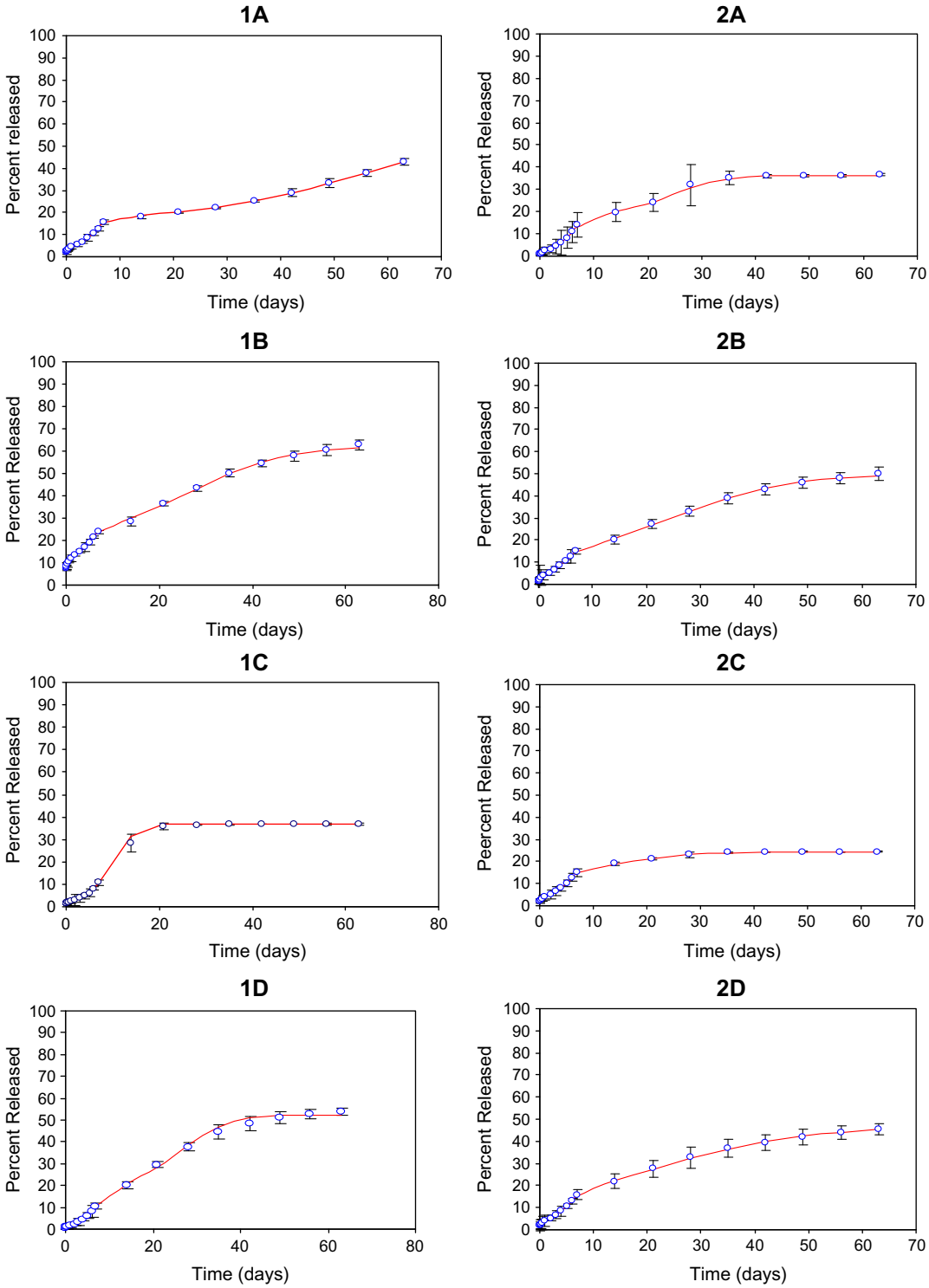

Fig. 4. Ciprofloxacin release from PLGA-excipient delivery systems. Open circles indicate the percent of ciprofloxacin released as a function of time (in days). The fitted line represents the ternary Gaussian model best-fit model. (*Key*: the terms a, b, c, and d refer to implants with constitution of PLGA90:10/ Span 85, PLGA 75:25/Tween 80, PLGA 65:35/Tween 80, and PLGA 50:50/PEG 300, respectively. Terms 1 and 2 refer to a lower and moderate level of drug loading as shown in Table 3.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(means (m_i), standard deviations (d_i), and coefficients (K_i)) for each release used in the Gaussian fitting as well as the descriptive statistics for each fit are given in Table 4.

The ternary release pattern (3G) was shown to have a superior fit when compared to the binary release pattern (2G) based on the Modified Akaikean Model selection criterion (MSC) using the Wilcoxon Matched-Pairs Signed-Ranks Test ($p < 0.0078$). The model demonstrates the result of the summation of three different, overlapping release patterns occurring throughout the time studied. Actual release patterns are shown in Fig. 4.

4. Discussion

Solvent/non-solvent phase separation processes have been exploited widely to encapsulate drugs in polymeric delivery systems. Conventional phase separation processes consist of dropwise addition of a miscible non-solvent into polymer solution containing dispersed drug. The gradual increase in the non-solvent concentration causes a corresponding decrease in polymer solubility, eventually causing precipitation of the polymer. Although used extensively, the application of this phase separation process has been limited to the fabrication of particulate delivery systems such as microcapsules. This research shows that by reversing the conventional process of phase separation, polymeric implants with cottony or plastic consistency can be designed. The results further demonstrate that hydrophilic excipients such as mannitol do not significantly modify the thermal or mechanical properties of PLA and PLGA polymers. Surfactants such as Tweens, Spans, and PEGs are a better choice, as these excipients are capable of plasticizing these polymers to lower glass transition temperatures and Young's moduli. Overall, this study shows that carefully varying the choice of polymers and excipients, PLGA-based implants can be fabricated that possess a significant ability to deform upon relatively minor stress that can be as small as 0.4 N/mm^2.

This research also demonstrates that the implants designed by this reverse phase separation coacervation technique can entrap up to 8% drug load that can be released at a controlled rate for at least 65 days in vitro. The release rate of ciprofloxacin HCl encapsulated in the various polymer–excipient combinations was shown to consistently fit a ternary Gaussian release rate pattern with an $R^2 > 0.99$.

It is postulated that these release patterns could be related to three methods or types of bonding/trapping of ciprofloxacin HCl within the polymeric matrix: loosely or poorly bound (burst release), trapped within the polymer matrix, and encapsulated by the polymer. The initial rapid burst release profile with mostly negative values for m_1 and narrow standard deviations (see Table 4) correspond to burst release. Burst release is a significant problem in pharmaceutical dosage forms, and numerous studies have been devoted to limiting burst release in controlled release drug delivery systems [24–28]. But release may not always be undesirable especially in conditions such as osteomyelitis, as the initial amount of drug released can serve as a loading dose.

Corresponding percent values of burst were calculated using the coefficients described in Table 4 and are reported in Table 5. It was observed that implants fabricated using PLGA 65:35 showed low burst profiles of <26%. Burst release was generally higher for implants containing PLGAs with higher lactide ratios, with the exception of P90SM (Table 5). It is possible that the relatively higher hydrophilicity of PLGAs with higher glycolide content can more readily entrap ciprofloxacin HCl, thereby resulting in lower burst release. Overall, this studies show that it is possible to significantly limit burst release by choice of polymer–excipient combinations as well as the extent of drug loading in flexible PLGA implants.

Table 5
Percent drug release occurring through each of the three mechanisms described by the ternary Gaussian model in Table 4.

S. No	Designation	Implant constitution	Burst release (%) $K_1/(K_1 + K_2 + K_3)$
1A	$P90S_L$	PLGA 90:10/Span 85	52
2A	$P90S_M$	PLGA 90:10/Span 85	04
1B	$P75T_L$	PLGA 75:25/Tween 80	79
2B	$P75T_M$	PLGA 75:25/Tween 80	57
1C	$P65T_L$	PLGA 65:35/Tween 80	05
2C	$P65T_M$	PLGA 65:35/Tween 80	20
1D	$P65P_L$	PLGA 65:35/PEG 300	03
2D	$P65P_M$	PLGA 65:35/PEG 300	26

5. Conclusion

This research demonstrates that reversed phase separation coacervation technique may be used to fabricated PLA- and PLGA-based implants that show a flexible characteristics at room temperature, as indicated by relatively low glass transition temperatures and Young's moduli in the range of 2.0–12.7 N/mm^2. The properties may be further modified by the inclusion of excipients such as PEG 300, Span 80, and Tween 80, thereby enhancing flexibility and improving ease of deformation at room temperature. The implants can successfully entrap up to 8% of ciprofloxacin HCl by weight and show controlled release profiles for at least 65 days in vitro. Overall, these implants can significantly improve the treatment efficacy for conditions such as chronic osteomyelitis and periodontitis.

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