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Thermal behavior and stability of biodegradable spray-dried microparticles containing triamcinolone

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ABSTRACT

Thermal analysis has been widely used for obtaining information about drug–polymer interactions and for pre-formulation studies of pharmaceutical dosage forms. In this work, biodegradable microparticles of poly (D,L-lactide-*co*-glycolide) (PLGA) containing triamcinolone (TR) in various drug:polymer ratios were produced by spray drying. The main purpose of this study was to study the effect of the spray-drying process not only on the drug–polymer interactions but also on the stability of microparticles using differential scanning calorimetry (DSC), thermogravimetry (TG) and derivative thermogravimetry (DTG), X-ray analysis (XRD), and infrared spectroscopy (IR). The evaluation of drug–polymer interactions and the pre-formulation studies were assessed using the DSC, TG and DTG, and IR. The quantitative analysis of drugs entrapped in PLGA microparticles was performed by the HPLC method. The results showed high levels of drug-loading efficiency for all used drug:polymer ratio, and the polymorph used for preparing the microparticles was the form B. The DSC and TG/DTG profiles for drug-loaded microparticles were very similar to those for the physical mixtures of the components. Therefore, a correlation between drug content and the structural and thermal properties of drug-loaded PLGA microparticles was established. These data indicate that the spray-drying technique does not affect the physico-chemical stability of the microparticle components. These results are in agreement with the IR analysis demonstrating that no significant chemical interaction occurs between TR and PLGA in both physical mixtures and microparticles. The results of the X-ray analysis are in agreement with the thermal analysis data showing that the amorphous form of TR prevails over a small fraction of crystalline phase of the drug also present in the TR-loaded microparticles. From the pre-formulation studies, we have found that the spray-drying methodology is an efficient process for obtaining TR-loaded PLGA microparticles.

1. Introduction

Triamcinolone (TR) is a steroidal anti-inflammatory drug usually administered by the parenteral route (Fig. 1). This compound has been used in ophthalmology, administered by intravitreal route to treat chronic inflammations of the posterior segment of the eye (Florian et al., 2004; Cardillo et al., 2005; Audren et al., 2006; Thomas et al., 2006; Morrison et al., 2007).

The development of a controlled release system for TR would be quite valuable for treatment of inflammatory ocular diseases. Microparticles have been used as prolonged release systems for several drugs, including antimicrobial, chemotherapic, and anti-inflammatory agents such as corticosteroids (Faisant et al., 2003; Gavini et al., 2004; Martínez-Sancho et al., 2004). Poly (D,L-lactide-*co*-glycolide) (PLGA) is a copolymer of lactic and glycolic acid (Fig. 2) widely used in particular drug release systems owing to its biodegradability and biocompatibility (Anderson and Shive, 1997; Uhrich et al., 1999; Jain et al., 1998; Kunou et al., 2000).

Several microencapsulating methods are currently described for obtaining biodegradable microparticles. Among them, spray drying is an important and widely used method for drug microencapsulation and presents several advantages, including a one-stage continuous process, easy adaptation to industrial scale, and high

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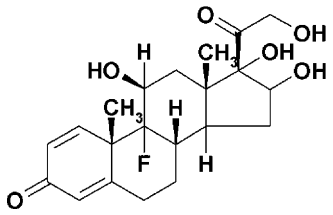

Fig. 1. Chemical structure of triamcinolone.

drug-loading efficiency (Giunchedi and Conte, 1995; Jain, 2000; Bruschi et al., 2003). On the other hand, this technique involves some stress conditions, such as shearing stress in the nozzle and thermal stress during the droplet-drying phase, making possible interactions between drug/polymer/solvent that can affect the stability of microparticle components during and after the microencapsulation process. In some cases the changes in the structural organization of crystalline drug into the polymeric matrix can occur after the solvent evaporation (Kurkuri and Aminabhavi, 2004; Mundargi et al., 2007; Murnane et al., 2008; Muller et al., 2007).

Polymorphism and pseudopolymorphism for the glucocorticoids as triamcinolone diacetate were well described (Suitchmezian et al., 2006a,b). Two polymorphic solvent-free forms and one pseudopolymorphic form were described for triamcinolone (Suitchmezian et al., 2007). The authors reported that the TR polymorph A is metastable and can be transformed into the polymorph B by the effect solvent. The TR polymorph B represents the thermodynamic stable form at room temperature. The formation of the pseudopolymorphic (monohydrate) form C was verified only in the presence of water as a solvent (Suitchmezian et al., 2007).

In addition to the maintenance of the chemical structure of triamcinolone, knowing the crystalline form present in the polymeric matrix and the physico-chemical properties of PLGA after the spray-drying process is important for obtaining the therapeutic effect from drug-loaded biodegradable microparticles (Lim and Kim, 2002; Dhanaraju et al., 2004; Elkordy et al., 2004).

Thermal analysis associated with X-ray diffraction has been extensively used to obtain information about drug–polymer interactions and pharmaceutical pre-formulation (Ebube et al., 2000; Heng et al., 2004; Elkordy et al., 2004; Schüle et al., 2007; Sipos et al., 2008). These techniques have been used to monitor the physico-chemical interactions among drug–excipient and excipient–excipient, and to investigate the effect of the production process of microparticles on the physical and chemical properties of pharmaceutical materials (Bond et al., 2002; Araújo et al., 2003; Lopes et al., 2006; Kim et al., 2006; Wang et al., 2007). Thus, X-ray diffraction provides information about the structural organization of the drug, while the DSC and TG/DTG can provide qualitative and quantitative information about the physical and chemical properties of the drug in the finished microparticles (Han and Suryanarayanan, 1999; Gaisford and Buckton, 2001; Horvat et al., 2005; Coughlan and Corrigan, 2006).

In this study, the spray-drying process was used to obtain TR-loaded PLGA microparticles with various TR:PLGA proportions. The stress effect of the microencapsulating process on the formulations was investigated by thermal analysis (DSC, TG/DTG) associated with the X-ray diffraction and infrared spectroscopy. The possible interactions between the drug and the polymer used in the microparticles were investigated. Physical mixtures with identical drug:polymer ratios used in the microparticle formulations were used as control.

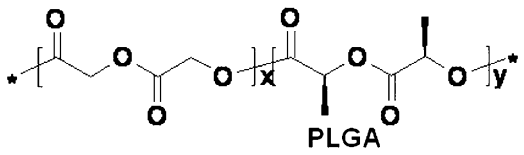

Fig. 2. Schematic representation of Chemical structure of poly (D,L-lactide-*co*-glycolide) (PLGA).

2. Experimental

2.1. Materials

TR was purchased from Sigma–Aldrich Inc., USA PLGA 50:50 (inherent viscosity 0.63 dl/g at 30 °C) was purchased from Birmingham Polymer Inc., USA. Methanol HPLC grade from J.T. Baker, Mexico, and acetone from Merck S.A., Brazil. Water was prepared with a Milli Q Plus water purification system (Millipore) and its resistivity was 18.2 MΩ cm. All other solvents and chemicals were analytical grade.

2.2. Microparticle preparation

Suitable amounts of TR were dissolved in acetone and then the polymer was added to give solutions with drug:polymer proportions of 1:1, 1:2, 1:3, and 1:5 (w/w). The microparticles were obtained using a Büchi 191 mini Spray Dryer equipped with a 0.7 mm nozzle, spray-rate feed about 5–6 ml min^{-1}, inlet air temperature of 70 °C, outlet air temperature of 45 °C, and spray pressure of 206 kPa. The solid microparticles were collected and stored under vacuum at room temperature for 48 h.

2.3. Morphology and particle size distribution analysis

The shape was assessed by scanning electronic microscopy (SEM) and the particle size analysis was performed using the image-processing software Leika qwin® by Feret diameter method.

2.4. Drug-loading efficiency

An appropriate amount of microparticles was dissolved in acetone to obtain 1 mg ml^{-1} of triamcinolone. The amount of TR entrapped into microparticles was determined by HPLC. The analytical method was previously developed and validated (Silva-Júnior et al., 2006). A volume of 300 μl was transferred to a 5 ml volumetric flask and the volume was completed with methanol to obtain 60 μg ml^{-1}. This solution was diluted with a mobile phase in order to obtain a theoretical concentration of 1250 ng ml^{-1} of triamcinolone. The samples were injected into a balanced Shimadzu Chromatographic system, using a Merck® Lichospher 100RP-18 column, 250 mm × 4.6 mm, particle size 5 μm, at 30 ± 2 °C. The mobile phase was methanol:water (45:55) with an isocratic flow rate of 1 ml min^{-1}. Rheodine injector with 10 μl loop and the UV–vis detector at 239 nm were used. The analytical concentration of TR was determined from a standard curve (r = 0.999). The analyses were performed in triplicate. The drug-loading efficiency was determined as the ratio between the analytical and theoretical drugs.

2.5. Thermal analysis

Differential scanning calorimetry (DSC) analysis was carried out in a DSC-50 cell (Shimadzu), using aluminum pans with lids with about 1 mg of sample, under dynamic nitrogen atmosphere (100 ml min^{-1}), heated at 10 °C min^{-1} from 25 to 500 °C. The DSC cell was calibrated with indium (melting point 156 °C and

ΔH = 28.4 J/g) and zinc (melting point 419.4 °C) standards. Thermogravimetry (TG) and thermogravimetry derivative (DTG) curves were obtained with a TGA-50 thermogravimetric analyzer (Shimadzu), using platinum pans with about 5 mg of sample, under dynamic nitrogen atmosphere (50 ml min^{-1}), at a heating rate of 10 °C min^{-1}, from 25 to 900 °C.

2.6. X-ray diffraction (XRD)

The X-ray diffraction analyses were performed for the drug, the polymer, and for drug-loaded PLGA microparticles (1:1, 1:2, 1:3 and 1:5, w/w) using a Rikugu, model Dmax 2500PC X-ray diffractometer with a 2θ range between 5° and 45° using Cu Kα radiation (λ = 1.5406 Å). The XRD patterns were recorded under ambient temperature conditions.

2.7. Infrared spectroscopy (IR)

Infrared spectroscopy was performed on the pure drug, pure polymer, drug-loaded microparticles, and 1:1, 1:2, 1:3, and 1:5 (w/w) TR:polymer physical mixtures at ambient temperature, in the range of 400–4000 cm^{-1}, using KBr pellets in a Shimadzu FTIR-8300 spectrometer.

2.8. Statistical analysis

The results are expressed as mean ± standard deviation (S.D.). A one-way analysis of variance was employed in the comparison of the experimental data. Post hoc multiple comparisons were done by Tukey's test for significance at *P*-values less than 0.05 ($P < 0.05$).

3. Results and discussion

Triamcinolone-loaded PLGA microparticles were produced with successful using the selected parameters in the spray-drying technique. The material obtained was a white powder, with a small particle size visually uniform; this particular characteristic was confirmed by SEM (Fig. 3).

The methodology that uses the dissolution of both drug and polymer in the solvent system provides a homogeneous distribution of the drug and the polymer into the microdroplet during the solvent evaporation in the spray-drying process. In fact, depending on the rate of the solvent evaporation and on the hydrophilicity-lipophilicity character of the drug and polymer a homogeneous molecular distribution of the drug into the matrix structure of the polymeric microparticles may be expected. Thus, suitable amounts of TR were dissolved in acetone and then the polymer was added to give the solutions with drug:polymer proportions of 1:1; 1:2; 1:3 and 1:5 (w/w). The microparticles were obtained using a Büchi 191 mini Spray Dryer equipped with a 0.7 mm nozzle, spray-rate feed about 5–6 ml min^{-1}, inlet air temperature of 70 °C, outlet air temperature of 45 °C, and spray pressure of 206 kPa.

The SEM images indicated a mostly spherical smooth shape for all TR-loaded PLGA microparticles that is associated with a crust formation without any loss of the droplet structure during the first stage of the drying process (Masters, 1972; Tewa-Tagne et al., 2007), demonstrating the success of the parameters selected for the particle formation process in the spray-dryer equipment.

The particle size distribution of different TR-loaded PLGA microparticles is shown in Fig. 4. The particles obtained exhibited monomodal distribution with the most frequent particle size between 0.5 and 1.5 μm. All microparticles presented a peak of particle size distribution very similar to that associated with the composition of the spray-dried drug–polymer solution. The same copolymer was used for all formulations, and the different concentrations of the drug–polymer solutions used were not able to modify the particle size distribution profile. The uniformity verified in the particle size distribution of TR-loaded PLGA microparticles is a very important technological property of powders, mainly because the relationship of this property with the drug release rate

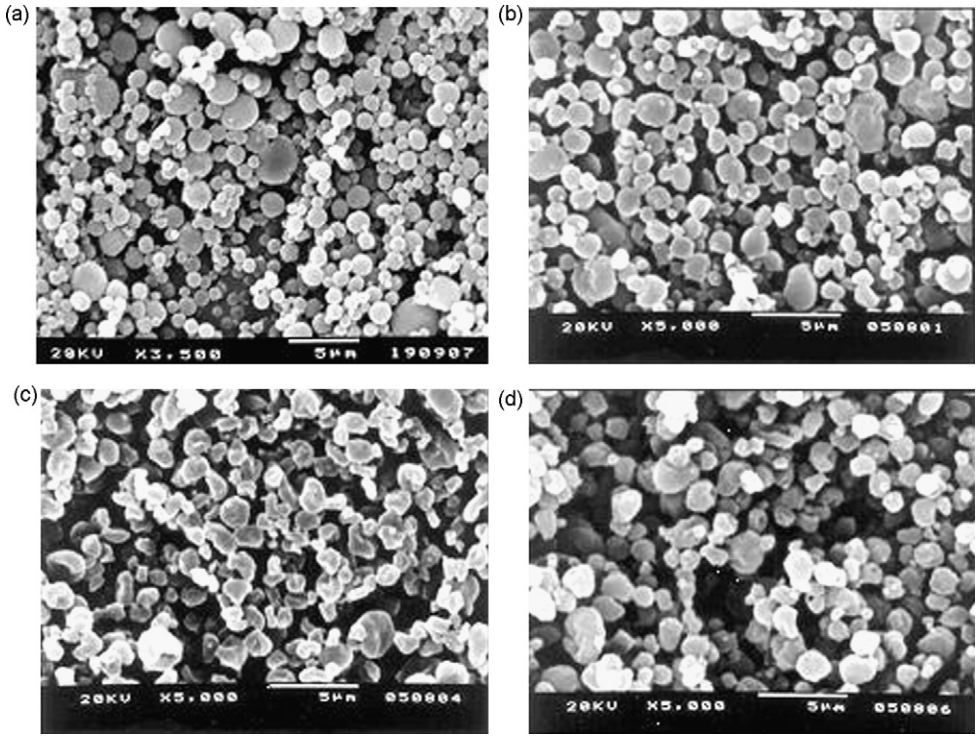

Fig. 3. SEM images of triamcinolone-loaded PLGA microparticles with drug/polymer proportions (w/w) of (a) 1:1; (b) 1:2; (c) 1:3; (d) 1:5.

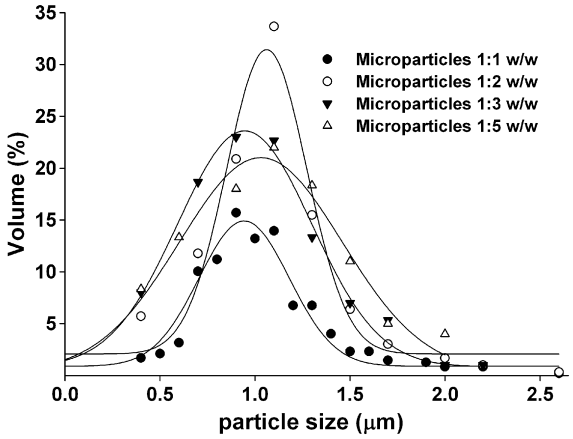

Fig. 4. Particle size distribution of different TR-loaded PLGA microparticles.

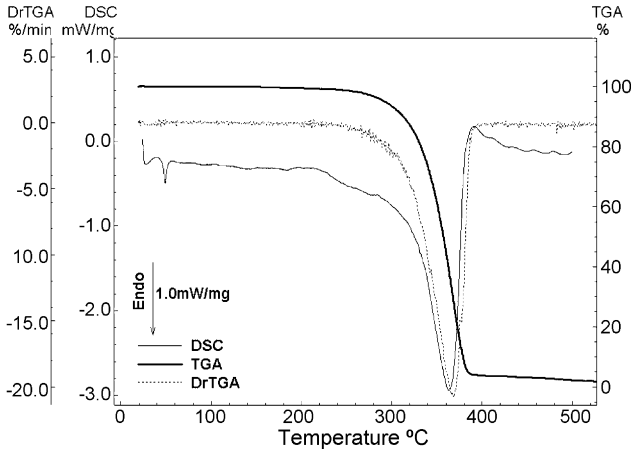

Fig. 5. DSC and TG/DTG curves of D,L-PLGA.

from the polymeric matrix (Silva-Júnior, 2005; Silva-Junior et al., 2008).

In the pharmaceutical field, spray drying is used to manufacture microparticles that form the basis for dry drug dosage forms for ocular/intraocular, parenteral, nasal, or pulmonary application, and these systems may be administered as suspensions, powders, or aerosols (Masters, 1972; Silva-Júnior, 2005; Vehring et al., 2007; Silva-Junior et al., 2008; Mundargi et al., 2008). Morphological aspects, particle size distribution, drug-loading efficiency, and the structural microorganization of the obtained particles are directly related to the technological parameters used for the production of PLGA microparticles (Masters, 1972; Vehring et al., 2007; Mundargi et al., 2008). The mean diameter of the particles was assessed and the measured values were very similar for the microparticles with different drug:polymer compositions. The quantitative results on the microparticles formed, such as the particle size analysis and the drug-loading efficiency are shown in Table 1.

The technological parameters used for spray drying lead to microparticles with small mean diameter (about 1.0 μm) when compared with other techniques. The particle size did not vary statistically ($P < 0.05$) among the different formulations. This feature can be explained by the low viscosity and the low concentrations of the drug/polymer polymer mixture of the sprayed organic solution (Masters, 1972). The efficiency of encapsulation of TR-loaded PLGA microparticles was determined by HPLC. Neither any peak for a degradation product nor any alteration of the chromatographic pattern of triamcinolone was observed, indicating that the selected parameters for the microencapsulating process did not affect the stability of the drug. Good levels of drug-loading efficiency were achieved for all microparticle systems, with values varying from 90.8 to 99.9%, depending on the drug:polymer proportions. The results demonstrating the high level of triamcinolone entrapped into PLGA microparticles are shown in Table 1. Similar drug:polymer proportions to those analytically determined in the microparticles were used for preparing the different physical mixtures that were used as control for thermal analysis and IR studies.

The thermo-mechanics behavior of the polymeric particles is directly related to the physico-chemical properties of the microparticle components. The polymer phase transition (Tg) may supply information about the flexibility of the polymeric chains, which may indicate the organization of the polymeric matrix that is directly associated with the rate of drug release. The DSC analysis may provide the organizational state of the drug (Giron, 2002; Markovic et al., 2006; Bartolomei et al., 2007) and drug–polymer interactions or physic stability of material after the technological process (Jeong et al., 2003; Ambike et al., 2004; Ohtaa and Bucktona, 2005; Corti et al., 2007;). The DSC curve and TG/DTG thermograms for pure PLGA are shown in Fig. 5.

From the DSC curve of PLGA, it is possible to observe two thermal events. The glass transition of polymer occurred in the range 45.5–52.4 °C with an enthalpy of relaxation of 0.05 mW/mg and midpoint of 43.12 °C. The endothermic degradation of PLGA occurred in a single step in the range of 309.2–381.0 °C ($\Delta H = -550.6$ J/g) with a weight loss of 90.1%. The DSC and TG/DTG curves for pure triamcinolone are shown in Fig. 6, which in the DSC curve it is possible to observe initially three endothermic peaks in the range of 242–280 °C, characteristic of polymorph B (Suitchmezian et al., 2007). The first occurred in 242.7–262.1 °C ($\Delta H = -4.7$ J/g) due to the characteristic polymorphic transition to form A, just followed by two more peaks in the ranges of 262.1–271 °C (−1.5 J/g) and 271.1–280 °C (−7.5 J/g), which may be attributed to the melting of triamcinolone. A fourth endothermic event occurred in the range of 280.1–330.4 (−37.1 J/g) and may be attributed to the TR decomposition afterward its melting. From the TG/DTG curves (Fig. 6) it could be confirmed that the thermal degradation occurred only after 265 °C, in two steps, with the first occurring in the range of 265–298.1 °C with a weight loss of 12.3% and the second occurring in the range of 298.2–468.3 °C with a weight loss of 58.5%.

The thermal behavior of TR used for preparing TR-loaded PLGA microparticles (Fig. 6) was characteristic of polymorph B. The X-ray diffratogram of TR is shown in Fig. 7 and can be observed a well-

Table 1
Quantitative analysis of the TR-loaded PLGA microparticles.

Theoretical drug/polymer ratio	Mean diameter (μm)	Analytical drug content (%)	Drug loading efficiency (%)
1:1	1.04 ± 0.34	49.00 ± 0.55	98.00 ± 1.10
1:2	1.07 ± 0.35	33.01 ± 1.84	99.85 ± 1.28
1:3	1.03 ± 0.37	24.87 ± 1.91	99.51 ± 0.77
1:5	1.09 ± 0.39	15.13 ± 2.13	90.78 ± 4.66[a]

[a] Statistically different ($P < 0.05$).

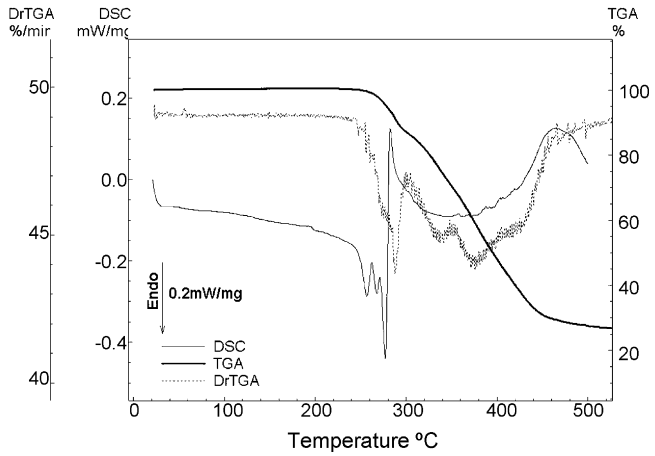

Fig. 6. DSC and TG/DTG curves of triamcinolone.

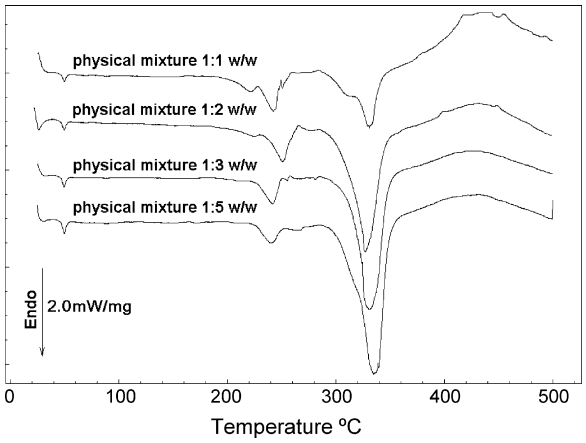

Fig. 8. DSC curves obtained from different physical mixtures (PM).

defined diffraction peaks which are characteristic of the crystalline structure of TR form B. The X-ray pattern of the drug is in agreement with the results of thermal analysis (Suitchmezian et al., 2007). The characterization of the drug state in the PLGA microparticles is very important, as the polymorph B is more stable at ambient temperature. The possible presence of the polymorph A in the PLGA microparticles could provoke polymorphic transitions at long the time. The XRD pattern from the pure PLGA shows its amorphous characteristics.

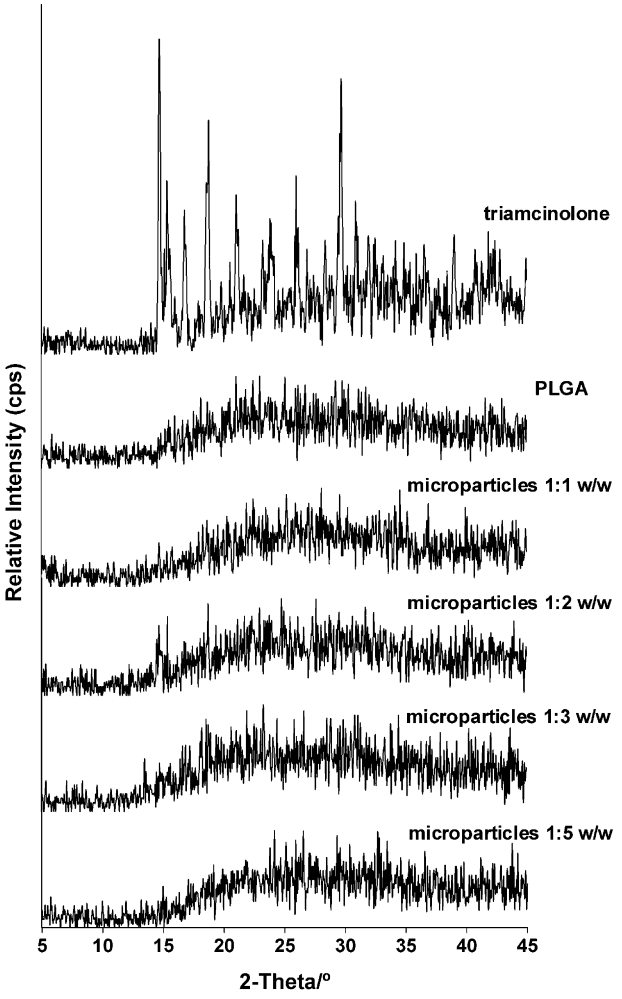

Fig. 7. XRD patterns obtained from triamcinolone, D,L-PLGA and TR-loaded PLGA microparticles.

The drug distribution into the polymeric matrix of microparticles is an important parameter to be considered mainly due to the direct effect on the release of the drug and bioavailability. The results of this study show that the X-ray diffractograms of TR-loaded PLGA microparticles were similar to that obtained for PLGA microparticles without drug (Fig. 7), which not contain any diffraction peaks indicating the presence of crystalline structures. However, we cannot discard that a very small fraction of crystalline structures of the drug may be present due to failure to register the X-ray diffraction peaks in the mixtures with large proportion of drug:polymer in the amorphous state.

The compatibility of the materials used for preparing the drug delivery system should be characterized before analyzing the effect of the microencapsulation process on the stability of different materials involved (Arias et al., 1998; Bikiaris et al., 2005). In this study, the physical and chemical interactions between TR and PLGA present in the physical mixtures with identical proportions to TR-loaded microparticles were analyzed with the aim of predicting the thermal behavior of the biodegradable microparticles. The data in Fig. 8 show that the glass transition of PLGA occurred in the range of 42–53 °C. An endothermic event was verified in the range of 195–229 °C due to the polymorphic transformation of TR (form B to form A). This event was observed only for physical mixtures with drug:polymer 1:1 (w/w) and 1:2 (w/w). The absence of this event for other physical mixtures may be attributed to the small drug proportion present in the sample. An endothermic event due to the melting of the drug occurred straight away in a temperature range of about 220–265 °C, followed immediately by the start of its thermal decomposition. Another endothermic event occurred in the range of about 286–355 °C, which may be attributed to the start of thermal decomposition of PLGA, followed by exothermic events. The appearance of polymorphic transition and the drug melting point at a lower temperature than that identified for the neat drug, with thermal decomposition just at the beginning of drug melting, occurred due to the possible dissolution of part of the drug in the melting phase of the polymer occurring during the heating. This is characteristic when carriers with low melting point/glass transition are used (Arias et al., 1998; Naima et al., 2001; Yamashita et al., 2003; Bikiaris et al., 2005; Silva-Junior et al., 2008). The data obtained from DSC analysis of all physical mixtures of microparticle components were confirmed by TG/DTG analysis (Fig. 9), which showed the T_{max} of the thermal decomposition occurring only after around 245 °C.

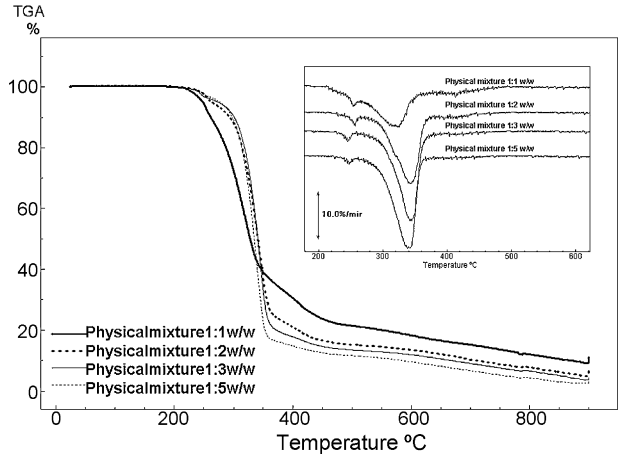

Fig. 9. TG and DTG curves obtained from different physical mixtures (PM).

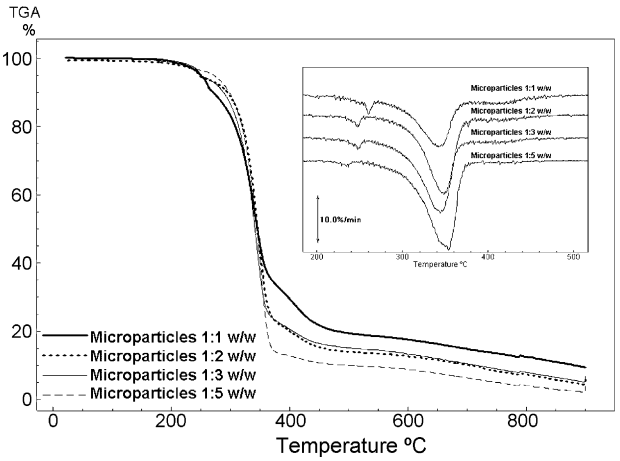

Fig. 11. TG and DTG curves obtained from different TR-loaded PLGA microparticles (Mc).

The thermal events of weight loss were confirmed by TG/DTG data (Fig. 9). It was then possible to clearly identify three steps. The first step was in the range of 224–261 °C due to initial decomposition of the drug, just after the beginning of its melting. The second step of drug decomposition occurred in the range about 262–348 °C, followed by the start of the polymer decomposition in the range of 348–463 °C; and after these steps, the decomposition of material occurred slowly with probable elimination of carbonaceous material. The beginning and intensity of the thermal events varied according to the drug:polymer proportion.

After characterizing the thermal properties of the physical mixtures, the DSC analysis of the different TR-loaded microparticles was performed (Fig. 10). The glass transition of PLGA occurred in the range of 41–53 °C. A thermal behavior similar to that identified for physical mixtures was observed, with the first endothermic event, due to polymorphic transition, occurring in the range of 195–221 °C for drug-loaded PLGA microparticles with 1:1, 1:2, and 1:3 (w/w) drug:polymer proportion. However for the drug:polymer proportion 1:5 (w/w) this event was absent. Although in the X-ray diffraction results it was not clearly identified the peaks due to presence of the crystalline fraction of the microencapsulated drug leading us to conclude that only a very small proportion of polymeric form of the drug is present.

Since after the spray-drying procedure only the presence of the amorphous form of triamcinolone was detected by X-ray diffraction analysis although the DSC thermograms indicate the presence of a small fraction of crystalline drug mainly in high proportion of triamcinolone in the microparticles, it is possible to suggest that the drug was predominantly dissolved as a stable molecular dispersion in the polymer matrices of microparticles. For low drug proportions (drug:polymer ratio 1:5, w/w) the DSC thermograms not show the polymorphic transition peaks in the region of 195–221 °C, indicating the complete dissolution of the triamcinolone into polymeric matrices.

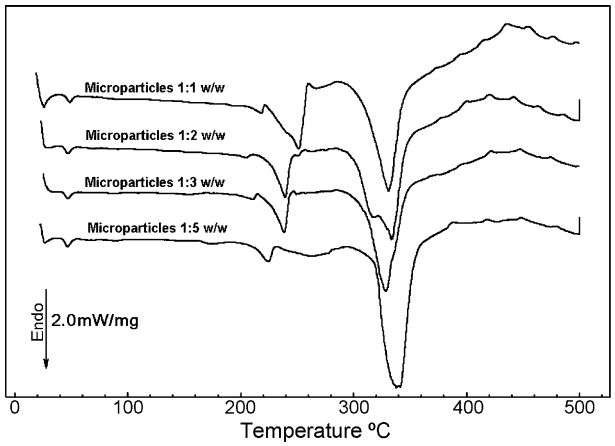

Fig. 10. DSC curves obtained from different TR-loaded PLGA microparticles (Mc).

The second endothermic event occurred in a temperature range of 210–258 °C due to melting of the drug, followed immediately by the start of thermal decomposition of the drug. The third endothermic event occurred in the range of about 286–356 °C, due to the start of thermal decomposition of PLGA.

The microencapsulating procedures are complex processes and involve many parameters such as solvent, temperature range and solvent evaporation rate that may affect the drug stability, drug–polymer interactions, or amorphous/crystalline ratio present in the microparticles (Dhanaraju et al., 2004; Mateovic-Rojnic et al., 2005). For compounds that exist in more than one crystalline form, it is fundamental to characterize the crystalline form after the solvent evaporation (Brittain, 1999).

From TG/DTG data (Fig. 11) it was possible to confirm a very similar thermal behavior to that identified for the respective physical mixtures. The first weight loss event due to initial decomposition of drug entrapped in the PLGA microparticles was identified in the range of 223–267 °C, followed by a second event occurring in the range around 240–373 °C due to both the second step of the drug decomposition and the start of the polymeric decomposition. In the range of 366–472 °C, the thermal decomposition of polymeric material continued and then the decomposition of material occurred slowly with the elimination of carbonaceous material. The beginning and intensity of the thermal events varied according to drug:polymer proportion.

The effect of the selected parameters for microencapsulating methodology was evaluated and the data from thermal analysis of different drug-loaded PLGA microparticles (Mc) was correlated with the respective physical mixtures (PM) (Table 2).

The temperature ranges of the thermal events were very similar, indicating that the conditions selected for preparation of the drug-loaded PLGA microparticles did not alter the thermal properties and the stability of the components; these results were confirmed by the quantitative analysis performed by HPLC. The DSC and TG/DTG analysis provided information about the drug–polymer interactions and about the drug state in the polymeric matrix. It was possible to establish a correlation between the amount of entrapped drug in the polymeric matrix and the intensity of

Table 2
Correlation between thermal properties determined for drug–polymer physical mixtures (PM) and drug-loaded microparticles (Mc).

Thermal analysis data				
Sample	1st event	2nd event	3rd event	4th event
DSC analysis				
PM	41–53 (46.5 °C)	195–227 (221.3 °C)	227–257 (242.4 °C)	285–343 (331.2 °C)
1:1 (w/w)	$\Delta H = -0.07$ mW/mg	$\Delta H = -9.9$ J/g	$\Delta H = -48.3$ J/g	$\Delta H = -148.5$ J/g
PM	43–52 (46.5 °C)	198–229 (225.3 °C)	229–264 (250.7 °C)	288–349 (327.2 °C)
1:2 (w/w)	$\Delta H = -0.08$ mW/mg	$\Delta H = -3.73$ J/g	$\Delta H = -58.6$	$\Delta H = -345.8$
PM	43–52 (46.5 °C)	–	224–248 (241.6 °C)	293–351 (331.5 °C)
1:3 (w/w)	$\Delta H = -0.08$ mW/mg	–	$\Delta H = -31.0$ J/g	$\Delta H = -385.0$
PM	43–52 (46.9 °C)	–	220–248 (240.5 °C)	289–354 (334.9 °C)
1:5 (w/w)	$\Delta H = -10$ mW/mg	–	$\Delta H = 21.5$ J/g	$\Delta H = -489.4$
Mc	42–53 (44.8 °C)	205–221 (218.4 °C)	221–258 (251.4 °C)	291–351 (330.9 °C)
1:1 (w/w)	$\Delta H = -0.04$ mW/mg	$\Delta H = -5.0$ J/g	$\Delta H = -129.9$ J/g	$\Delta H = -336.6$ J/g
Mc	41–50 (43.4 °C)	195–208 (204.4 °C)	217–246 (239.5 °C)	287–348 (333.6 °C)
1:2 (w/w)	$\Delta H = -0.08$ mW/mg	$\Delta H = -2.01$ J/g	$\Delta H = -65.5$ J/g	$\Delta H = -383.6$ J/g
Mc	41–52 (43.2 °C)	198–214 (210 °C)	219–244 (238.4 °C)	285–351 (328.8 °C)
1:3 (w/w)	$\Delta H = -0.05$ mW/mg	$\Delta H = -3.3$ J/g	$\Delta H = -56.8$ J/g	$\Delta H = -343.3$ J/g
Mc	40–50 (42.9 °C)	–	209–230 (224.7 °C)	311–355 (337.9 °C)
1:5 (w/w)	$\Delta H = -0.06$ mW/mg	–	$\Delta H = -18.3$ J/g	$\Delta H = -413.3$ J/g

Sample	1st event	2nd event	3rd event
TGA analysis			
PM	224.0–261.1	261.2–347.6	347.7–463.8
1:1 (w/w)	$T_{max} = 253$ ($\Delta m = 8.8\%$)	$T_{max} = 324$ ($\Delta m = 50.3\%$)	$T_{max} = 412$ ($\Delta m = 17.2\%$)
PM	234.0–261.6	261.7–370.2	370.3–452.8
1:2 (w/w)	$T_{max} = 256$ ($\Delta m = 3.9\%$)	$T_{max} = 342$ ($\Delta m = 70.8$)	$T_{max} = 404$ ($\Delta m = 8.0\%$)
PM	230.1–257.1	257.2–365.1	365.2–4385
1:3 (w/w)	$T_{max} = 245$ ($\Delta m = 3\%$)	$T_{max} = 345$ ($\Delta m = 75.2\%$)	$T_{max} = 403.6$ ($\Delta m = 5.9\%$)
PM	239.0–254.3	254.4–361.1	361.2–431.1
1:5 (w/w)	$T_{max} = 247$ ($\Delta m = 1.9\%$)	$T_{max} = 338$ ($\Delta m = 79.9\%$)	$T_{max} = 407$ ($\Delta m = 4\%$)
Mc	231.5–266.7	266.8–368.1	(368.2–472.7)
1:1 (w/w)	$T_{max} = 260$ ($\Delta m = 6.6\%$)	$T_{max} = 341$ ($\Delta m = 55.3\%$)	$T_{max} = 406$ ($\Delta m = 15.1\%$)
Mc	232.5–255.3	255.4–367.6	367.7–470.3
1:2 (w/w)	$T_{max} = 247$ ($\Delta m = 3\%$)	$T_{max} = 348$ ($\Delta m = 68.9\%$)	$T_{max} = 399$ $\Delta m = 10.6\%$
Mc	229.4–254.6	254.7–66.0	366.1–458.6
1:3 (w/w)	$T_{max} = 247$ ($\Delta m = 3.5\%$)	$T_{max} = 344$ ($\Delta m = 69.8\%$)	$T_{max} = 383.7$ ($\Delta m = 8.5\%$)
Mc	223.4–240.2	240.3–373.3	373.4–431.8
1:5 (w/w)	$T_{max} = 236$ ($\Delta m = 1.4\%$)	$T_{max} = 353.6$ ($\Delta m = 82.5$)	$T_{max} = 413$ ($\Delta m = 2.9\%$)

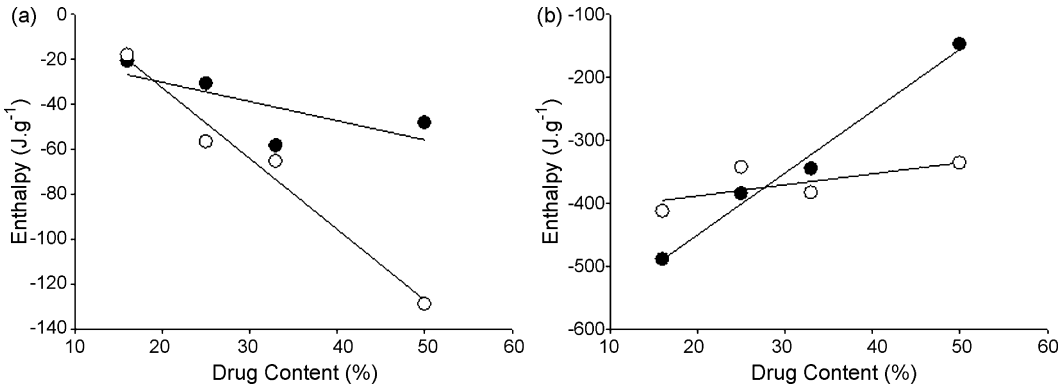

Fig. 12. Correlation of enthalpy values and drug content determined for both (a) third and (b) fourth DSC events for both (●) physical mixtures and (○) TR-loaded PLGA microparticles.

some occurring thermal events. The determined enthalpy values involved in the thermal events for triamcinolone-loaded PLGA microparticles were different from those reached for the respective physical mixtures. This could probably be attributed to the different organizational level of the drug present in the physical mixture and in the PLGA microparticles, which may be evidenced by the lower relaxation enthalpy identified for glass transition of polymer in the microparticles than that reached for the physical mixtures. It is well established that the particles produced by the spray-drying technique have a different aggregation state from that of the physical mixtures (Corrigan, 1995; Gustafsson et al., 1998; Anshuman et al., 2004; Ohtaa and Bucktona, 2005). However, a small crystalline fraction of the drug was identified in the PLGA microparticles and its prevalent form was the polymorph B.

The glass transition temperature (Tg) is an important parameter to characterize the mechanical behavior of polymers, due to its relation with the polymeric chains mobility. It has an important role in the mechanical properties of the polymer, allowing the diffusion of small molecules across the polymeric matrix (Vyazovkin and Dranca, 2005, 2006; Kim et al., 2007). The Tg values observed for drug-loaded PLGA microparticles were smaller than those identified for physical mixtures ($P < 0.05$), indicating a structural state more disorganized in PLGA microparticles as was confirmed by the X-ray diffraction analysis (Fig. 7). These relaxation enthalpies for glass transition values diminished according to the amount of drug loading, indicating a more homogeneous mixture of polymer matrix with the small amount of drugs. The intensity of thermal events for both the physical mixtures and for PLGA microparticles was perfectly correlated with the drug polymer proportion present in the sample, for example, as that observed for both the third and fourth DSC events (Fig. 12).

Through the correlation between the enthalpy values for the third DSC event and the drug content for both physical mixtures ($y = -0.85x - 13.29$; $r = 0.729$) and the drug-loaded PLGA microparticles ($3.14x - 30.0$; $r = 0.989$) (Fig. 12a), it was possible to verify that the intensity of the endothermic event decreased with the drug content, demonstrating that this feature occurred due to drug decomposition just as the melting began. Fig. 12b illustrates the correlation between the enthalpy values for the fourth DSC event and the drug content for both the physical mixtures ($y = 9.81x - 643.1$; $r = 0.993$) and the drug-loaded PLGA microparticles ($1.75x - 423.5$; $r = 0.703$). The intensity of this endothermic event increased with the diminishing of the drug content, demonstrating that this event is related to polymer decomposition. Moreover, this may be observed from the TG/DTG data (Table 2).

The infrared spectroscopy (IR) analysis was performed to complement the results from thermal analysis. The IR spectra for both triamcinolone and PLGA are shown in Fig. 13.

The characteristic bands observed from the IR data of TR included the OH group in the range 3390–3462 cm^{-1}, C=O bands at 1706 cm^{-1}, C=C bands in the range 1660–1600 cm^{-1}, C–H stretching of sp3 and sp2 carbons in the range of 3000 and 2900 cm^{-1}, and C–O stretching at 1200 cm^{-1} (Fig. 13a). From the IR data of PLGA the characteristic absorption bands at 1759 cm^{-1}, related to the ester group of PLGA, were identified, and the axial stretching of sp2 and sp3 carbons in the range 2900–3000 cm^{-1} were assigned (Fig. 13b).

The IR spectra for TR-loaded microparticles and the respective physical mixtures of the microparticle components are shown in Fig. 14. For both TR-loaded PLGA microparticles and the different physical mixtures of TR with the microparticle components, the

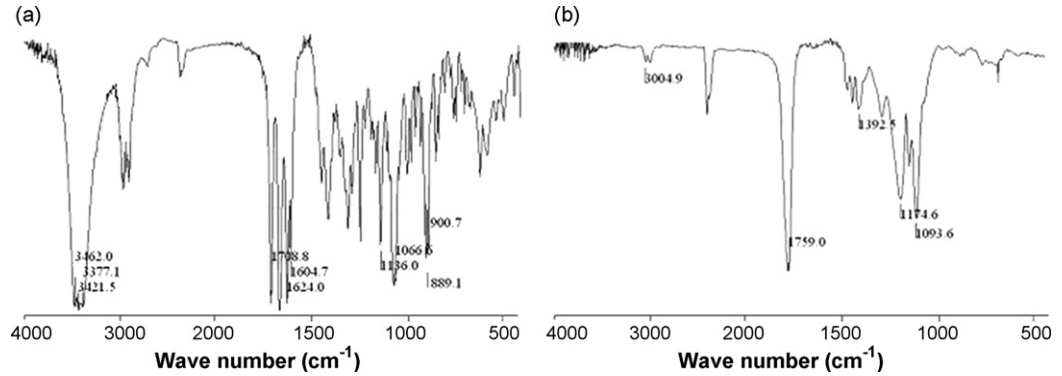

Fig. 13. Infrared spectra (IR) for both (a) triamcinolone and (b) PLGA.

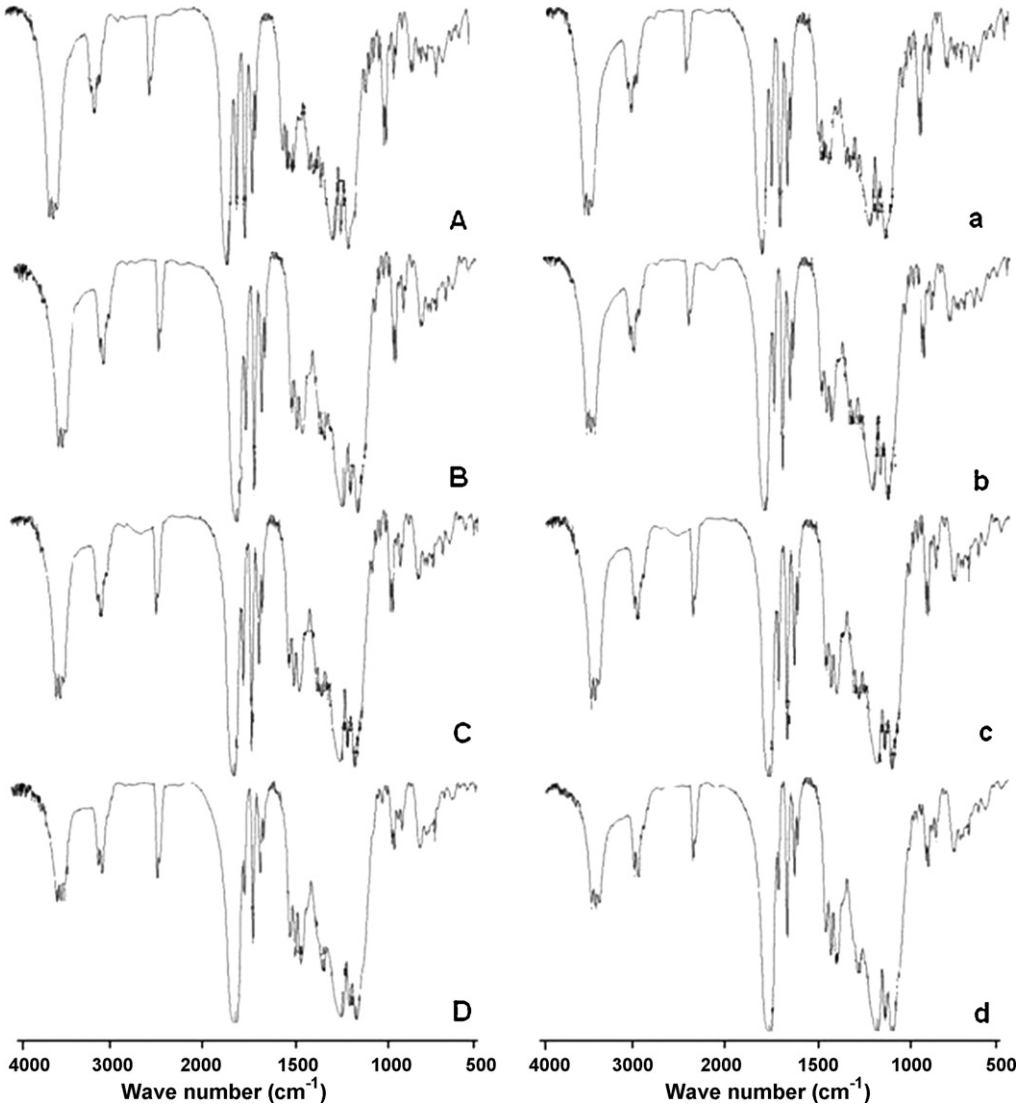

Fig. 14. Infrared spectra from TR-loaded PLGA microparticles with various drug:polymer proportions (w/w) (A) 1:1; (B) 1:2; (C) 1:3; (D) 1:5, and their corresponding physical mixtures (a) 1:1; (b) 1:2; (c) 1:3; (d) 1:5.

characteristic IR spectra was very similar, showing all the bands of the functional groups of TR and PLGA identified in the isolated compounds.

The maintenance of these characteristic bands of both the drug and PLGA polymer, as well as the absence of new IR bands, indicates that there was no chemical interaction between the TR and the PLGA, demonstrating that TR does not react with the polymer and is only dissolved in the PLGA polymeric matrix (Silva-Junior et al., 2008). Any new chemical specie formed after the drying process was identified in the thermal analysis experiments. In fact, since both the drug and the polymer have similar lipophilicity character a homogeneous distribution of the molecular drug into the matrix structure of the polymeric microparticles could be expected. Also, due to the low reactivity of both the drug and polymer functional groups in the very low water contents microenvironments of microparticles no chemical interaction between then was expected. The results of the IR analysis are in complete agreement with the thermal analysis data, for which no new chemical species after the microencapsulating process was also observed, proving that the thermal analysis may be used in the pre-formulation studies of polymeric drug delivery systems.

4. Conclusion

The results of this work demonstrated that the parameters selected for the microencapsulating process were adequate and did not provoke any change in the physical and chemical stability of the microparticle components. The distribution of the drug into the microparticles was found to be homogeneous with the drug predominantly dissolved as a stable molecular dispersion in the polymer matrices of microparticles. This result is supported by DSC and X-ray diffraction analysis. Using thermal analysis it was possible to perform the pre-formulation study for TR-loaded biodegradable microparticles produced by spray-drying technique. Furthermore, it was possible to establish a relation between drug content and the structural and thermal properties of drug-loaded PLGA microparticles. From the IR and DSC analyses it was found that no interactions between the drug and the polymer in the microenvironments of microparticles occurred. The technological parameters used provided a high degree of triamcinolone entrapment in the polymeric microparticles; thus, the spray-drying technique was demonstrated to be an efficient and trustworthy microencapsulating process for production of TR-loaded microparticles.

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