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Drug release from a polymer
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PREPARATION AND EVALUATION OF THE IN VITRO DRUG RELEASE PROPERTIES OF NOVEL MATRIX OF LOW MOLECULAR WEIGHT PLLA

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Abstract – This work studied the behavior of a poly(L-lactic acid)-based polymer with low molecular weight (LMW PLLA), synthesized by azeotropic condensation of L-lactic acid and used as a carrier matrix. For that, ibuprofen (IBF)-loaded polymer matrices were prepared by using physical mixtures (PMs) and solid dispersions (SDs). The possible interactions between IBF and LMW PLLA were investigated, using SEM, XRD, and FT-IR. The release of IBF from LMW PLLA matrices was also examined. The mechanism of drug release was found to be a drug diffusion through the LMW PLLA matrix, and that the interactions between IBF and LMW PLLA appeared to be via hydrogen bonding. On the basis of the results obtained, it was concluded that solid dispersion is a good approach to enhance bioavailability of poorly-soluble ibuprofen.

Résumé – Préparation et évaluation du relâchement in vitro d'un polymère à base de PLLA de faible masse moléculaire. Ce travail porte sur le comportement d'un polymère à base de poly(L-acide lactique) de faible masse molaire (LMW PLLA), élaboré par polycondensation azéotropique de L-acide lactique et utilisé comme excipient de type matriciel. Des matrices PLLA chargées en ibuprofène (IBF) ont été préparées en utilisant les mélanges physiques (PMs) et les mélanges par évaporation du solvant (SDs). Les interactions entre IBF et LMW PLLA ont été étudiées par MEB, DRX et IR-TF. Le mécanisme de libération de l'IBF s'avère s'effectuer par la diffusion de ce dernier à partir de la matrice LMW PLLA. Les interactions entre l'IBF et le LMW PLLA semblent mettre en jeu des liaisons hydrogènes. Les résultats obtenus confirment que la méthode d'évaporation du solvant représente une bonne approche pour augmenter la biodisponibilité de l'ibuprofène faiblement soluble.

1. INTRODUCTION

Biomaterials and biodegradable materials represent two of the most interesting areas of material science, in which chemical, medical, and environmental scientists are contributing to

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human health care, improving the quality of life, protecting environment from white pollution, and reducing dependence on fossil fuels [1]. One of the major polymers in this arena is poly(lactic acid) or poly(lactide) (PLA). This latter is highly biocompatible, being bioresorbed via the Krebs cycle [2]. PLA is derived from renewable resources such as corn, potato, cane molasses and beet sugar. From these renewable resources, a potential feedstock for production of PLA (i.e. lactic acid) can be produced by fermentation [3].

There are two major routes to produce poly(lactic acid) from the lactic acid monomer: direct condensation polymerization of lactic acid and ring-opening polymerization through the lactide intermediate. The first route involves the removal of water by condensation and use of solvent under high vacuum and temperature. With this route only low to intermediate molecular-weight polymers can be produced, mainly because of the presence of water and impurities. The second route is indirect, developed by Cargill Dow Company. It consists of producing by the first process, a low molecular weight PLA. Then, this latter is depolymerized and converted into lactide which is transformed to PLA with a higher and more homogeneous molecular weight distribution [4].

When PLA is used for orthopedic and oral surgeries as fixation of augmentation devices, PLA of high molecular weight is needed to produce devices of high mechanical strength. On the contrary, such high molecular weights are not necessary, if it used as a carrier for drug delivery systems [5]. In polymeric drug delivery systems the drugs are incorporated into a polymer matrix. The rate of release of drugs from such a system depends on a multitude of parameters such as the nature of the polymer matrix, the matrix geometry, the drug properties, the initial drug loading, and the drug-matrix interaction [6]. It was reported that polymer/drug interaction plays a significant role in the drug release behavior of the examined delivery system [7].

Ibuprofen (IBF, *figure 1*), α-methyl-4-(2-methylpropyl)-benzene acid is a non-steroidal anti-inflammatory, antipyretic and analgesic drug [8]. Even if the pharmacological activity of this drug resides in the S-enantiomer, IBF is usually administered as a racemate (RS-IBF) since an extensive bioconversion of the R-enantiomer to S-enantiomer occurs after oral administration [9].

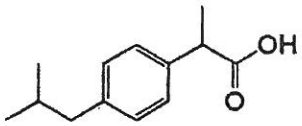

Figure 1. Chemical structure of ibuprofen.

This drug is indicated for the relief of mild to moderate pain and inflammation in conditions such as dysmenorrea, migraine, postoperative pain, dental pain. It is also used in chronic disorders as ankylosing spondylits, osteoarthritis and rheumatoid arthritis. It has low aqueous solubility, and hence poor dissolution [8,10].

The drug is readily absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 1 to 2 hours after ingestion [8]. Aside from its interesting active effects, ibuprofen has an undesirable secondary effect on the gastric mucosa, which may also suffer direct injury from this molecule, a weak acid, that presents itself in the non-ionic form at gastric pH [11]. Therefore, a great attention has been devoted to formulate oral controlled release systems, to protect the gastric mucous membrane from drug irritation or to mask its unpleasant taste.

The pharmacological properties of ibuprofen make of it an ideal model drug for the application of various sustained release technologies. A number of techniques are reported in the literature to extend the duration of action by delaying the release of the drug. These usually involve the direct coating of the drug, the coating of granules, pellets or the final solid dose unit, or the incorporation of the drug into a matrix which slowly releases the drug through the processes of erosion and/or diffusion [12].

In this paper, LMW PLLAs were synthesized by azeotropic condensation of L-lactic acid. The microstructure of the materials was carefully analyzed by means of several complementary techniques including thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FT-IR). IBF-loaded LMW PLLAs matrices were prepared by physical mixtures and solid dispersions. The prepared drug/carrier systems were characterized by SEM for morphological analysis; XRD for the physical state of the drug in the polymer matrix; and FT-IR to assess the interactions between the drug and polymer. In addition dissolution testing was performed to investigate the influence of the carrier and preparation methods on dissolution rate of IBF.

2. EXPERIMENTAL

2.1. Materials

L-lactic acid monomer was obtained as an aqueous solution (purity 85%); stannous dichloride dihydrate ($SnCl_2.2H_2O$) (purity 98%) was used as catalyst; Ibuprofen (IBF, purity 84%) was supplied by Saidal Group (Algeria) and solvents, p-xylene (99.02%), chloroform (99.9%) and methanol (99.5%), were purchased from BIOCHEM Chemopharma. All solvents were used without further purification.

2.2. Synthesis of LMW PLLA

An aqueous solution of L-lactic acid (100 mL) was poured into a three-neck reactor (500 mL) and then immersed in an oil bath at 100°C under nitrogen atmosphere for 24 h to remove the free initial water present with the monomer. Thereafter, 0.2 wt.% of $SnCl_2.2H_2O$ and 250 mL of p-xylene were added into the reactor and the mixture was heated to the polymerization temperature of 138°C. During polymerization water was continuously distilled off azeotropically. After a predetermined time, the final solution was poured into an excess of methanol with vigorous stirring to precipitate the polymer. The obtained LMW PLLA was filtered and dried at 40°C for one week. Three polymers (LMW PLLA) with different molecular weights 1000, 3000 and 9000 g/mol, determined by viscosimetric measurements using Ubbelhode viscosimeter, were synthesized. The molecular weights obtained are conditioned by the reaction time.

2.3. Characterization of Chemical Structure of LMW PLLA

The thermal stability of LMW PLLA was measured using thermogravimetric analysis (TGA, SETARAM TG-DT A92). The temperature range was from 20°C to 500°C under nitrogen flow with a heating rate of 10°C/min. The thermal properties of LMW PLLA were also measured using differential scanning calorimeter (DSC). Samples (8.5 - 9.5 mg) were loaded into aluminum pans and the DSC thermograms were recorded on a DSC apparatus (DSC 2920, TA Instruments, Version 0.4, USA). The DSC thermograms were obtained with a heating procedure during which, by using nitrogen flow, the heating rate reached 10°C/min in the range of 20°C to 180°C.

The structure of LMW PLLA was confirmed using X-ray diffraction (PANalytical X'Pert HighScore) with monochromatic $CuK\alpha_1$ radiation (λ = 1.54056 Å). The voltage and current were 45 kV and 30 mA, respectively. The diffraction patterns were recorded in the range of $5° \leq 2\theta \leq 50°$, with a step size of 0.02°, and a time of 7 seconds per step. The structure of LMW PLLA was also confirmed through FT-IR (IR Affinity-1 CE Shimadzu, Japan) on specimens pressed to a plate with KBr. The scanning range was from 4000 to 400 cm^{-1}.

2.4. Preparation of Solid Dispersions (SDs)

The SDs of IBF with LMW PLLA containing three different weight ratios (20:1, 20:3, 20:5 IBF/LMW PLLA) and denoted as SD 20/1, SD 20/3, and SD 20/5, respectively, were prepared with solvent evaporation method. Weighed amount of IBF and LMW PLLA were co-dissolved in 150 mL of dimethylformamid (DMF) in a 250 mL Erlenmeyer with stirring at 700 rpm for 30 hours. Organic solvent was removed from the dispersion by the evaporation technique under reduced pressure at 60°C. The resulting residue was dried at 50°C for two days. The hardened mixture was poured in a mortar and stored at room temperature until use.

The physical mixtures (PMs) having the same weight ratio as SDs were prepared by mixing the required amount of IBF and LMW PLLA for 15 min in a mortar. The resulting mixtures are denoted as PM 20/1, PM 20/3 and PM 20/5, respectively. The mixtures were stored at room temperature until use.

2.5. Characterization of Solid Dispersions

SEM (FEG 600) was used to observe the morphology of SDs. To study the existence of the interactions between the IBF and the LMW PLLA, FT-IR and XRD analyses were carried out on the samples.

2.6. In Vitro Release Experiment

The dissolution rate of pure drug and drug release rate from the polymer matrix were studied using the paddle method (Pharma Test DT70, Germany). Ibuprofen particles equivalent to 20 mg of drug were first molded into tablets and then immersed into the dissolution vessel containing 900 mL buffer solutions at pH 5.8 and 7.4 maintained at 37°C ± 0.5°C and stirred at 50 rpm. The release was followed by recording the drug concentration using ultraviolet spectroscopy. Aliquots of 3 mL of the release medium were withdrawn at predetermined time intervals. The initial volume of the release medium was maintained by adding equivalent amount of fresh medium after each sampling. The concentration of ibuprofen released was determined spectrophotometrically at 223 nm on a UV/Visible spectrophotometer (Optizen 2120UV, Korea).

3. RESULTS AND DISCUSSION

3.1. Synthesis and Characterization of LMW PLLA

The reaction mechanism of the dehydrative condensation for the stannous catalysts is not yet understood. However, a possible mechanism for the catalytic activity of the stannous compounds can be proposed. The synthesis of the LMW PLLA involves three steps.

1. Self-condensation of two molecules of $SnCl_2.2H_2O$ to form an activated hydrate form, which is tin(II)-oxide "1" [3,13].
2. Terminal groups of LMW PLLA react with hydroxyl groups of reactant "1" to produce water and the reaction center "2" [14].
3. The hydroxyl terminal groups of LMW PLLA should be coordinated toward the reaction center "3" so that condensation may be induced around the metal such as tin so as to form polymer "4" having ester-linkage and an activated hydrate form. Finally, the activated hydrated form of the catalyst should be regenerated [14].

PLLA homopolymers with low molecular weights (1000, 3000 and 9000 g/mol) were synthesized by azeotropic condensation of L-lactic acid (the reaction yields were around 40-50%).

Thermogravimetric (TG) and derivative thermogravimetric (DTG) curves of LMW PLLA are shown in *figure 2*. LMW PLLA starts to decompose at around 230°C and complete decomposition is observed at nearly 281°C. LMW PLLA decomposes in a single step process, indicating that there is principally one reaction stage during thermal degradation of the polymer which is most probably associated with the loss of ester groups [15]. The maximum degradation temperature of LMW PLLA is observed at $T_d = 258°C$.

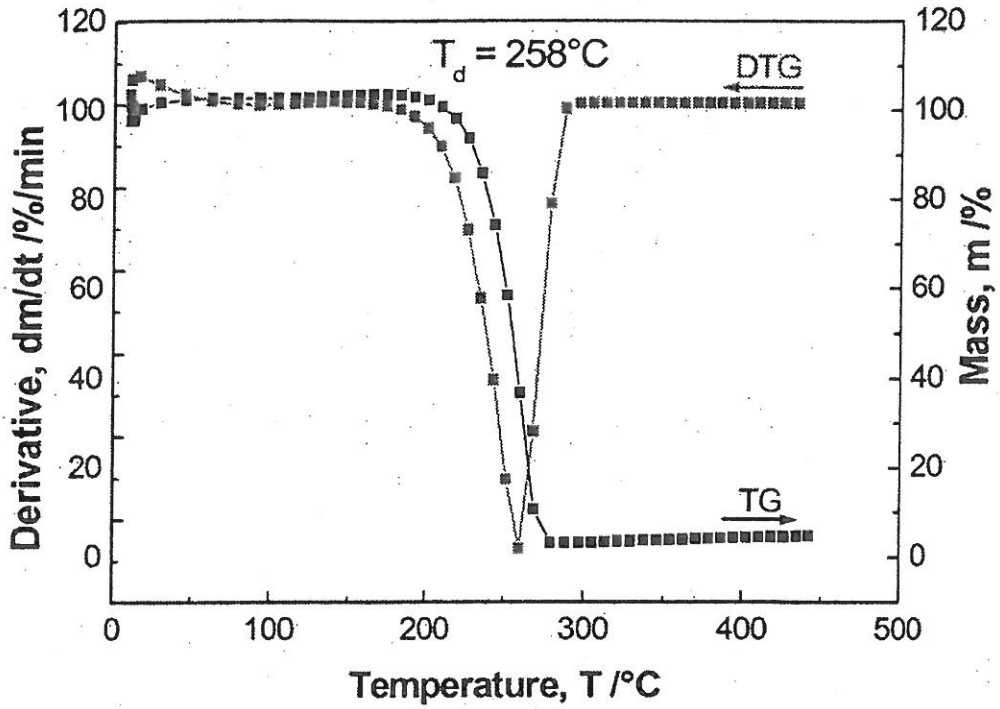

Figure 2. TG/DTG curves obtained under nitrogen atmosphere at 10 °C min^{-1} for LMW PLLA.

The thermal properties of LMW PLLA were measured and the representative DSC traces are shown in *figure 3*. A glass transition (T_g = 56,49°C), a crystallization peak (T_c = 102,76°C) and double melting peaks (T_m) at 134.00°C and 140.80°C were observed depicting semi-crystalline behavior. The enthalpy of melting was used to determine the degree of crystallinity of the polymer. The melting peaks measured with DSC indicate the type of crystallization present in the polymer, and the observation of double melting peaks of the synthesized PLLA might indicate the presence of different morphological populations of crystals or crystals with imperfections [16]. The results of thermal characterization are shown in *table I.*

The first scan values for T_g, T_m and crystallinity denote the properties of LMW PLLA just after recrystallization. The second scan values are results after heating to 180°C cycle. LMW PLLA after recrystallization does not show glass transition because the crystallinity is important. It should be pointed out that our LMW PLLA samples have lower melting points than previously reported values, this may be attributable to the few D-lactic acid units incorporated in our LMW PLLA samples.

Figure 4 shows the XRD profile of the synthesized LMW PLLA. According to this *figure*, the XRD profile of LMW PLLA presents four characteristic peaks of the orthorhombic α phase, with the most prominent being a very strong reflection at $2\theta = 16.7°$ (due to diffraction from (200) and/or (110) planes) and a strong reflection at $2\theta = 19.0°$ (arising from (203)). The two others are weak reflections observed at $2\theta = 14.7°$ and 22.3° (due to diffraction from (010) and (015) planes, respectively). These results are comparable to those reported in the literature [14,17].

Table I. Thermal characterization results.

LMW PLLA	T_g (°C)	T_c (°C)	T_m (°C)	ΔH_m (J/g)	ΔH_c (J/g)	Cristallinity (%)
1st scan	/	93.77	140.10	29.52	3.588	31.4
2st scan	56.49	102.76	140.80	25.11	19.952	26.7

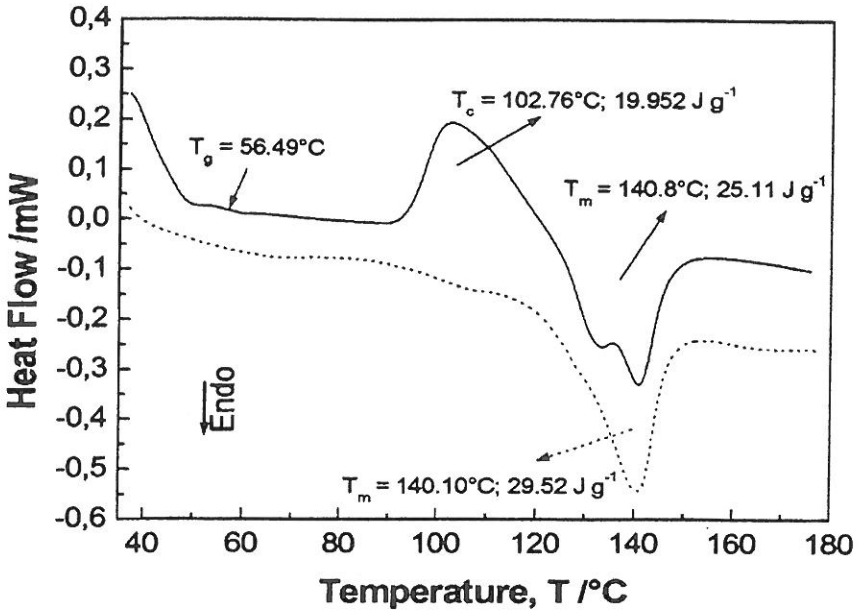

Figure 3. DSC thermograms of LMW PLLA: 1st scan dotted line, 2nd scan solid line.

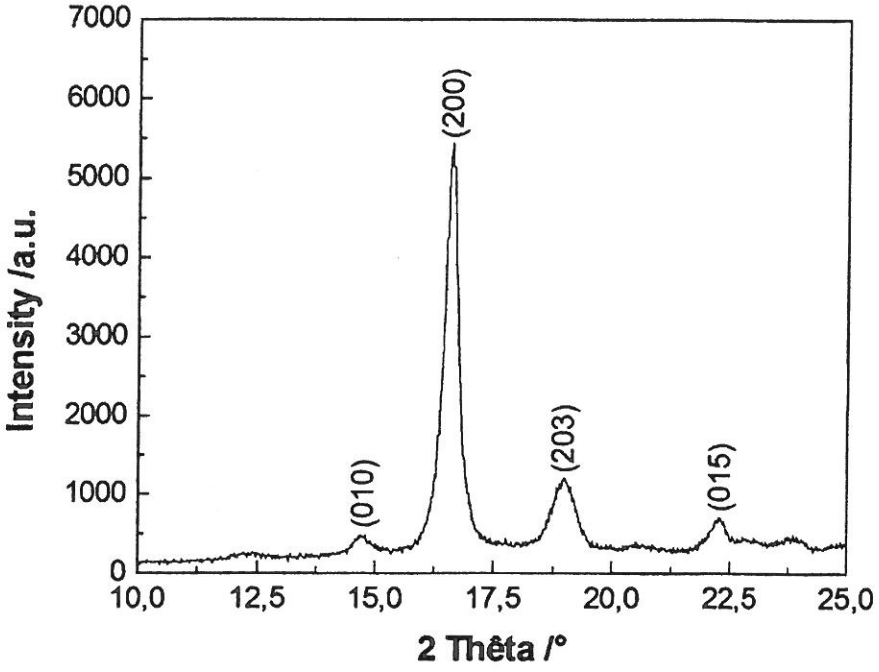

Figure 4. X-ray diffraction pattern of LMW PLLA.

Figure 5 shows the FT-IR spectrum of the LMW PLLA synthesized. The strong band at 1759 cm^{-1} corresponds to C=O bond stretching, and the bands at 3001 cm^{-1} and 2953 cm^{-1} are assigned to C-H stretching of $-CH_3$. C-O-C stretching mode is observed at 1188 cm^{-1} and the peak at 3508 cm^{-1} is the stretching of the terminal hydroxyl O–H groups, and may be used as an indication of the low molecular weight of the polymer [18].

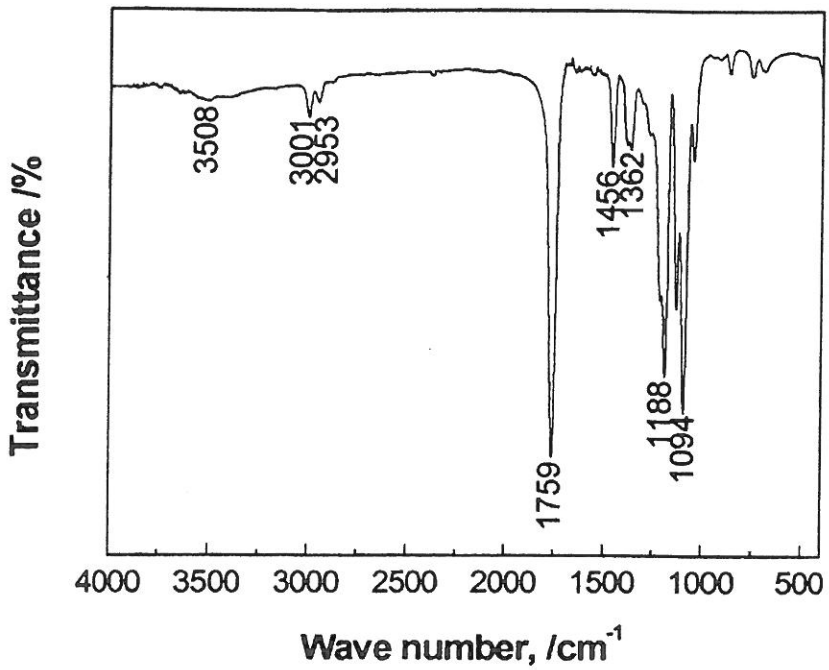

Figure 5. FT-IR spectrum of LMW PLLA.

3.2. Characterization of Solid Dispersions

The morphology of pure IBF (6a), pure LMW PLLA (6b), PMs (6c), and SDs (6d) is shown in *figure 6*.

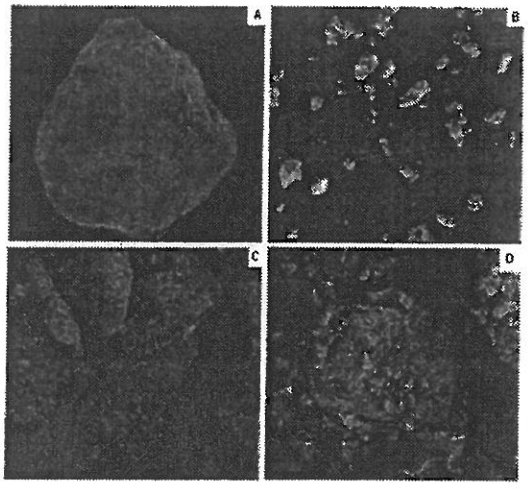

Figure 6. SEM micrographs of (A) IBF, (B) LMW PLLA, (C) PMs and (D) SDs.

Pure ibuprofen appears as a crystalline structure, almost round in shape with a slightly rough surface and LMW PLLA appears as small-size particles with a rough surface. The SEM images of

PMs and SDs shows bulky particles (IBF) with small particles (LMW PLLA) adherent to its surface. The latter present a smaller crystal size compared with the raw materials. The change in the morphology in all the produced materials gives evidence for the existence of interactions between IBF and LMW PLLA.

Figure 7 shows the XRD spectra of LMW PLLA (7a), pure ibuprofen (7b), PMs (7c) and SDs (7d). Characteristic peaks of ibuprofen can be observed at diffraction angles of 2θ at 6.14°, 12.26°, 16.36°, 20.22° and 22.39°, and are comparable to those reported in the literature [19]. Both of the PMs and SDs of LMW PLLA/IBF indicate the presence of crystalline IBF. Nevertheless, some changes like peak locations, peak intensities and small changes in the d values are observed in the diffractograms of the PMs and SDs. But these changes are more important in the case of the SDs. These results indicate the possibility of some types of interactions between IBF and LMW PLLA [20]. In addition, the small variation in the relative intensities of the peaks can be attributed to the different crystal morphologies of IBF crystals [21].

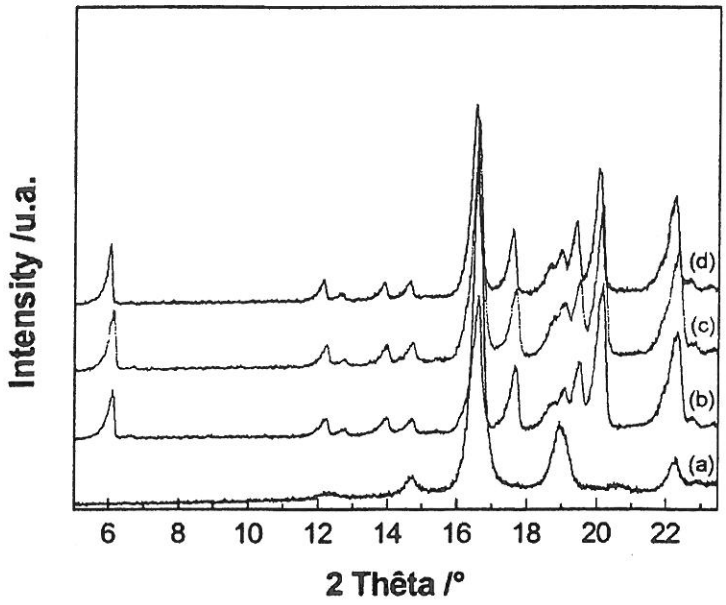

Figure 7. XRD profiles of (a) LMW PLLA, (b) IBF, (c) PMs and (d) SDs.

The existence of interactions between the drug and the polymer is again proved by FT-IR study. *Figure 8* exhibits FT-IR spectra of pure IBF (8a), LMW PLLA (8b), PMs (8c) and SDs (8d). The FT-IR spectrum of pure IBF shows a well-defined intense infrared band at around 1720 cm^{-1} (carbonyl-stretching of isopropionic acid group) and the multiplet observed at around 3000 cm^{-1} can be attributed to C–H stretching vibrations. In the spectra of PMs and SDs, this band is shifted towards higher wave numbers at 1724 cm^{-1} and 1726 cm^{-1}, respectively. The shift of the carbonyl stretching to the high-wave number region was reported in the literature [22-24]. According to Kasarian et al. [22], the carbonyl absorption band at 1720 cm^{-1} indicates the crystalline form of IBF. But this band is shifted to higher wavenumber when ibuprofen is loaded into LMW PLLA matrix. This result is obviously associated with chemical interactions as hydrogen bonding between carbonyl groups of LMW PLLA and hydroxyl groups of IBF as shown in *figure 9 (a)*. The presence of the stretching vibration of ibuprofen carbonyl peak in the PMs and SDs indicates that the drug crystalline form is not lost during the solid dispersion formation. Thus, IBF is present as a combination of dimers and LMW PLLA/IBF species, while a fraction of non-hydrogen bonded LMW PLLA also exists as shown in *figure 9*.

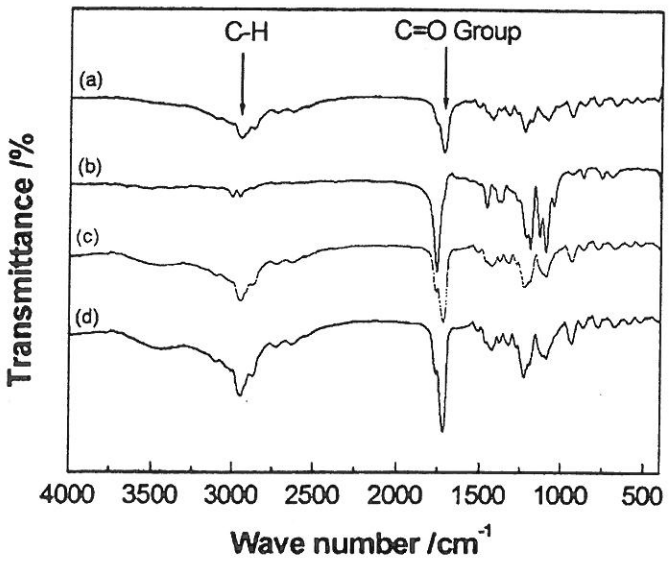

Figure 8. FT-IR spectra of (a) IBF, (b) LMW PLLA, (c) PMs and (d) SDs.

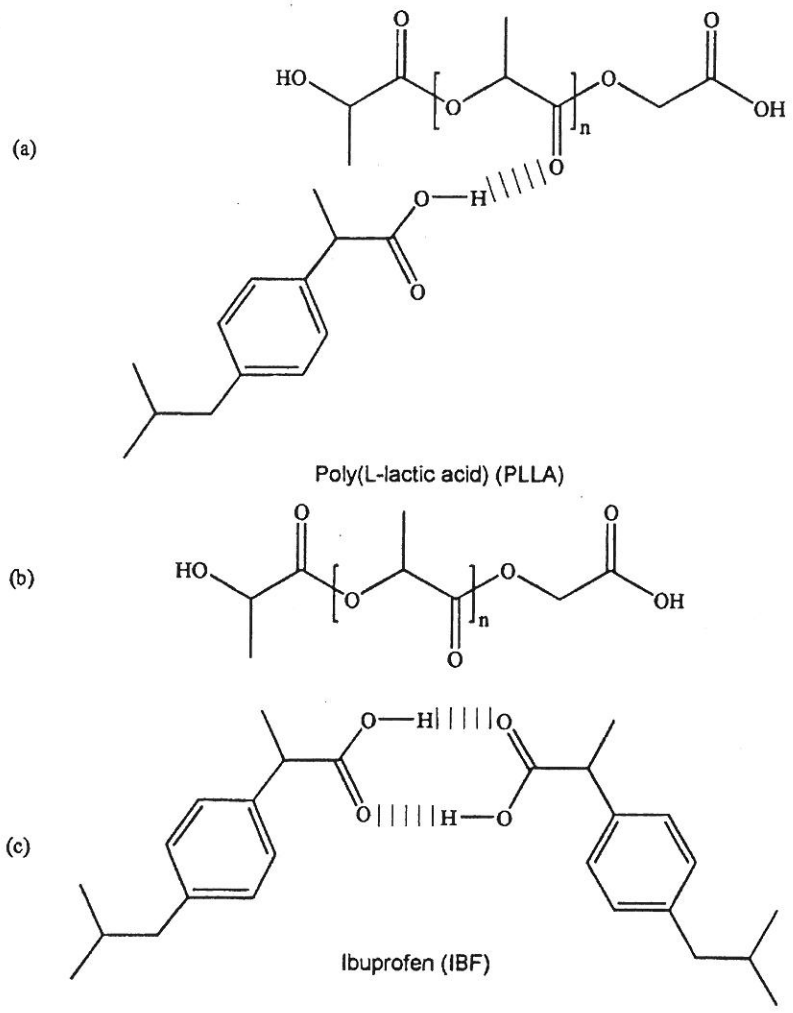

Figure 9. Species present IBF/LMW PLLA solid dispersions: (a) hydrogen bonded IBF/LMW PLLA species, (b) non-hydrogen bonded LMW PLLA and (c) ibuprofen symmetric dimer.

Finally, the results from SEM, XRD, and FT-IR techniques confirm a coexistence of a molecular and particular dispersion of ibuprofen in the LMW PLLA matrix.

3.3. In Vitro Drug Release Studies

3.3.1. Effect of Polymer Concentration. The free IBF crystals reveal a faster release showing about 98% drug release within 75 min in comparison to the treated form of the drug which displays sustained release at pH 7.4 and pH 5.8 as shown in *figures 10A and 10B*, respectively. It is clearly noticeable that the release rate of IBF from the LMW PLLA3000 matrix depends on the LMW PLLA3000 concentration in the system.

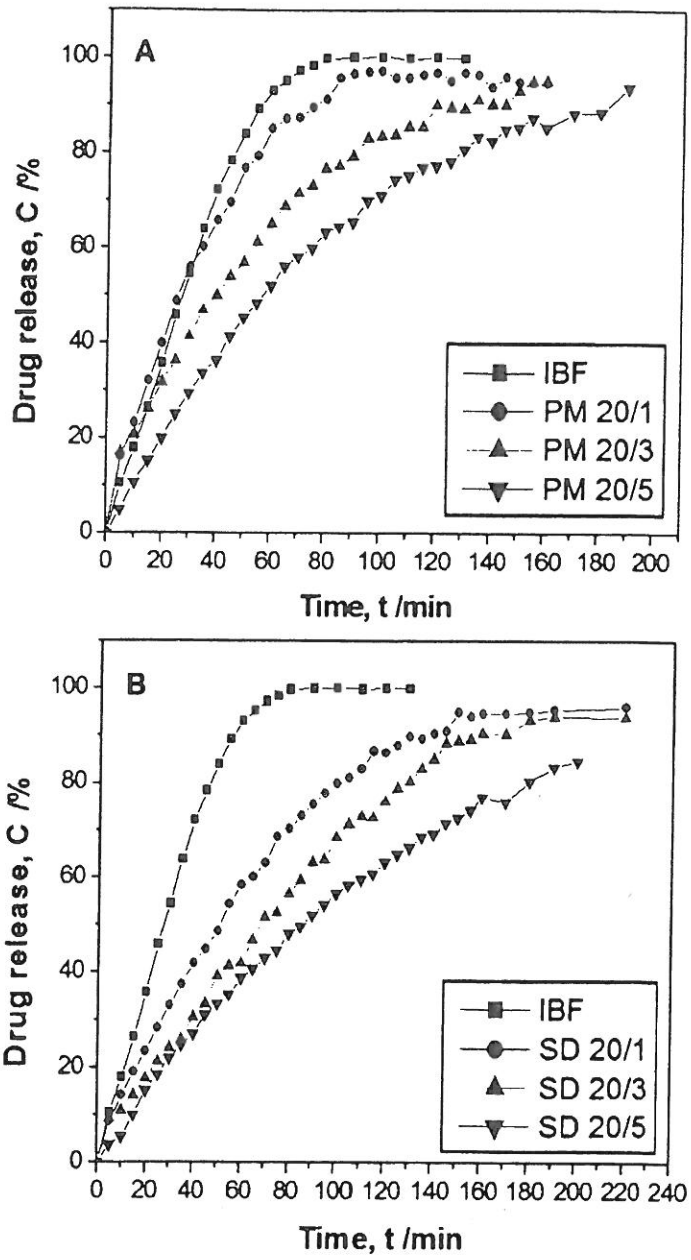

Figure 10. Release profiles of IBF from LMW PLLA3000 matrix prepared with different drug/polymer weight ratio in pH 7.4 phosphate buffer solution: (A) PMs and (B) SDs.

When the concentration of the polymer in the system increases, the release rate of drug decreases. These results are in agreement with those reported in the literature [8,20,25,26].

The increase of the polymer concentration in the formulation leads to the formation of a dense polymer matrix, resulting in smaller pores and a more tortuous structure, which in turn decreases the drug release [27,28]. It was found that a significant initial "burst release" profile was obtained from all the formulations, which was caused by the release of poorly entrapped or surface-associated IBF and IBF diffusion occurring through porous channels. After the burst release stage, there was a lag time of little release, followed by a phase of constant IBF release. Both burst and subsequent rate of IBF release depended on dissolution/diffusion of drug, not on polymer degradation as suggested by Thompson et al. [29]. Indeed, a hydrolytic degradation of the specimens of PLA was performed in PBS (Phosphate Buffer Solution) (pH 7.4) by Xiong et al. [30]. However, in our work it is clear that the degradation time of the LMW PLLA3000 matrices is relatively slight as compared with the period of drug release. In addition, the interactions occurring between IBF and LMW PLLA3000 lead to a complex mechanism of drug release, in which both the drug solubility in the external medium and its diffusion capacity within the polymer play an important role.

3.3.2. Effect of the Polymer Molecular Weight. *Figures 11A and 11B* show the release profiles of IBF from LMW PLLA matrices at pH 7.4 and pH 5.8 respectively, using LMW PLLA1000, 3000 and 9000 g mol^{-1}. Concerning the *figures 11A and 11B*, it is clear that the delayed release rate of IBF is obtained only with LMW PLLA9000. This may be due to the greater hydrophobic nature of LMW PLLA9000 compared to LMW PLLA3000 and LMW PLLA1000. Indeed, this effect could be associated with the increasing number of extra hydroxyl and carboxylic acid groups in low molecular weight polymers [30,31]. A more hydrophilic matrix probably results in faster ingress of aqueous medium, producing a faster rate of drug dissolution [22,29].

3.3.3. Effect of pH on the Release Profiles. The release profiles of IBF from polymer matrices tested in buffer solutions of pH 5.8 and 7.4 are presented in *figures 12A and 12B*. It can be shown that the release rate of ibuprofen is higher in the buffer solution with higher alkalinity. This behavior was reported in previous studies [7,32,33,34]. To explain these results, it is important to monitor the swelling of tablet-based PLLA into aqueous media at different pH (acidic and basic medium). However, Proikakis et al. [35] studied the stability of PLA in aqueous solutions. According to these authors, PLA tablets immersed into buffer solution (pH 7.4) gave about ten times higher swelling index in comparison with the tablets immersed in a buffer of pH 5.4. Indeed, the differences of release between pH 7.4 and 5.8 can be explained by the acidic character of ibuprofen. On one hand, at higher pH most of the carboxylic groups of LMW PLLA3000 and IBF acid are in anionic form of COO^-, the repulsive forces among LMW PLLA3000 chains give bigger mesh size and further enhance drug release. At acidic pH, the carboxyl anions are protonated and therefore, the repulsive forces are eliminated, resulting in a decreased release rate [7]. On the other hand, as already mentioned [12] the solubility of ibuprofen is proportional to the pH of the surrounding solution. In acidic solutions, the solubility is lower than 1 mg/mL (pK_a = 5.2) and increases at higher pH values.

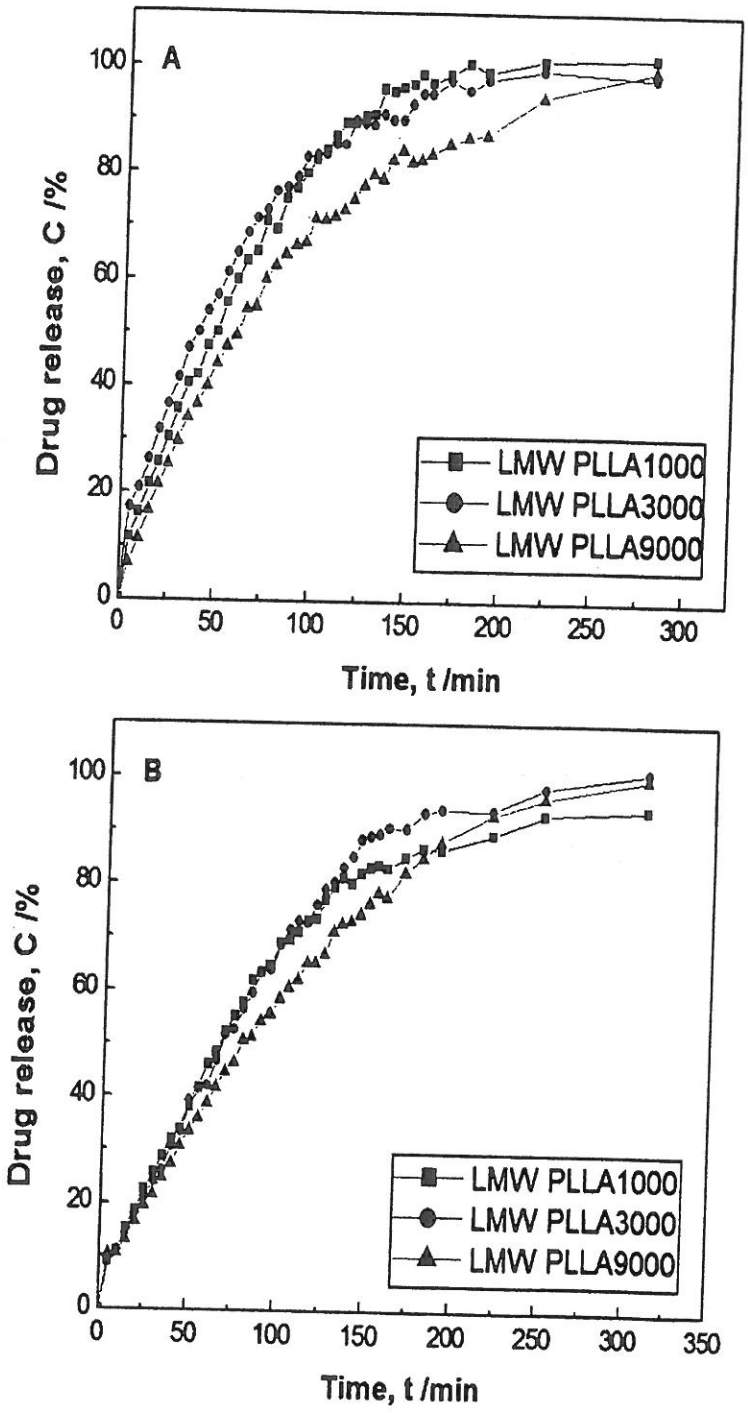

Figure 11. Release profiles of IBF from LMW PLLA matrix prepared with different molecular weights of polymer in pH 7.4: (A) PMs 20/5 and (B) SDs 20/5.

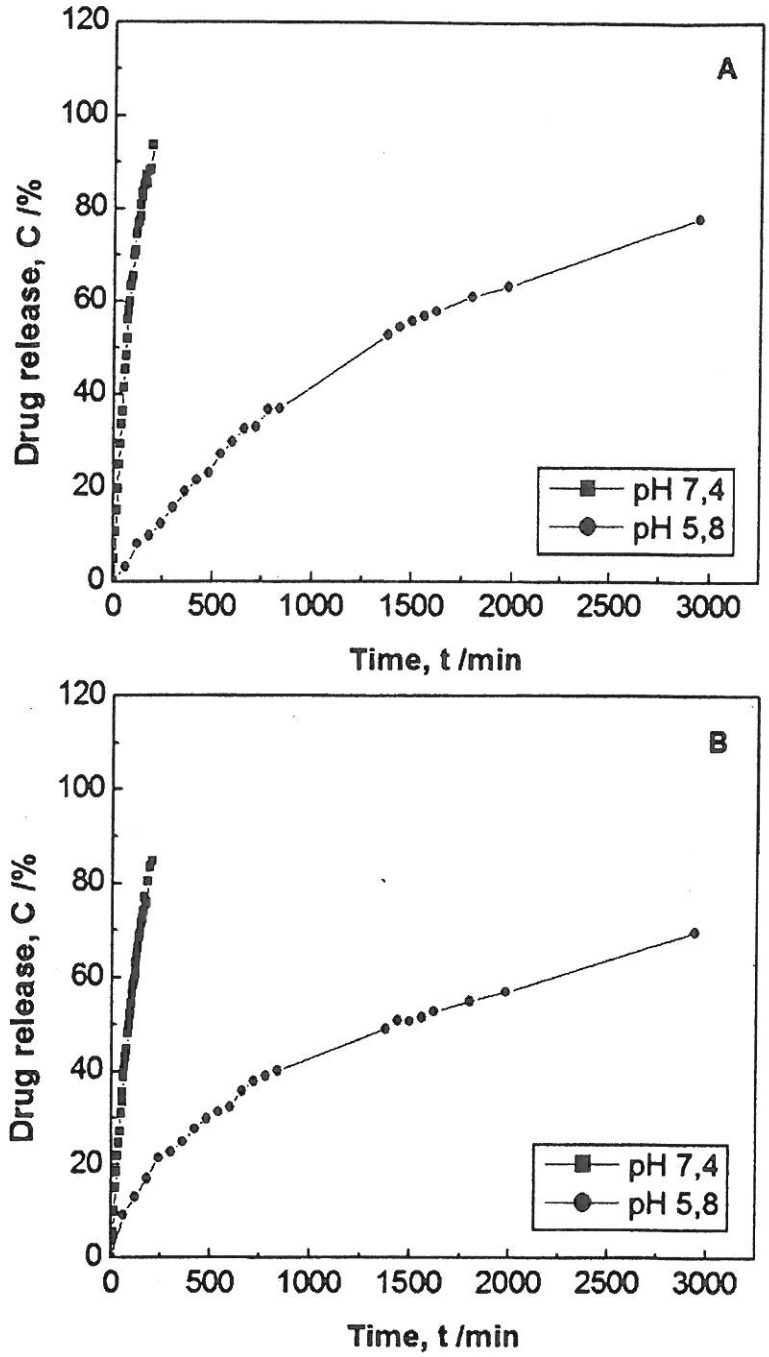

Figure 12. Release profiles of IBF from LMW PLLA3000 matrix in mediums with different pH value: (A) PMs 20/5 and (B) SDs 20/5.

In vitro dissolution testing of IBF from PMs 20/5 and from SDs 20/5 at pH 7.4 is shown in *figure 13*. According to this *figure*, the weakest dissolution rates were apparent with solvent evaporation systems. This trend can be attributed to the dimethylformamid influencing drug-polymer interactions. Pignatello et al. [26], found that better interactions between drugs (NSAID) and polymers (Eudragit) were obtained in solution (i.e. in a common solvent) and not with a simple mixture between the compounds.

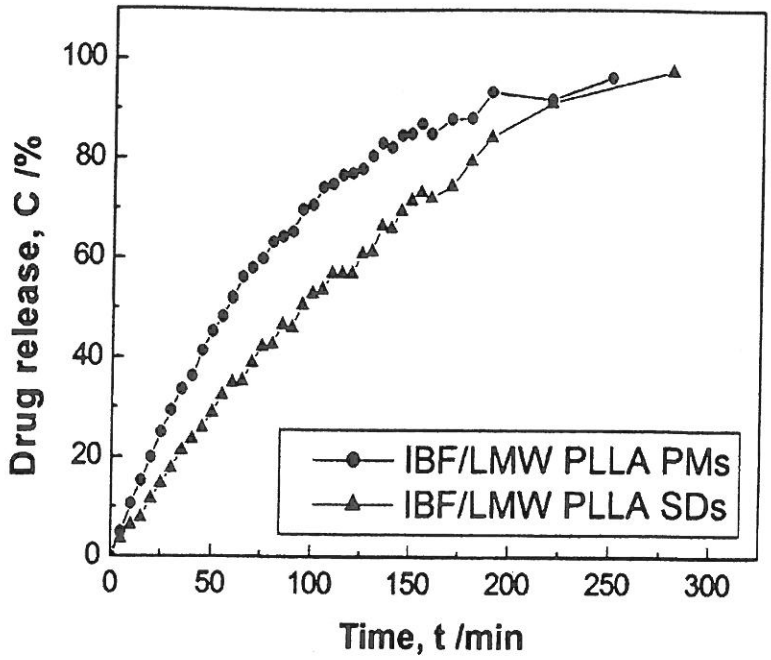

Figure 13. Release profiles of IBF from LMW PLLA3000 matrix prepared with different methods in pH 7.4.

4. CONCLUSION

LMW PLLA was synthesized by azeotropic condensation of L-lactic acid, and characterized by different techniques (TGA, DSC, FT-IR and XRD). The solubility and dissolution rate of ibuprofen can be delayed by formulating SDs of ibuprofen with LMW PLLA. The results of infrared spectroscopy, X ray diffractometry and MEB indicate that some interactions such as intermolecular hydrogen bonding between the functional groups of IBF and LMW PLLA occurred at the molecular level, which decreased the solubility and the dissolution of IBF from the solid dispersion. The results indicate that the solid dispersion prepared by solvent evaporation method represents a promising approach for the bioavailability enhancement of ibuprofen and can be used for the solid dosage development.

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