Effect of Formulation Variables on the Prediction of Release from Microparticles with Experimental Design

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ABSTRACT: Different formulations of triamcinolone acetonide (TA) encapsulated in microparticles (MPs) based on poly(D,L-lactide-*co*-glycolide) (PLGA), poly(ε-caprolactone) (PCL), and poly(methyl vinyl ether-*co*-maleic anhydride) (Gantrez AN119) blends were obtained by spray-drying with a mixture experimental design. The goal of this study was to investigate the influence of the mixture composition, particle size, particle shape, enthalpy of melting (ΔH_m) of PCL, enthalpy of depolymerization of PLGA, and glass-transition temperature of Gantrez on drug release at pH 1.2 and 6.8. The presence of Gantrez in the MPs made PCL more amorphous because of the reduction of its ΔH_m. The determination of the activation energy (E_a) associated with TA release from the MPs was used to calculate the fitting equation of the drug-release profile, and subsequently, a thermodynamic (Arrhenius-like) model was established. Drug release increased as E_a and ΔH_m decreased. Our results suggest that this approach was capable of predicting *in vitro* TA release from these MPs, which allowed us to develop formulations with low-release patterns at pH 1.2 and to modulate drug release at enteric pH. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 4546–4553, 2006

Key words: biodegradable; blends; drug delivery system; differential scanning calorimetry (DSC); microencapsulation

INTRODUCTION

In the treatment of colonic pathologies, such as ulcerative colitis and Crohn's disease, local delivery of drugs is required to prevent associated effects due to systemic absorption of prolonged treatments if they are absorbed at sites in the small intestine. Therefore, various approaches have been commonly proposed for colonic delivery for the administration of anti-inflammatory drugs with enteric formulations, such as pellets or tablets. The efficacy of these systems might be reduced due to the presence of diarrheas frequently associated with these kind of pathologies. To achieve successful colonic drug delivery, the drug needs to be protected from absorption and the environment of the gastrointestinal tract, and once the formulation reaches the proximal colon, ideally, the drug should be released.

One approach for obtaining selective colonic drug delivery has been the development of formulations based on polymers that show pH-dependent solubility (Eudragit) or the use of pellets coated with polymers capable of being degraded by colonic enzymes.[1,2]

In this study, biodegradable polymers blend of poly (D,L-lactide-*co*-glycolide) (PLGA) copolymer (PLGA RG502H), poly(ε-caprolactone) (PCL), and poly (methyl vinyl ether-*co*-maleic anhydride) (Gantrez AN119) were selected as the polymeric matrix for triamcinolone acetonide (TA) encapsulation with spray-drying. TA, a glucocorticoid, is a current drug of choice for the treatment of ulcerative colitis and Crohn's disease. It is poorly soluble in water and is very effective at low doses compared to other drugs such as sulfasalazine.

PCL is a biocompatible and biodegradable low-cost polyester polymer that degrades slowly, and it has been widely used in drug delivery.[3] It exhibits a low melting temperature ($T_m = 68.3^\circ$C) and a low glass-transition temperature ($T_g = -63^\circ$C).[4]

PLGA is one of the biodegradable copolymers that has been more extensively studied as a carrier for microparticles (MPs). These PLGA polymers have already been marketed for the delivery of protein and

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peptide drugs,[5] whose biomedical applications have been demonstrated.[6] Finally, the third component, the copolymer poly(methyl vinyl ether-*co*-maleic anhydride) (Gantrez AN119), is a polymer that belongs to the vinyl ethers group with major pharmaceutical applications. It is a biodegradable polyanhydride that is hydrolyzed in two free acid groups.[7] At acid pH, this polymer (pKa = 2.5) shows slow dissolution rates, which makes it a suitable material for colonic drug delivery.

Polymer blend formulations might improve TA delivery because the drug is incorporated in small MPs, which maintain their biodegradable character, to achieve a local action and, therefore, to reduce the secondary effects. Moreover, MPs obtained with spray-drying as a conventional microencapsulation method offers a simple, reproducible, and versatile technique for TA encapsulation due to their easy scale-up.

The aim of this study was to design MPs made of biodegradable and biocompatible polymers with spray-drying for colonic delivery. A mixture experimental design was performed to build a model (a polynomial equation) that could estimate and quantify the effect of formulation variables on drug release and, therefore, to obtain the optimal formulation for TA delivery in simulated physiological circumstances. For this purpose, each formulation was characterized by differential scanning calorimetry (DSC), size, sphericity, and loading efficiency. *In vitro* release properties were evaluated. Finally, the TA release profiles over 12 h were used to establish a thermodynamic model that related the TA release and the thermal behavior of the samples.

EXPERIMENTAL

Materials

The biodegradable polymer blend used as the matrix was composed on PCL, (molecular weight = 42,500 Da; Sigma-Aldrich, Madrid, Spain); 14,000-Da nonsterified PLGA 50 : 50 (Resomer RG502H) was purchased from Boehringer Ingelgheim (Ingelgheim, Germany). Poly(methyl vinyl ether-*co*-maleic anhydride) (Gantrez AN119; molecular weight = 200,000 Da) was kindly gifted by ISP (Barcelona, Spain), and TA was from Roig Farma S. A. (Barcelona, Spain).

Experimental design

To easily optimize the formulation and evaluation of the influence of each component on the dissolution rate, the mixture experimental design was used to prepare systematic model formulations of the drug. This experimental mixture design was built with Design-Expert Software version 5 (Stat-Ease, Inc., Minneapolis, MN). Solvent volume (ethyl formate), polymer concentration for spray-drying, and drug concentration were fixed at 3.7 and 3% w/w, respectively. Obviously, the solvent volume (ethyl formate) was adjusted to the total polymer concentration, both already mentioned in the text. The solvent volume is clearly deduced by the reader when the concentration of polymer and drug is mentioned. According to the constrained experimental design, PLGA, PCL and Gantrez AN119 proportions were selected as input variables. Limits values for the experimental design are shown in Table I.

To evaluate the influence of the partial replacement of PLGA in the formulations by other polymers such as PCL or Gantrez AN119, various parameters were selected as output variables as follows: the percentage of TA released at 120 and 720 min, the encapsulation yield, the shape and size of MPs, and the enthalpies and T_g values obtained from the thermograms of the final formulations.

All formulations were prepared and assayed in terms of TA release as randomized to minimize the effect of systematic errors.

Ternary diagram

Once ranges of the variation of input variables were established, the number of formulations to investigate that were in good agreement with the restrictions mentioned previously was finally set at 11.

For the experiments, the total sum of the three substances was considered as 100%, and all possible mixtures were plotted on a ternary diagram (Fig. 1) whose vertices represented the pure components (Table I).

The experimental results were analyzed with the Design Expert software. We established, by analysis of variance (ANOVA), the input variables that had a significant effect on the response variables already measured. The experimental results were also analyzed from the fitting thermodynamic model for pH values of 1.2 and 6.8. The equation of models for every output variable was also obtained, and we fit the response of the output variables. Also, with ANOVA, the significance of the fitting was determined.

TABLE I
Composition of Variables Investigated in Every Formulation of Biodegradable MPs

Formulation	X_1	X_2	X_3
F1	70.0	0.0	30.0
F2	78.5	0.0	21.5
F3	87.0		8.0
F4	68.5	1.5	30.0
F5	87.0	0.0	13.0
F6	75.6	4.6	19.8
F7	67.0	3.0	30.0
F8	67.0	10.0	23.0
F9	87.0	10.0	3.0
F10	67.0	6.5	26.5
F11	77.0	10.0	13.0

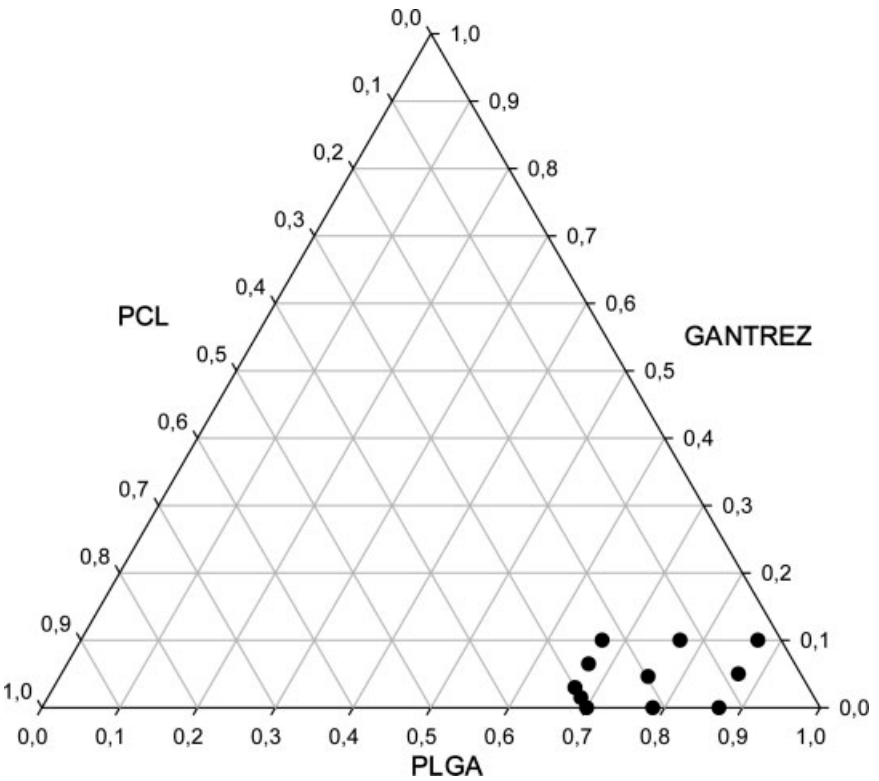

Figure 1 Ternary diagram illustrating the experimental composition of the MP formulation.

Preparation of MPs by spray-drying

According to the experimental design (Table I), solutions of the mixtures of the polymers of 2.2 g were prepared. The amount of TA was maintained to be always constant at 66 mg in 60 mL of ethyl formate.

We obtained the MPs by spraying the solutions for every sample through the nozzle (0.5 mm diameter) of a spray-dryer (model Mini Büchi 190, Büchi Labortechnik AG, Flawil, Switzerland). The process parameters were set as follows: inlet temperature = 43 ± 2°C, outlet temperature = 39 ± 2°C, aspirator setting = 100%, pump setting = 3 mL/min, air flow rate = 500 L/h, and spray flow pressure = 6 bar. MPs were collected and dried *in vacuo* for 18 h.

Morphological analysis and particle size analysis

The external morphology of the MPs were analyzed by optical microscopy (Olympus BX-60, Barcelona, Spain) equipped with a video camera JVC TK-350 (JVC, Tokyo). The pixel size used in the analysis was 0.16 μm. Pictures were digitalized with a video card (Matrox Comet, Matrox Electronic Systems, Ltd., Quebec, Canada) with PC image VGA 24 software (Foster Finlay Associates, Newcastle, England). To assess the size of MPs from the images obtained, Sigma Scan Pro 5.0 (SPSS, Inc., Chicago) image analysis software was used. Fifty pictures of MPs were taken from every formulation. Analysis of the pictures was performed, and the following parameters were calculated to characterize the MPs: Feret's diameter (the measured distance between parallel lines that are tangent to a MP's profile and perpendicular to the ocular scale), mean radio, and two factor forms useful for MP characterization: the parameter indicating shape (V_r) and the parameter related to surface roughness (V_p).[8]

Surface hydrophobicity of the MPs

The surface hydrophobicity of MPs was determined with the Rose Bengal (Sigma-Aldrich) partitioning method.[9] A concentration of 5 mg/mL for every formulation of MPs was resuspended in 0.1*M* phosphate buffer saline (PBS) solution (with 10 μg/mL of Rose Bengal). After incubation at room temperature of 2 h, samples were centrifuged at 14,000 rpm. Absorbances were measured at 540 nm. The relation between the partition quotient and the surface area of MPs was selected as a relative parameter for the comparison of the hydrophobicity of the MP surfaces.

Loading efficiency

To determine the amount of TA encapsulated, accurately weighted samples of 30 mg of MPs from every formulation were dissolved in ethyl formate. The TA concentration was determined by spectrophotometry (242 nm; Hewlett-Packard Co., Palo Alto, CA). The analytical method was previously validated in terms of

accuracy, reproducibility, and precision. The loading efficiency was given as the relationship between the weight of TA found in every batch of MPs and the initial weight of TA. The results are expressed as the amount of TA per milligram of MPs.

Release studies

Release studies from the MPs were performed in automatic dissolution test equipment (Prolabo, Barcelona, Spain) with a connection to a diode array spectrophotometer (Hewlett-Packard 8452A, Palo Alto, CA). System N° 2 according to USP XXIII was used. Every formulation with a weight of 266 mg of MPs was dispersed in 450 mL of gastric medium (pH = 1.2 ± 0.1). After 120 min, 228 mL of PBS buffer/NaOH was added to increase the pH to 6.8. The second part of the assay was performed over 600 min. These studies were carried out in triplicate at 37 ± 1°C with a stirring speed of 100 rpm. A wavelength of 242 nm was selected for TA determination.

DSC

A differential scanning calorimeter (Q100, TA Instruments, New Castle, DE) was used to determine different calorimetric parameters [T_g, enthalpy of melting (ΔH_m), and enthalpy of depolymerization (ΔH_d)].

The calorimeter required three calibrations: T_{zero} calibration, cell constant calibration, and temperature calibration. The T_{zero} calibration requested two experiments: the first one was done without samples, and the second one was performed with sapphire disks (without pans) on both the sample and the reference position. The same method was used in both experiments. It was started with equilibration at an initial temperature, isothermal was held for 5 min, and then it was heated at a constant rate to a final temperature and held at isothermal for 5 min. The range of temperatures necessary for this calibration was between −90 and 400°C.

The enthalpy constant calibration was based on a run in which one standard metal (indium) was heated through its melting transition. The calculated heat of fusion (27.66 J/g) was compared to the theoretical value (28.39 J/g). The cell constant was the ratio between these two values.[10]

Temperature calibration was based on a run in which a temperature standard (indium) was heated through its melting transition. The recorded T_m of this standard (157.95°C) was compared to the known T_m (156.61°C), and the difference was calculated for temperature calibration. The same file used for the cell constant calibration was used for this calibration.[10]

All of the experiments were carried out under a dry nitrogen atmosphere at about 5°C to prevent any interference in the sample (chemical aging). The experiments were carried out in a temperature range from 20 to 200°C.

RESULTS AND DISCUSSION

The selected ranges for the three components of the polymer mixture given by the experimental design were 67–87% for PLGA, 0–10% for Gantrez AN119, and 3–30% for PCL. However, on the basis of preliminary studies, the formation of particles was not possible when high concentrations of any of these polymers in solution for spray-drying were used, either one polymer alone or a mixture of three components. In the case of PCL, for example, the maximum percentage of PCL in the spray-drying solutions was 1.32% w/w. Higher concentrations caused nozzle clogging. Similar problems were observed for Gantrez AN119.

The TA content of MPs prepared by spray-drying was satisfactorily high, independent of the components used in the mixture. The loading yield of MPs recovered was around 90% with a very similar content homogeneity for the different formulations. This loading efficiency was similar to those obtained before by other authors,[11] for example, in the case of encapsulation of cyclosporin A in a PLGA/PCL system by an emulsion-solvent evaporation technique.

Generally, MP size is a very important issue for pharmaceutical applications because it greatly affects *in vitro* and *in vivo* drug-release studies and, therefore, its efficacy in biological conditions. The particle size characteristics of MPs loaded with TA were exactly the same as those whose particles were empty (plain MPs). The mean diameters of the MPs obtained with different mixtures varied from 3.36 ± 0.91 μm (F3) to 4.84 ± 1.9 μm (F7), which was indicative of the extreme reproducibility of the spray-dying technique, independent of the materials used.

The morphological examination of all of the formulations with image analysis showed similar values for Feret diameter, $V_{p,}$ and V_r. For example, the values for Feret diameter were between 3.54 ± 0.99 μm (F3) and 5.12 ± 2.0 μm (F7). On the other hand, no significant differences were found among the minimum and maximum values obtained for V_r (5.39 ± 2.23 μm for F8 and 7.20 ± 2.63 μm for F1) and V_p (8.40 ± 2.72 μm for F11 and 7.39 ± 2.43 μm for F2). V_r is considered a statistical measure of radius variability, indicating shape. V_p is defined as a geometric measure of perimeter circularity, indicating surface roughness.[7] These form factors should be interpreted together. According to other authors, these results indicate that the MPs in all of the formulations were slightly elliptical with a certain superficial roughness. No significant differences were found in all of the formulations examined, which suggested, first, the reproducibility of the technique and, second, that the mixture composition did not affect the

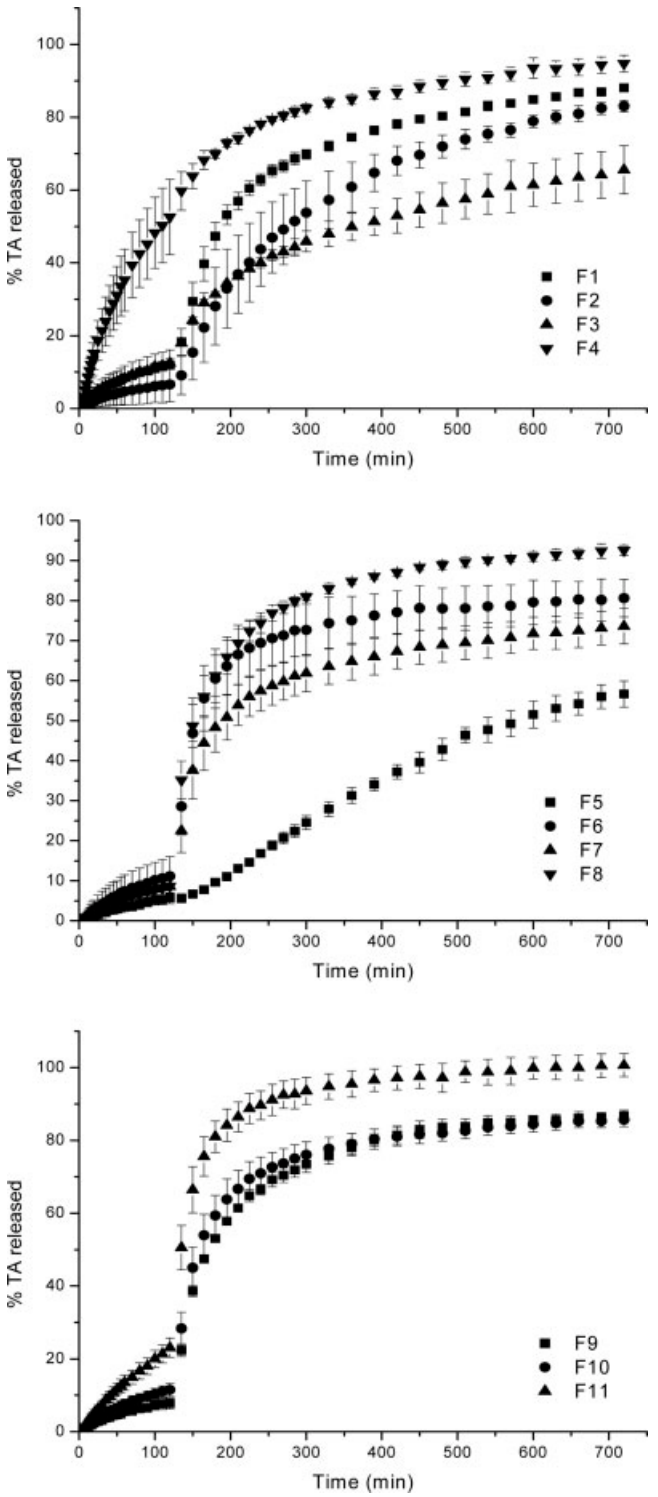

Figure 2 Experimental dissolution profile of MP formulations.

particle size and shape in the spray-drying processes. Additionally, no particle preparation was possible out of the range values obtained from the analysis of the experimental design.

The dissolution profiles of all of the formulations given by the mixture experimental design are shown in Figure 2. Table II summarizes the experimental dissolution profiles for all of the formulations.

To evaluate the drug release from MPs, we used the percentage of TA released between 0 and 120 min and between 120 and 720 min.

No significant differences were found for the drug-release rate at pH 1.2 (0–120 min) of all of the formulations, probably because of the wide dispersion of data, although some of the formulations did show low-released drug under these conditions. This behavior might have been due to the high hydrophobicity of most of the formulations, especially those showing these low proportions of Gantrez compared to batches with higher proportions of this polymer in the mixture (data not shown).

To evaluate the release profile at 720 min, we used normalized values for drug content in such a way that the amount of drug remaining at 120 min was considered as total (100%) loading for all MP formulations. The results are shown in Table II.

To investigate the influence of each component on the TA dissolution pattern, the causal factor and response variables were related with a polynomial equation [eq. (1)] and statistical analysis. Furthermore, a computer optimization technique based on a response surface methodology with a polynomial equation [eq. (1)] was used to search for the optimal TA release formulation. The prediction model was obtained as follows:

$$R_2 = 2953.41X_2 - 15.78X_1 - 508.03X_3 - 2271.74X_1X_2 1195.71X_1X_3 - 4673.15X_2X_3 \quad (1)$$

where R_2 is the total amount of TA released between 120 and 720 min, X_1 is the percentage of PLGA RG502H in the mixture, X_2 is the percentage of Gantrez AN119 in the mixture, and X_3 is the percentage of PCL in the mixture.

The statistical analysis (ANOVA) and the correlation coefficient deduced from the calculated response with the regression equation, our prediction model, and the

TABLE II
Experimental Dissolution Profile for All Formulations

Formulation	R_1 (pH = 1.2)	R_2 (pH = 6.8)
F1	11.86 ± 4.22	86.52 ± 1.08
F2	6.60 ± 4.78	81.86 ± 3.56
F3	12.51 ± 0.77	60.59 ± 5.44
F4	52.60 ± 10.35	88.05 ± 11.67
F5	5.67 ± 1.38	54.07 ± 1.86
F6	11.14 ± 4.87	78.33 ± 0.75
F7	8.61 ± 2.58	71.18 ± 1.97
F8	8.65 ± 1.81	91.82 ± 0.41
F9	7.76 ± 1.50	85.66 ± 2.54
F10	11.48 ± 1.82	83.88 ± 0.33
F11	23.07 ± 2.66	100.9 ± 1.98

R_1 = percentage of TA released at 0–120 min.

values obtained experimentally ($p = 0.0047$; $r^2 = 0.94$) showed that this mathematical model gave as a result a good prediction for drug release at pH 6.8. The response surface (represented in Fig. 3) allowed us to estimate the TA release patterns according to the formulation composition.

Another of the objectives of this study was to determine the activation energy (E_a) associated with the drug (TA) release process from the release profiles. Subsequently, we tried to establish a thermodynamic model (which related the percentages of TA released and E_a). An equation was deduced on the basis of drug percentages released between 0 and 120 min and between 120 and 720 min and the time of release during the experiments. The equation properly predicted the experimental values with a very good fitting ($r^2 = 0.99$) for the two conditions of release. The equation obtained was as follows:

$$Y = ae^{-b/x+c}$$

where Y is the percentage of TA released, x is the time, the coefficient a is related to the asymptotic value that the equation takes at greater times (i.e., the maximum in the TA release), b is related to the E_a corresponding to the release process, and c is the time correction factor. The optimal coefficients determined for every fitting equation [eq. (1)] are shown in Table III. On the other hand, we propose the following Arrhenius-like model, which allowed us to calculate E_a for all of the formulations (Table IV) for the two conditions of pH investigated:

$$E_a = \left(\frac{b}{c}\right) RT \quad (2)$$

where R is the gases Arrhenius constant (units : kj/kelvin* mol) and T is the temperature (units : kelvin degree).

Finally, to determine whether the variables of the design (percentages of each component of the blend) had any effect on the percentages of drug released, we established a prediction model for ΔH_m of PCL (R_4).

Figure 4 shows different thermograms in the dynamic mode from 20 to 200°C at a heating rate of

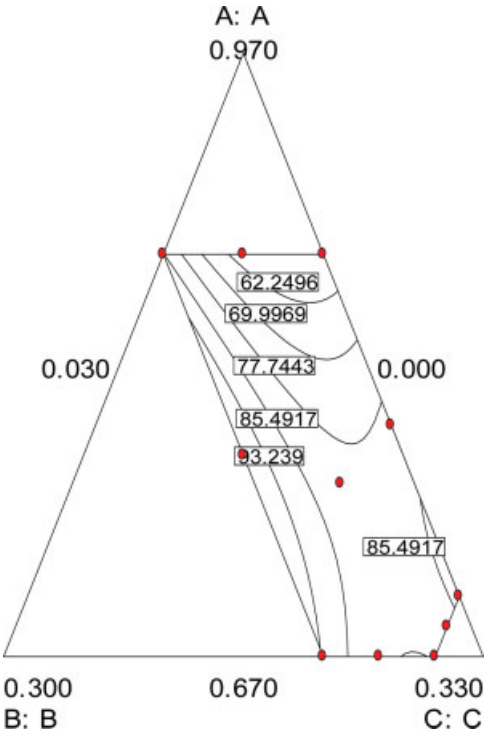

Figure 3 Response surface (R_2) for the percentage of TA released at 720 min (pH 6.8): A : A = PLGA; B : B = Gantrez AN119; C : C = PCL. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE III
Optimal Coefficients (a, *b*, and *c*) for the Fitting Equation [Eq. (1)] Determined for Every Formulation for pH 1.2 (Upper Number) and pH 6.8 (Lower Number) in the TA Release Experiments

Formulation	A	*B*	*C*
F1	16.39 ± 0.51	−45.66 ± 3.25	10.38 ± 1.46
	94.76 ± 0.63	−58.51 ± 2.16	−98.68 ± 1.97
F2	9.23 ± 0.23	−46.64 ± 2.61	9.38 ± 1.15
	103.77 ± 0.94	−148.99 ± 4.53	−69.54 ± 2.88
F3	17.73 ± 0.70	−51.66 ± 4.44	12.66 ± 1.91
	79.76 ± 1.58	−153.26 ± 11.96	−21.0 ± 9.61
F4	79.28 ± 1.97	−57.37 ± 2.90	13.30 ± 1.19
	103.11 ± 0.72	−63.59 ± 3.42	−15.97 ± 6.25
F5	9.34 ± 0.50	−71.0 ± 6.78	13.27 ± 2.51
	108.94 ± 2.61	−461.98 ± 19.22	9.86 ± 7.25
F6	17.58 ± 0.41	−62.55 ± 2.78	12.37 ± 1.09
	82.73 ± 0.35	−20.97 ± 0.88	−114.74 ± 1.12
F7	12.37 ± 0.40	−50.66 ± 3.52	11.07 ± 1.51
	76.61 ± 0.67	−38.84 ± 2.53	−100.17 ± 3.0
F8	15.79 ± 0.56	−84.75 ± 4.90	18.35 ± 1.70
	98.50 ± 0.20	−39.73 ± 0.73	−95.59 ± 0.80
F9	11.85 ± 0.44	−58.74 ± 4.41	14.53 ± 1.81
	93.28 ± 0.48	−44.90 ± 1.52	−101.74 ± 1.58
F10	17.28 ± 0.51	−56.70 ± 3.35	10.05 ± 1.36
	89.17 ± 0.25	−29.17 ± 0.68	−108.83 ± 0.83
F11	42.93 ± 1.95	−93.89 ± 6.66	22.36 ± 2.24
	102.83 ± 0.19	−17.03 ± 0.39	−110.91 ± 0.67

TABLE IV
E_a at pH 1.2 and 6.8 for Every Formulation

	E_a (kJ/mol)	
Formulation	pH 1.2	pH 6.8
F1	11.3	1.5
F2	12.8	5.5
F3	10.6	18.8
F4	11.1	10.3
F5	13.9	120.7
F6	13.1	0.5
F7	11.8	1.0
F8	11.9	1.1
F9	10.4	1.1
F10	14.5	0.7
F11	10.8	0.4

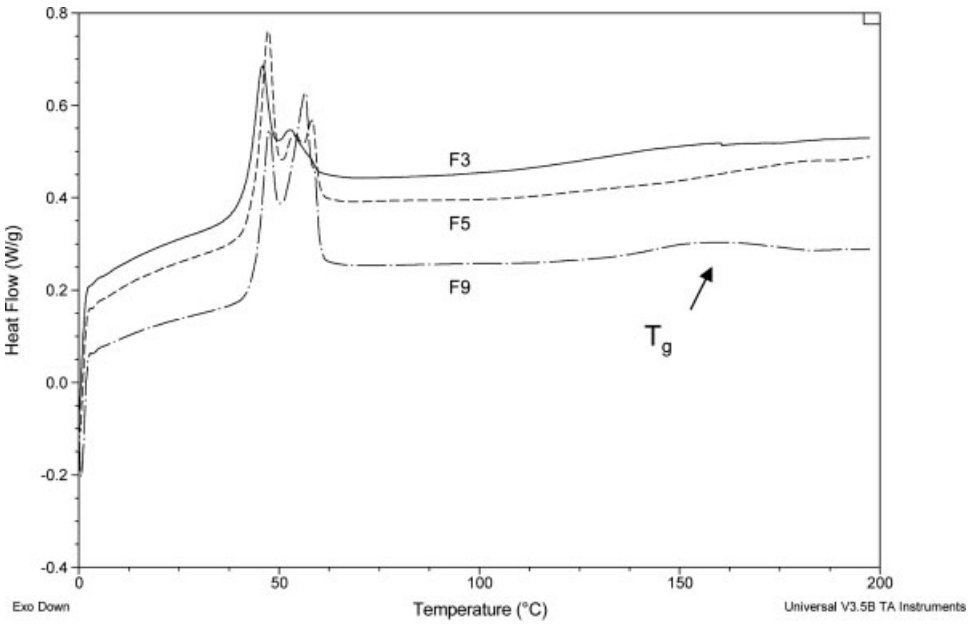

Figure 4 Overlay of DSC plots for 3 (F3, F5, and F9) of the 11 polymer mixtures investigated.

20°C/min for formulations F3, F5, and F9. The appearance of different endothermic peaks allowed us to calculate ΔH_m and ΔH_d. A T_g was found in the thermogram made for formulation F9. ΔH_d for PLGA, the enthalpy of PCL, and T_g are given in Table V.

As described previously, a quadratic model was obtained to relate variable R_4 with the blend composition variables. According to this equation, the significant factors were the lineal mixture and the interactions between PLGA (X_1) and PCL (X_3) and between Gantrez AN119 (X_2) and PCL (X_3):

$$R_4 = 779.22X_2 - 3.71X_1 + 134.89X_3 - 741.80X_1X_2 - 85.70X_1X_3 - 1513.51X_2X_3 \quad (3)$$

where $R^2 = 0.98$.

As shown previously, ΔH_m of PCL was affected by the presence of the other two components in the mixture. The presence of Gantrez, for example, seemed to increase the degree of amorphous structure of the substance in the mixture. Thus, formulations with identical proportions of PCL but with various Gantrez proportions had lower ΔH_m values (Table V). This effect was more pronounced at low concentrations of Gantrez.

Formulations with a low proportion of PCL (e.g., 13% of PCL from F11) showed higher ΔH_m values than formulations with high proportions, such as 23% (F8). This phenomenon might have been influenced by the presence of some kind of interaction with PCL, such as London–Van der Waals, probably due to the particle size difference.[12]

In this study, we found a direct relationship among the three parameters obtained: T_m, percentage of released drug, and E_a. The two first were determined experimentally, and E_a was calculated from the thermodynamic model. For example, when we compared formulations F3, F5, and F9, F9 had the lowest ΔH_m (3.75 J/g). It also showed a lower E_a (1.13 kJ/mol) and, therefore, an increased release percentage compared to the other two formulations. This fact confirmed the good behavior of the model to predict the drug profile.

The statistical model did not find any significant differences among the T_g values obtained for the different formulations. No differences were observed in T_g values. This suggests that Gantrez did not interact chemically, or at least, the changes were not quantified from a calorimetric point of view.

In Figure 4, only a T_g is shown. This means that Gantrez was present as one amorphous phase, and therefore, there was no miscibility with PCL and PLGA.

TABLE V
Measured Responses

Formulation	R_3 (μg of TA)	R_4 (J/g)	R_5 (J/g)	R_6 (°C)
F1	29.7	18.77	1.49	—
F2	29.3	12.13	3.71	—
F3	27.4	1.24	4.84	138.6
F4	25.9	18.51	3.4	—
F5	33.1	4.79	6.84	—
F6	34.2	7.92	5.9	140.05
F7	33.5	15.14	4.39	139.36
F8	31.6	8.75	4.52	140.69
F9	25.6	8.18	3.75	142.42
F10	31.6	10.67	4.19	144.38
F11	28.2	6.46	6.31	139.86

R_3 = content of TA/mg of MPs; $R_5 = \Delta H_d$ of PLGA; $R_6 = T_g$ of Gantrez. The data show the mean ($n = 3$).

Otherwise, a new inflection point (T_g) would appear corresponding to the new amorphous phases.[13]

This behavior was observed by other authors, who found a T_g for pure PLGA of 46.8°C,[11] which disappeared when PLGA–PCL was used. This phenomenon was due to the fact that this endothermic effect was overlapped by the melting peak of PCL, which took place in the same temperature range.[14]

The presence of PLGA at certain proportions caused the splitting of the endothermic peak due to the PCL, which suggests the presence of at least two crystalline microphases, both of them, characterized by its endotherm of melting.

According to the coefficient in the prediction model, the interaction between PLGA and PCL was not very strong; however, we should bear in mind that the PLGA proportion in the mixtures was very high compared to the other two components. Therefore, we suggest that when with low proportions of Gantrez, this substance was probably placed at the interphase between PLGA and PCL, thus reducing the crystal growth. When the proportions of Gantrez in the mixture were as high as in mixture F9, a new phase appeared, as clearly shown in Figure 4, where a T_g is well defined.

Prediction models showed that drug release was affected by the interactions among components. We have suggested some explanations for understanding these interactions better, but whether these modifications produced in the microstructure depend on the mixture composition used remains to be established.

In summary, this article describes the utility of mixture experimental design to develop optimal formulations successfully with different drug-release profiles at pH values of 1.2 and 6.8. We also evaluated the effects of the variables of drug-release behavior from MPs based on blends of biodegradable polymers. Furthermore, our approach allowed us to build a prediction model of drug release from MPs by the thermal characterization of materials included and *in vitro* drug-release experiments with a few selected batches.

CONCLUSIONS

We were able to develop formulations by spray-drying biodegradable blends of the polymers PLGA, Gantrez, and PCL using an experimental mixture design. The formulations here presented were able to control the release the glucocorticoid TA with different release profiles to minimize the drug release at pH 1.2. The other parameters investigated, including particle shape, particle size, ΔH_d, ΔH_m, and T_g, did not contribute significantly to the explanation of the drug-release behavior.

E_a associated with the process of TA release was calculated by a thermodynamic Arrhenius-like model in which the parameters involved in fitting equation (b and c) were included.

There was a direct relationship between the percentages of TA released, ΔH_m of PCL, and E_a calculated by the thermodynamic Arrhenius-like model. The presence of Gantrez in high proportions in the mixtures modified the thermal behavior and possibly the microstructure of the blend and greatly affected the E_a of the process, which resulted in an increased TA release. The prediction model obtained was well-suited to represent the experimental results and was, therefore, an efficient tool for estimating TA release under physiological conditions.

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