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hGH release from directly compressed hGH-PLGA biodegradable implantable tablets: Influence of physicomechanical factors

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ABSTRACT

The incidence of compression conditions, porosity and polymer degradation on human growth hormone (hGH) release from PLGA implantable tablets was evaluated with the aim of gaining insight in the mechanism involved in drug delivery from biodegradable matrices. Tablets elaborated by direct compression of hGH with PLGA, applying various compression forces for different times, kept the integrity and the stability of the hormone. Tablet dimensions, viscoelastic properties, glass to rubber transition temperature (T_g), PLGA degradation rate and water uptake were analyzed in the freshly prepared implantable tablets as well as at several times during release test in phosphate buffer pH 7.4. Placebo tablets were also prepared to evaluate the incidence of hGH on the physicomechanical properties of the device and PLGA degradation rate. Porosity remarkably determined the amount of hGH released, through an effect on the easiness of water penetration in the tablet and on the beginning of PLGA degradation. The decrease in PLGA molecular weight during the first days in the release medium, despite of being minor, significantly conditioned hGH release rate. The more dramatic changes in PLGA molecular weight observed after 20 days in the release medium notably reduced the T_g and the viscous and elastic moduli of the tablets. The overall analysis of the events underwent by the tablets in contact with the aqueous medium was used to explain the drug release profile and may help to optimize the design of the PLGA-based implantable tablets as peptidic drug delivery systems.

1. Introduction

Human growth hormone (hGH) is a neuroendocrine peptide useful for the management of pathologies that affect to the growth and the immune system [1–3]. Most treatments with hGH require daily injections for several years, which involve patient discomfort, non-compliance and risk of dosing errors. To overcome these limitations, sustained-delivery devices are gaining raising attention [4–6]. Biodegradable polyesters, such as poly(D,L-lactide-co-glycolide) (PLGA), are widely used as components of marketed biodegradable parenteral drug delivery systems, in form of microparticles, matrices, fibres and films, intended to be injected, implanted or inserted for local or systemic treatments [7–12]. Polymer structural properties, such as monomers ratio, mean molecular weight and polydispersivity, as well as particle size and the processing for preparing the device determine the glass transition temperature (T_g), the water penetration rate, the drug diffusion through the matrix, and the polymer degradation rate [13,15]. As a consequence, the mechanisms of drug release from PLGA devices are complex and still not fully understood [11,16]. PLGA films undergo remarkable physicomechanical changes when exposed to an aqueous environment [16]. The monitoring of the evolution of viscoelastic properties as the delivery of an antimalaric peptide progressed in a physiological mimicking medium has been shown useful to gain insight into the release profiles from PLGA films obtained by the solvent cast method [16–18].

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An attractive approach to obtain sustained-delivery devices is direct compression of mixtures of the active pharmaceutical ingredient (API) with a suitable polymer. In this way the incorporation of the whole API dose to each dosage unit is ensured and, at the same time, API potential degradation causes, such as contact with organic solvents or intense shaking, are minimized [7]. Devices obtained by compression have evidenced drug release profiles notably dependent on the composition of the formulation and on the compression conditions, which also determine the physical properties of the implantable tablet [8]. Importantly, the interactions between the polymer, the drug and the release medium have to be taken into account for a better understanding of the sometimes observed incomplete drug release and drug instability during PLGA biodegradation [11,19–22]. The nature of the drug included in the tablet also influences the polymer degradation and the release rate [14]. If the drug is a protein, the use of hydrophilic polymers and the creation of a viscous microenvironment as well as the prevention of the protein refolding in the release medium are relevant factors to achieve a sustained and complete protein release from the devices [13].

The aim of this work was to deepen into the knowledge of PLGA-based implantable tablets through the study of the dependence of the physical properties and hGH release behaviour on the compression variables. To carry out the work, hGH-PLGA blends were directly compressed. PLGA tablets were used as controls. Tablet microstructure, glass transition temperature and heat capacity, water sorption capability, PLGA degradation rate, storage and loss moduli were characterized in detail as a function of the time in the release medium.

2. Materials and methods

2.1. Materials

Biosynthetic 2-Cistron Human Growth Hormone (hGH) Cysteine ex. dDAP (batch ID 274881, manufactured in January 2007, HPSEC 99.8% purity, 4.8% water) was provided by Lilly S.A., Spain. Poly(D,L-lactide-co-glycolide) (PLGA, Resomer® RG 504H) was from Boehringer Ingelheim, KG, Germany. Other chemicals were HPLC grade.

2.2. PLGA characterization

The particle size distribution of the polymer (Fig. 1) was measured using a LS™ 100Q laser diffraction particle size analyzer (Beckman Coulter, Fullerton, USA). The mean volume-length diameter of PLGA particles was 35.9 ± 17 μm. The content in lactic acid (LA) and glycolic acid (GA) was determined by ^{1}H NMR with a Bruker AMX-400 spectrometer (Ettlingen, Germany) using deutered chloroform ($CDCl_3$, Sigma–Aldrich, Spain) as solvent. The proportion of lactic–glycolic (LA–GA) and glycolic–glycolic (GA–GA) acid bonds was assessed by ^{13}C NMR at 100.61 MHz, using dimethyl-sulphoxide-d6 (DMSO-d6, Sigma–Aldrich, Spain) as solvent [17]. The ratio of LA/GA was 53/47 and of LA–GA/GA–GA was 2/1.

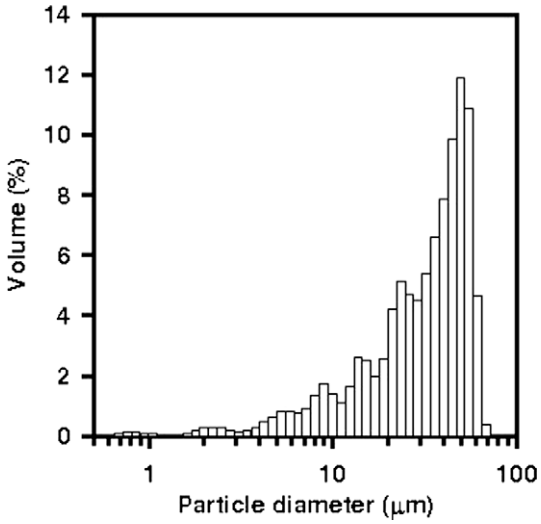

Fig. 1. Particle size distribution of PLGA.

The weight-average molecular weight (M_w) and number-average molecular weight (M_n) of PLGA, as received and after being compressed, were determined by gel permeation chromatography (GPC, Waters, Milford MA, USA) using Waters Ultrastyragel columns previously calibrated with 2800–700,000 Da polystyrene standards (Tokyo Soda Ltd., Tokyo, Japan), with a refractive index detector Waters 2414 (Milford MA, USA). Tetrahydrofuran (THF) was used as mobile phase at 0.9 ml/min. The effective M_n, M_w, and the polydispersivity of PLGA were found to be 31 ± 1 KDa, 54 ± 3 KDa, and 1.74 ± 0.03, respectively. This method was also used for evaluating the change in M_n and M_w during the release tests carried out with the tablets. The degradation index [23]:

$$DI = \frac{M_n^0}{M_n^t} - 1 \quad (1)$$

was estimated from M_n^0 which is the initial M_n, and M_n^t which represents M_n at time t.

2.3. PLGA tablets preparation

Four formulations of PLGA tablets with and without hGH were prepared by direct compression in a hydraulic press (Carver 4120, Wabash IN, USA) fitted with a 6 mm test cylinder and a pellet mold, under aseptic conditions and room temperature. Twenty units of each formulation were prepared in continuous. The composition, maximum compression force and compression time are indicated in Table 1.

2.4. Dimensions and porosity of the tablets

Each tablet was weighed (AG285, Mettler Toledo, Columbus OH, USA) and its thickness and diameter measured using a digital micrometer (Mitutoyo, Kawasaki, Japan). Porosity and the pore size distribution (180–0.1 μm) were characterized in duplicate using a mercury-intrusion porosimeter with a Micrometrics 9500 pore sizer

Table 1
Composition, compression conditions, physical properties and hGH content as determined by HPLC of the implantable tablets (n.d.: not determined).

Formulation	hGH (mg)	PLGA (mg)	Maximum compression force (T_n)	Time (s)	Weight (mg)	Thickness (mm)	Porosity (%)	hGH content as determined by SEC (%)
A_0	0	80	0.05	30	79.0 ± 1.6	3.75 ± 0.1	n.d.	0
A	1.6	80	0.05	30	80.1 ± 0.9	3.67 ± 0.09	41.8 ± 2.8	64.5 ± 0.1
B_0	0	80	0.05	90	79.3 ± 0.5	3.70 ± 0.1	n.d.	0
B	1.6	80	0.05	90	80.4 ± 1.3	3.77 ± 0.07	44.3 ± 2.1	70.6 ± 0.1
C_0	0	80	0.15	30	79.4 ± 0.5	2.70 ± 0.1	n.d.	0
C	1.6	80	0.15	30	81.4 ± 1.9	2.73 ± 0.1	22.2 ± 0.0	110.5 ± 0.3
D_0	0	80	0.15	90	79.5 ± 0.6	2.70 ± 0.03	n.d.	0
D	1.6	80	0.15	90	81.3 ± 1.0	2.67 ± 0.05	18.7 ± 1.1	111.0 ± 0.2

(Norcross GA, USA), fitted with a 3 ml powder penetrometer. Working pressures were in the range of 1–18,000 Psi.

2.5. Glass transition temperature

The glass transition temperature (T_g) of PLGA in the tablets was estimated using a Mettler Toledo 821^e modulated temperature differential scanning calorimeter (MTDSC) equipped with STAR^e software (Greifensee, Switzerland). The calorimeter was calibrated in temperature and heat with indium and zinc standards. Samples were accurately weighed in aluminium pans (1–3 mg), covered with a lid and hermetically closed, and heated from 15 to 60 °C at 1 °C/min, applying a modulation amplitude of 1 °C every 60 s. T_g was estimated as the midpoint of the glass transition signal. The runs were analyzed applying the alternating differential scanning calorimetry method (Mettler Toledo STAR^e Software, v. 6.10, Greifensee, Switzerland), which consists in processing together the blank measurements, the calibration curve and the sample curve. This approach is based on thermal analysis principles with additional calibration and, thus, the evaluations result in absolute values for the reversing and non-reversing part of the periodical measuring curve. The reversing part is also given as heat capacity (C_p) and its complex value is divided into two components: $C_{p\ \text{inphase}}$ and $C_{p\ \text{outphase}}$. Freshly prepared tablets and those vacuum dried for 72 h after the release assay were analyzed in duplicate.

2.6. Rheological behaviour

The storage (G') and the loss (G'') moduli and the phase angle (δ) of each tablet was recorded in a Rheolyst AR 1000N rheometer (TA Instruments, New Castle DE, USA) equipped with an AR2500 data analyzer, an environmental test chamber and a solid torsion kit. The sample was fixed between two clamps with a 3 mm gap. The experiments were carried out applying an angular frequency of 0.1 rad/s at 0.5% strain while increasing the temperature from 20 to 90 °C. The temperature at which tan δ reached a maximum was considered as the glass transition temperature (T_g). Freshly prepared tablets as well as those immersed for 10, 20 and 30 days in the release medium (after being vacuum dried during 72 h) were analyzed in duplicate.

2.7. hGH release

Each tablet was placed in an individual vial containing 1 ml of isotonic phosphate buffer (Sörensen) pH 7.4 at 37 °C for 30 days. The release medium was periodically replaced by equal volume of fresh buffer in order to prevent the degradation of the hormone [5]. The content in hGH of samples taken at predetermined release times was quantified using a 600 E multisolvent delivery HPLC (Waters, Milford MA, USA), a 717 Plus autosampler, a 2487 dual absorbance detector, a gel filtration column (Protein-Pak 125 300 × 7.8 mm) packed with 10 μm particles of 125 Å pore size, and Millenium32 data acquisition software. The mobile phase was acetonitrile/water 30/70 (v/v) with 0.05% trifluoroacetic acid at 1.0 ml/min. The experiments were carried out at room temperature with UV detection at 214 nm and with an injection volume of 20 μl. The solvents were previously filtered through 0.45 μm membranes (Millipore Iberica S.A., Madrid, Spain). Before the analysis, the method was validated.

2.8. hGH content

The hGH content in the tablets before and at the end of the release assay was determined by dissolving each one in 9 ml THF. Once the polymer was dissolved after shaking during 1 h, the dispersion was centrifuged at 4000 rpm for 10 min (Econospin Sorvall Instruments, Waltham MA, USA), the supernatant was removed and the residue was vacuum dried. This precipitate was dissolved in mobile phase and was analyzed by HPLC. Ten tablets of each formulation were analyzed to determine the initial API content. The stability of hGH in THF was confirmed by suspending a known amount of hormone in a known volume of solvent and quantifying the hGH concentration by HPLC at predetermined intervals for 24 h. This latter assay was made in triplicate.

2.9. Water sorption

After the release test (30 days), the tablets were taken out from the medium and their surfaces wiped with a filter paper, and the weight (W_W), the thickness and the diameter of each wet tablet were measured. Then, the tablets were dried under vacuum during 72 h, and the weight (W_D), the thickness and the diameter of the dried tablets were measured again. The weight of salts (W_S) sorbed by the tablet with the release medium was calculated from the salts concentration in the release medium (1.13%, w/w). The water sorption capability (WSC) was determined by using the Eq. (2) [8],

$$\text{WSC}\ (\%, w/w) = \frac{(W_w - W_D)}{(W_D - W_S)} \times 100 \quad (2)$$

3. Results and discussion

Four formulations of implantable tablets, placebo or with hGH incorporated, were prepared with the composition and under the conditions shown in Table 1. The compression did not affect the stability of hGH as confirmed by HPLC analysis. The initial hGH content was lower than the expected one for formulations A and B due to the lost of API when it was introduced into the pellet mold because of static electricity. This problem was prevented for formulation C and D increasing the amount of API weighed before it was introduced into the mold. Freshly prepared, all formulations had the same diameter (6 mm) and similar weight (ca. 80 mg). The resulting thickness and porosity (Fig. 2) mainly depended on the maximum force applied, but not on the time this force was maintained. The weight, the thickness and the diameter of the tablets after being in contact with the release medium for 30 days are summarized in Table 2. All formulations absorbed remarkable quantities of water increasing the weight up to 50%. Except formulation B, the tablets with API absorbed less quantity of water than the placebo tablets. In general, the hGH-loaded tablets lost less weight than the placebo tablets after 30 days in phosphate buffer pH 7.4. Furthermore, the hGH-loaded tablets maintained their original shape at the end of the release test, while the placebos became deformed. These findings suggest that the presence of hGH modifies the glassy structure of PLGA, its interaction with water and its degradation rate [16,19].

Table 3 shows the T_g values estimated by MTDSC and by rheometry analysis before and at several times during the release test for all the studied formulations. The differences in the T_g values recorded using these techniques are explained by the different physical properties that are analyzed for detecting the glass to rubber transition [24]. We observed that T_g of the tablets slowly decreased during the first 20 days in the release medium. After 30 days, a sharp fall down in T_g was observed. Freshly prepared implantable tablets exhibited T_g values above 25 °C; i.e., they were at the glassy state at room temperature and at the beginning of the release test. After 30 days, the T_gs were clearly below 37 °C, which means that at the temperature of the release test all tablets were at the rubbery state. Such a decrease in T_g is explained by the degradation of PLGA as the release medium penetrates into the tablet. It has been previously shown for placebo PLA and PLGA microparticles that the shorter polymer chains act as plasticizers mainly at the core of the particles owing to a limited diffusion towards the release medium [15]. Our results indicate that, even after drying and removal of water, the mobility of the PLGA in the tablet matrix is favoured by the partially degraded chains. Since degradation is promoted by the entrance of water and by the catalytic effect of the acidic degradation products [15], the decrease in T_g should correlate with the amount of water sorbed by the tablets and with the decrease in molecular weight underwent by PLGA. To test the incidence of the first factor, we tried to fit the Gordon-Taylor/Kelley-Bueche equation [25,26]:

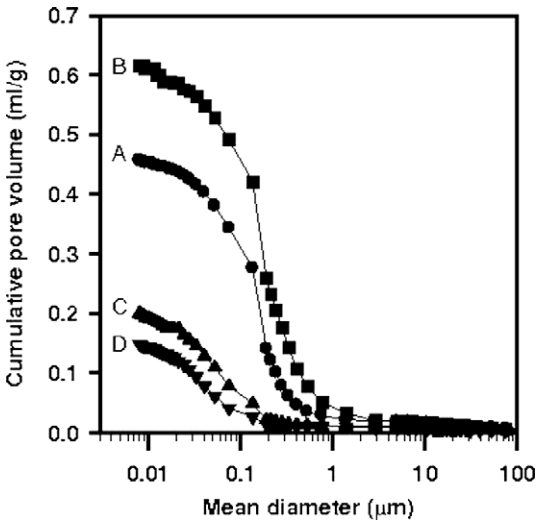

Fig. 2. Cumulative pore volume distribution of hGH-loaded implantable tablets.

$$T_{g\ mix} = \frac{(w_1 T_{g1} + K w_2 T_{g2})}{(w_1 + K w_2)} \quad (3)$$

and the Fox equation [25,26]:

$$\frac{1}{T_{g\ mix}} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \quad (4)$$

to the T_gs recorded for the implantable tablets prepared without hGH once freshly prepared and after 15 and 30 days of being immersed in phosphate buffer pH 7.4. In these equations, $T_{g\ mix}$ is the glass transition temperature of the tablets, w_n and $T_{g\ n}$ are the weight fractions and the T_g values of PLGA and water, and K is a constant calculated from the densities of the two components according to the Simha-Boyer rule (Eq. (5)),

$$K = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (5)$$

Equations (3)–(5) describe the behaviour of two components system (water + polymer). It should be noted that the T_g values were recorded for vacuum-dried implantable tablets after the release experiments and, thus, no water remains in their structure. Consequently, these equations cannot be strictly applied. We just used them to correlate the T_g of each tablet with its content in water during the release test, because we assume that the content in the acidic degradation products is directly proportional to the amount of water sorbed by the tablets. Thus, the content in water during the release test is used as a subrogate index of the changes that happen in the polymer structure when the tablets are in the aqueous medium. Under such assumptions, we observed that the T_g fitted well to Gordon-Taylor/Kelley-Bueche and Fox equations when the amount of water sorbed by the tablets is low (Fig. 3). However, the T_gs of those tablets with a greater water content

Table 2
Changes in the weight, the thickness and the diameter and amount of water sorbed by the implantable tablets after 30 days in phosphate buffer pH 7.4 release medium. The values are referred to those of freshly prepared implantable tablets (n.d.: not determined).

Formulation	Weight change (%)		Water sorbed (%)	Thickness change (%)		Diameter change (%)	
	Wet	Dry		Wet	Dry	Wet	Dry
A_0	122 ± 7.4	83.7 ± 8.7	46.9	27.4 ± 2.1	91.5 ± 1.1	n.d.	n.d.
A	130 ± 6.0	99.8 ± 0.1	40.8	105 ± 8.4	132 ± 0.0	85.1 ± 0.0	n.d.
B_0	116 ± 6.2	87.0 ± 3.3	33.6	22.3 ± 6.5	95.4 ± 6.6	n.d.	n.d.
B	144 ± 7.1	94.8 ± 6.0	52.6	102 ± 1.7	146 ± 2.8	90.2 ± 2.6	n.d.
C_0	147 ± 1.5	93.1 ± 0.8	58.4	48.4 ± 6.6	140 ± 1.5	n.d.	n.d.
C	141 ± 9.2	99.8 ± 1.2	41.9	127 ± 2.0	152 ± 3.1	93.5 ± 3.2	91.9 ± 0.4
D_0	135 ± 0.9	90.1 ± 3.4	50.7	48.1 ± 5.7	127 ± 1.2	n.d.	n.d.
D	134 ± 4.0	98.8 ± 2.9	35.5	119 ± 6.6	125 ± 1.0	86.4 ± 2.3	93.4 ± 2.8

Table 3
T_g values of dried placebo and hGH-loaded implantable tablets estimated by MTDSC and torsion rheometry analysis (n.d.: not determined).

Formulation	T_g (°C)						
	MTDSC		RHEOMETRY				
	0 days	30 days	0 days	10 days	15 days	20 days	30 days
A_0	42.1	20.8	52.0	n.d.	46	n.d.	<25.0
B_0	39.8	18.4	52.0	n.d.	46	n.d.	<25.0
C_0	41.8	21.1	51.9	n.d.	46	n.d.	31.0
D_0	41.8	20.1	52.0	n.d.	46	n.d.	<25.0
A	38.0	19.4	55.0	49	n.d.	46	28.0
B	37.8	23.6	52.0	46	n.d.	43	28.0
C	36.6	23.0	49.0	49	n.d.	43	34.0
D	40.2	22.3	49.0	49	n.d.	49	<250

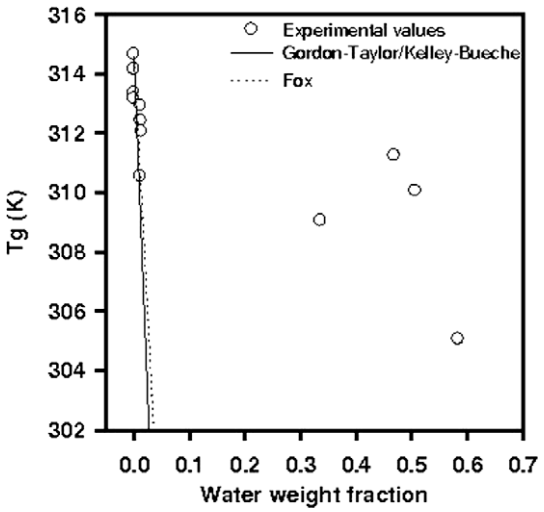

Fig. 3. Fitting of Gordon-Taylor/Kelley-Bueche and Fox equations to the T_g values obtained for implantable tablets at various times after being immersed in phosphate buffer pH 7.4 release medium. The samples were vacuum dried before the DSC analysis. The water weight fraction refers to content in water of the formulations before drying.

(>30%) are remarkably higher than those predicted by these equations. This suggest that, although a high content in water favours the degradation process, also facilitates the diffusion of the shorter PLGA chains towards the release medium, decreasing their plasticizing effect. To gain insight into these phenomena, the molecular weight of PLGA was determined in the tablets as freshly prepared and at various time intervals during the release test (Table 4). In the placebo tablets, the molecular weight decreased less than 2-fold from day 0 to day 15, and evidenced a 10-fold drop from day 15 to day 30. These data confirmed the degradation of PLGA and the remaining of low molecular weight chains in the vacuum-dried tablets used in the release test. Furthermore, the degradation rate profile resembles the first two phases of degradation (i.e., induction and acceleration of ester cleavage before erosion) found for PLA and PLGA microparticles [15]. It is important to note that these phases occurred in shorter periods of time in the implantable tablets than those previously reported for PLGA microparticles. This finding may be related to that the tablets have lower area exposed to the dissolution medium, which makes the release of the acidic degradation products more difficult and, consequently, promotes the ester chain cleavage. It should be noted that PLGA degradation was slower in the hGH-loaded tablets, probably due to the intercalation of hGH chains among the PLGA particles which could exert a certain protective effect. The chemical stability of the hGH remaining in the tablets after being 30 days in the phosphate buffer release medium was confirmed by HPLC.

Fig. 4 shows the viscoelastic behaviour of the hGH-loaded tablets as freshly prepared and after being in phosphate buffer pH 7.4 for 10, 20 and 30 days. Placebo tablets showed similar profiles. The freshly prepared tablets were quite rigid with G' and G'' above 10^6 Pa at temperatures

Table 4
Evolution of the weight (M_w) and number (M_n) average molecular weight of PLGA as the tablets were in the release medium for several days (standard deviations are shown in brackets).

Formulation	0 days	10 days	15 days	20 days	30 days
M_w (Da)					
A_0	55383 (833)	n.d.	37131 (450)	n.d.	3595 (131)
B_0	52041 (821)	n.d.	28596 (440)	n.d.	3725 (46)
C_0	54290 (436)	n.d.	30605 (396)	n.d.	4744 (64)
D_0	53011 (595)	n.d.	27717 (530)	n.d.	3744 (363)
A	50403 (405)	40411 (1523)	n.d.	22791 (485)	6404 (1342)
B	52046 (1110)	39291 (613)	n.d.	18964 (583)	4460 (176)
C	50383 (268)	42411 (2813)	n.d.	20131 (855)	5506 (500)
D	51271 (225)	43272 (5122)	n.d.	19394 (1873)	5720 (21)
M_n (Da)					
A_0	44641 (2589)	n.d.	20910 (3339)	n.d.	2128 (311)
B_0	37465 (322)	n.d.	20552 (835)	n.d.	2820 (187)
C_0	39228 (892)	n.d.	23176 (1533)	n.d.	3380 (561)
D_0	37766 (1791)	n.d.	17474 (3523)	n.d.	2022 (897)
A	32318 (1258)	27183 (3046)	n.d.	14132 (2319)	3529 (2912)
B	35599 (1563)	25686 (1650)	n.d.	11808 (1294)	2364 (83)
C	34232 (6513)	30752 (7645)	n.d.	13443 (1592)	3989 (477)
D	32359 (5836)	30805 (8147)	n.d.	12803 (2899)	3287 (600)

n.d.: not determined.

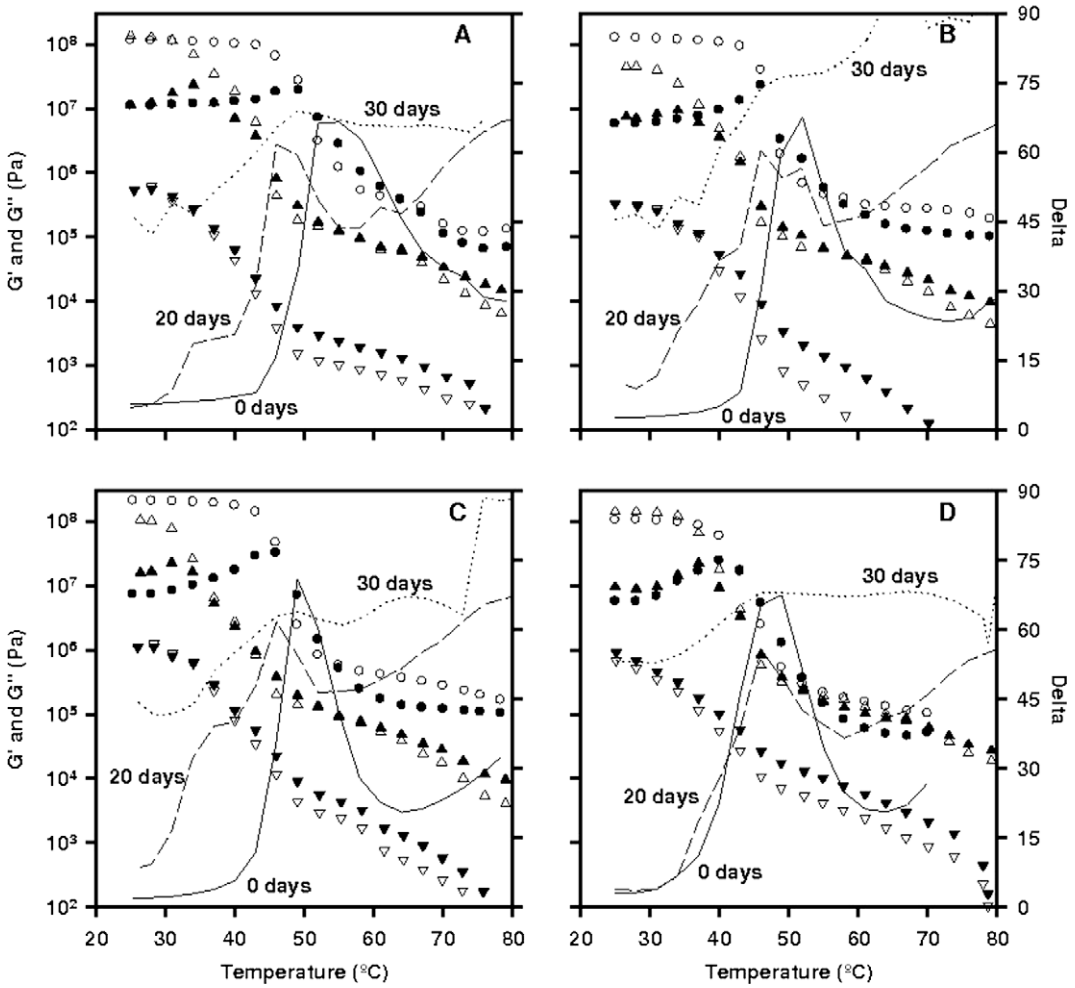

Fig. 4. Evolution of G' (open symbols), G'' (full symbols)and δ (lines) of the different implantable tablets as a function of time during which they were immersed in phosphate buffer pH 7.4 release medium. Legend: 0 days (circles and continuous line); 20 days (up triangles, dashed line); 30 days (down triangles, dotted line).

below the T_g. The decrease in G' and G'' at days 10 and 20 of the release test was of about one order of magnitude. After being in contact with the aqueous medium for 30 days, both moduli decreased by about two orders of magnitude; the change being more relevant in the case of G'. The evolution in time of the viscoelastic behaviour correlates with that of PLGA molecular weight. In the case of formulation B, the glass to rubber state transition seems to happen in a different way than in the other formulations. Above the T_g, a marked decrease in G' was observed, which indicates that the tablet lost its consistency. The evolution of C_p (specific heat capacity) was also different for formulation B compared to the others (Table 5). C_p is a fundamental thermodynamic property and changes in its value reflect alterations in the polymeric structure. The $C_{p\ complex}$ and $C_{p\ inphase}$ of formulations A, C and D increased after 30 days in the release medium, while they decreased for formulation B. These findings reveal that PLGA has a different mobility in formulation B than in the other formulations.

The hGH release profiles and the evolution of DI are shown in Fig. 5. All formulations showed a similar release profile, characterized by a fast delivery in the first days. After day 10, the release stopped. The amount released seems to be controlled by the porosity of the tablet; the most porous formulation (B) being the one that released more drug. The brusque acceleration in PLGA degradation observed after 20 days in the release medium did not cause relevant changes in the hGH release profile. After day 30, the tablets were analyzed to quantify the hGH remaining inside the polymer matrix. Incomplete release may be caused by a non-specific adsorption mechanism as described in the literature [27,28]. The non-released hormone was non-degraded and the mass balance was accomplished.

If one assumes that the drug release rate ($-dX/dt$) depends on the percentage of drug remaining inside the polymer matrix (X), and that polymer degradation provokes changes in the structure of the PLGA matrix, the following equation can be applied [5,16]:

$$-\frac{dLnX}{dt} = b_0 + b_1\frac{1}{M_w} \tag{6}$$

b_0 being the relative initial release rate and b_1 an index of the contribution of the polymer degradation to the release rate. All implantable tablets showed a release rate initially controlled by the PLGA molecular weight (Fig. 6). *In vivo* degradation is expected to be faster than *in vitro* due to an autocatalytic effect of the released degradation products that are confined in the surroundings of the tablet [29]. This means that the *in vitro* changes in molecular weight that take place in the first days determine the diffusion of the drug from the core of the tablet towards more external layers from where the hormone is released. Formulation B underwent greater changes in DI value than the other hGH formulations. Then, the fact that formulation B released more drug may be related to the highest initial porosity, which facilitates the entrance of more water, the softening of the polymer (decreasing in G' and G'' moduli and in C_p value), and the polymer degradation. Fig. 7 confirms the relationship between the water sorbed by each formulation and the quantity of drug released.

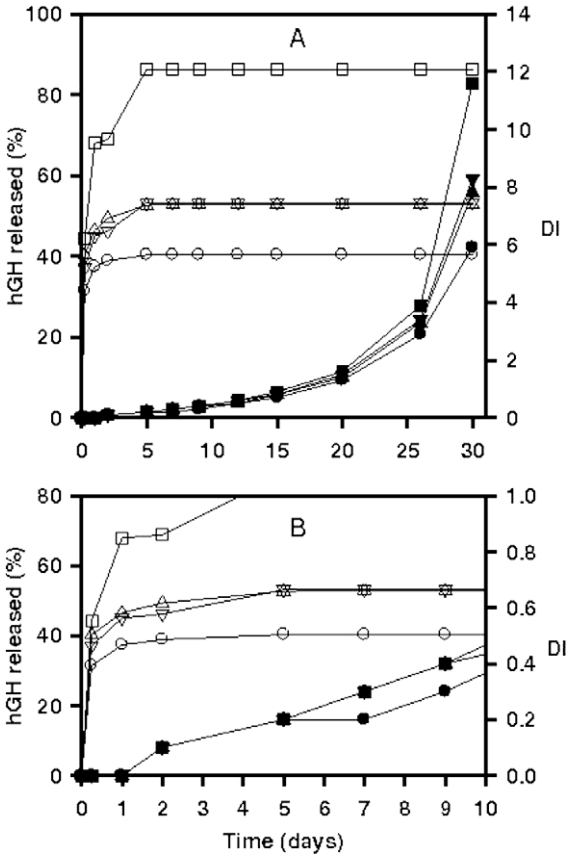

Fig. 5. hGH release profile from implantable tablets (left axis, open symbols) and DI of PLGA versus time plot (right axis, full symbols). Formulation A (circles), B (squares), C (up triangles) and D (down triangles). Fig. 4B shows in detail the evolution in the first 10 days.

Table 5
Specific heat capacity (C_p) values of hGH-loaded implantable tablets, freshly prepared and after 30 days in phosphate buffer pH 7.4 release medium.

Formulation	Time (days)	C_p (J/g°C)		
		Outphase	Inphase	Complex
A	0	−5.11	10.5	11.7
	30	−12.0	16.8	20.6
B	0	−4.77	10.2	11.3
	30	−5.71	9.28	10.9
C	0	−8.29	10.9	13.7
	30	−9.27	15.9	18.4
D	0	−8.82	14.0	16.5
	30	−41.1	18.3	45.0

4. Conclusions

Direct compression of hGH and PLGA blends does not compromise the stability of the hormone. Porosity and thickness of the implantable tablets depend on compression force, but not on the time this force was maintained.

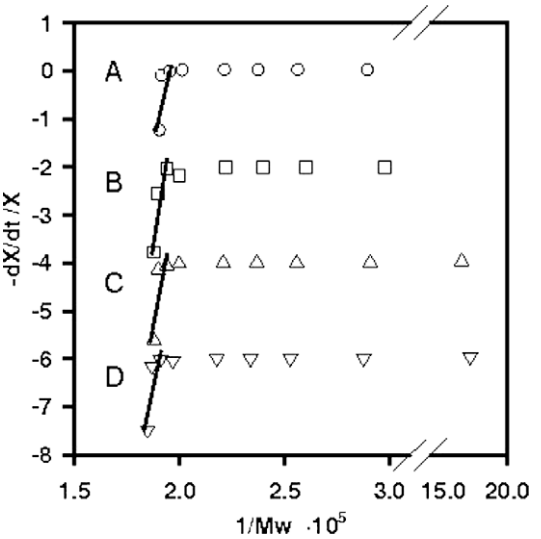

Fig. 6. Relationships between the time-derivative of the logarithm of the hGH amount released and the inverse of polymer M_w for the implantable tablets evaluated. The plots of formulations B, C, and D are down-shifted 2, 4 and 6 units on the *Y*-axis, respectively.

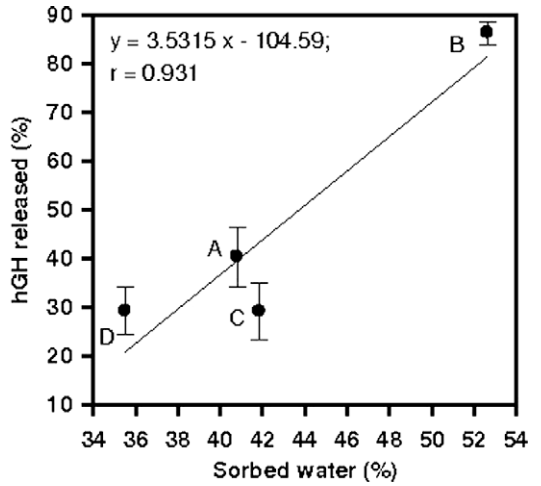

Fig. 7. Dependence of the amount of hGH released on the amount of water sorbed by the implantable tablets after 30 days in the release medium.

The hGH release rate is determined by the PLGA degradation until the second day and such a degradation is related to the initial porosity of the tablets and their capability to uptake water. Therefore, regulation of porosity by tuning the maximum compression force enables the control of hormone release rate and total hormone delivered. The more dramatic changes in PLGA molecular weight observed after 20 days in the release medium notably reduced the T_g and the viscous and elastic moduli of the tablets. The information obtained revealed that the microporous structure upon compression and the initial degradation of PLGA are key parameters that should be taken into account when designing PLGA-based implantable tablets as peptidic drug delivery systems.

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