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Biodegradable ibuprofen-loaded PLGA microspheres for intraarticular administration Effect of Labrafil addition on release in vitro

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Abstract

The objective of this study was the development and optimisation of biodegradable PLGA microspheres loaded with ibuprofen destined for intraarticular administration. The formulation was designed to provide "in vitro" therapeutic concentrations of ibuprofen (8 μg/ml) for as long as possible. The solvent evaporation method based on an o/w emulsion was used to form the microparticles. The polymer used was Poly (D,L-lactide-co-glicolide) 50:50 (PLGA), of different molecular weights (Mw) (34,000, 48,000 and 80,000 Da). In order to get a more controlled release rate of ibuprofen, a biodegradable oil, Labrafil® M1944CS, polyethylene glycol 300 derivative, was used as an additive. The formulation was optimised by means of an experimental design, 2^3 being the variables: X_1 = PLGA Mw; X_2 = initial ibuprofen:polymer ratio; X_3= percentage of Labrafil. The theoretical profile yielding in vitro "therapeutic" concentrations of ibuprofen (8 μg/ml) was calculated. The experimental profiles obtained for the formulations tested were compared with the theoretical one by means of the difference factor (f_1). In all cases, the addition of Labrafil lowered the initial ibuprofen burst, prolonging the release rate of the drug from 24 h (without additive) up to 8 days incorporating the oil. The microspheres made from the PLGA (Mw = 34,000 Da) with Labrafil addition (10%) and ibuprofen:polymer (15%) ratio (formulation 1) yielded the most suitable release profiles. Forty milligram of the selected formulation (formulation 1), was sufficient to provide in vitro "therapeutic" concentrations of ibuprofen (8 μg/ml) up to 8 days. Labrafil modulates the release rate of donor–acceptor substances such as ibuprofen.

Keywords: PLGA microspheres; Intraarticular administration; Ibuprofen; Labrafil; Additives

1. Introduction

Rheumatoid arthritis (RA) is one of the most common chronic diseases, affecting around 0.5–1% of the population. The medication used for its treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), slow-acting anti-rheumatic drugs (hydroxychloroquine, gold and methotrexate) and corticosteroids (Cohen et al., 2001). These medications are not always sufficiently effective. For this reason, in several cases, they must be administered jointly with intraarticular injections of corticosteroids. Nevertheless, the local administration of steroids generates serious adverse effects such as cartilage degeneration, Cushing's syndrome and risk of anaphylactic reaction

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(Steinmeyer, 2001; Fubini et al., 2001; Karsh and Yang, 2003).

Non-steroidal anti-inflammatory agents have been demonstrated to be effective in RA treatment. Intraarticular administration of NSAIDs could be an alternative to corticosteroid administration, avoiding their devastating effects. However, the short synovial half-life of NSAIDs would require frequent injections to maintain therapeutic intraarticular levels. For this reason, sustained drug delivery devices offer an excellent alternative to multiple intraarticular injections.

One of the technological resources used to improve the permanence of drugs at the site of action, in this case the joint cavity, is the use of therapeutical systems prepared from biodegradable polymers. Erodible devices offer the advantage of their biodegradation, disappearing gradually while releasing the drug from the site of action. Furthermore, the administration of these devices formulated as microparticles provides the advantage of facilitating their injection through standard infiltration needles.

The PLGA has been studied extensively as a polymeric carrier for biodegradable microparticles. The experience has demonstrated that multiple factors affect the drug release rate from these microparticles. Many researchers have considered the molecular weight of PLGA as one of the main factors affecting drug release profiles, with drug release rates decreasing as the molecular weight increases (Jalil and Nixon, 1990). On the other hand, some have reported that the molecular weight is not a determining factor and have instead attributed the effects obtained to the viscosity of the internal phase of the emulsion formed when preparing the microspheres (Spenlehauer et al., 1988). Additionally, some authors (Von Recum et al., 1995) have reported higher degradation rates with a faster release rate of the drug from low-molecular-weight polymers. The increase in the degradation rate is associated with a high content of terminal COOH groups on the low-molecular-weight polymers, the said groups acting as catalysts.

Microspheres loaded with an NSAID (diclofenac), destined for intaarticular administration, have been developed using different polyesters such as PLA, PLGA and Poli δ-valerolactona (PV) (Lin et al., 2000). In one of these studies, microparticles were prepared with PLGA, and the release of the drug was almost complete between 84 and 96 h. (Tunçay et al., 2000).

Taking into account that ibuprofen is an NSAID agent commonly used in the management of chronic rheumatoid arthritis, the development of a biodegradable ibuprofen system, based on microparticles, should be of great interest. Nevertheless, previous studies indicates that ibuprofen shows a high initial burst when formulated as microspheres. To avoid this effect, we considered the use of an additive in the formulation.

In fact, certain workers (Urata et al., 1999; Mallard et al., 2000a,b) have already proposed the use of different additives to modulate the diffusion of the active principle through the matrix.

Labrafil, a PEG derivative, is a non-ionic amphiphilic excipient, used as a co-surfactant in pharmaceutical systems such as microemulsions. This substance is biocompatible and biodegradable (Gao et al., 1995).

Taking into account the pharmacokinetics parameters of ibuprofen, we calculated the theoretical release rate of ibuprofen to achieve therapeutical concentrations (8 μg/ml) in the intraarticular cavity (Makela et al., 1981). The mean value of the transfer rate constant from synovial fluid to serum (K_{sp}) reported by different authors is 0.3 h^{-1} (Elmquist et al., 1994; Day et al., 1988). Considering the volume of synovial fluid to be 10 ml, the mean volume in rheumatoid arthritis, the zero-order rate (K_0) constant estimated to provide theoretical therapeutic ibuprofen concentrations in synovial fluid was found to be 24 μg/h.

The present study aimed to prepare PLGA microspheres loaded with ibuprofen for intraarticular administration, capable of releasing ibuprofen at 24 μg/h, over a long period as possible. The formulation was designed to obtain a local anti-inflammatory effect and thus minimise the negative side effects commonly experienced after corticosteroid intraarticular administration.

2. Materials and methods

Ibuprofen (R,*S*)-2(4-isobutylphenyl) propionic acid was supplied by Laboratories FAES (Madrid, Spain).

PLGA 50:50 poly(D,L-lactide-co-glycolide) was purchased from Boehringer Ingelheim (Ingelheim, Germany), in various molecular weights: Resomer® RG 503. Mw = 34,000 Da (GPC); Resomer® RG 504. Mw = 48,000 Da (GPC); Resomer® RG 505.

Mw = 80,000 Da (GPC).Labrafil® M 1944 CS is a mixture of mono-, di- and triglycerides and mono- and di-fatty esters of polyethylene glycol 300 (PEG), oleic acid being the predominant fatty acid. It was supplied by Gattefossé (Saint-Priest, France).

Dichloromethane (Merk, Darmstadt, Germany) and polyvinyl alcohol (PVA) (Mw = 49,000 Da) were supplied by Sigma-Aldrich (Madrid, Spain).

2.1. Preparation of microspheres

Solvent evaporation was employed as the microencapsulation method, using an o/w emulsion. In order to evaluate the influence of the molecular weight of PLGA on the formulation behaviour, the ratio between volumes of the inner and external phases of the emulsion as well as the viscosity of the internal phase were both held constant. Hence, depending on the molecular weight, different quantities of PLGA were used to form the inner phase of the emulsion; 195 mg (Mw = 34,000 Da), 138 mg (Mw = 48,000 Da), and 110 mg (Mw = 80,000 Da). The ibuprofen:polymer ratio was 20:100 (20%).

In the experiments carried out to evaluate the effect of Labrafil® M1944CS on the formulations, microspheres (ME) were prepared with PLGA (Mw = 48,000 Da) by adding the oil to the inner phase of the emulsion. (The oil did not change the viscosity of the polymeric organic solution.)

In all cases, a series of three replicates were prepared for each formulation.

2.1.1. Additive-free microspheres

The proper amounts of polymer and ibuprofen for each formulation were dissolved in 1 ml of dichloromethane. The external phase of the emulsion consisted of 5 ml of an aqueous solution of 1% PVA (Mw = 49,000 Da). Emulsion formation took place in a Polytron homogenizer (Kinematica, Lucerne, Switzerland) operated at 2000 rpm for 1 min. Upon formation of the emulsion, 9 ml of distilled water was added, and stirring continued at the same speed setting for 2 min. The immature microspheres were suspended in 200 ml of distilled water and stirred gently and continuously using a magnetic stirrer (RCT Basic-Ika) for 4 h, at room temperature, until the solvent was completely evaporated. Finally, the microspheres were filtered using a 5-μm filter, washed with distilled water and dried under vacuum at 25 °C for 48 h.

2.1.2. Microspheres containing Labrafil addition

Microencapsulation was carried out as described above, except that the polymer and ibuprofen were dissolved together, with an appropriate quantity of Labrafil, in the internal phase of the emulsion.

2.2. Determination of the ibuprofen content

To determine the quantity of encapsulated drug, 20 mg of microspheres was accurately weighed and dissolved in 0.5 ml of dichloromethane. Afterwards, 9.5 ml of acetonitrile FAR-UV (Lan-Scan, Dublin, Ireland) was added.

The amount of ibuprofen was determined by HPLC. The chromatograph used was equipped with a Gilson 305 solvent delivery pump and an UV-detector (Gilson, Villiers le Bel, France). The separation was achieved by reversed phase column C_{18} (Nucleosil 100-5). The detection wavelength was 264 nm. The mobile phase consisted of 60% acetonitrile (Lan-Scan, Dublin, Ireland) and 40% H_2O adjusted to pH 2.7 with ortho-phosphoric acid (Panreac, Barcelona, Spain), and the flow rate was 0.8 ml/min. Under these conditions, the polymer did not interfere with the drug at the specified wavelength.

2.3. Ibuprofen release from the microspheres

Drug release assays were carried out in a heated bath (Clifton model NE-28) at 37 ± 0.2 °C and constant shaking (50 rpm). Microspheres (20 mg) were suspended in 4 ml of phosphate buffer (sink conditions) at pH = 7.4. The buffer solution was drawn off completely at preset sampling times, and it was replaced with freshly prepared buffer solution. The ibuprofen solution was then filtered through a 0.45-μm filter (Teknokroma), and drug quantitation was performed by UV spectrophotometry at λ = 223 nm. All assays were done in triplicate for each formulation.

2.4. Microspheres formulation optimisation

Once the preliminary assays were complete in which the optimal effect of Labrafil addition was

Table 1
Formulations tested using the 2^3 factorial design

Formulation	Molecular weight (Da), X_1	Ibuprofen/ polymer ratio (%), X_2	Labrafil/ polymer ratio (%), X_3
1	34,000	15	10
2	80,000	15	10
3	34,000	25	10
4	80,000	25	10
5	34,000	15	30
6	80,000	15	30
7	34,000	25	30
8	80,000	25	30
R	48,000	20	20

demonstrated, optimisation of the formulation was performed by means of a 2^3 factorial design, with six replications at the central design.

The variables quantitatively analysed were: PLGA polymer molecular weight (Mw) [X_1]; percentage of ibuprofen:polymer ratio [X_2]; and percentage of Labrafil:polymer ratio [X_3]. Table 1 presents the formulations tested using the 2^3 factorial design.The responses evaluated were the following:

Y_1: encapsulation efficiency of ibuprofen (percentage);
Y_2: quantity of encapsulated drug/mg of microspheres;
Y_3: percentage of released ibuprofen (referred to the encapsulated drug) within the first hour.

Statistical analysis of the results for each response was performed by the Trial run program (SPSS Inc., Chicago, Illinois).

Once the responses were evaluated, we chose the formulations presenting higher values of encapsulation efficiency and quantity of incorporated ibuprofen (responses Y_1 and Y_2) with lower values of initial burst (Y_3).

2.5. Comparison with the theoretical release profile

In order to select the optimal formulation, the best release profiles of formulations from the experimental design were brought in line with the theoretical release pattern ($K_0 = 24\,\mu g/h$). To select the formulation with the release profile that was closest to the theoretical profile, an independent mathematical approximation was applied and the differential factor f_1 was calculated. An f_1 value between 0 and 15% was considered indicative of overlapping curves (Polli et al., 1996). To get the most similar profile, different amounts of microspheres were needed from each formulation.

2.6. Characterisation of the selected formulation

On analysing the data obtained from the experimental design, the most optimal formulation, according to the criteria mentioned above, was selected.

2.6.1. Microspheres morphology

Particle size was determined by means of laser diffraction in a Galai model Cis-1 (Migdal Haemek, Israel) particle analyser. In order to prevent clumping, the samples were sonicated for 1 min before each determination. The mean microsphere diameter measurement thus obtained was expressed as diameter-volume.

Scanning electron microscopy using a JEOL model JSM 6400 (Tokyo, Japan) microscope was employed to study external microspheres appearance and shape. Samples were attached to a specimen holder and gold sputter was coated before observation.

2.6.2. Thermal analysis

Differential scanning calorimetry (DSC) was performed using a Mettler model TA8000 calorimeter (Greinfensee, Switzerland). Approximately 10 mg of sample was weighed out and placed in a sealed aluminium pan. An empty aluminium pan was used for reference. The temperature range tested was from 25 °C to 100 °C, and the heating rate was 10 °C/min.

2.6.3. Powder X-ray diffraction analysis

X-ray patterns were obtained using a Philips X'Pert model MPD (Almedo, The Netherlands) with a Cu Kα radiation, θ-2θ powder diffractometer set for an angle range of 5–70° 2θ. The step size was 0.04° 2θ, and count times were of 1 s per step.

The analysis was carried out on the selected formulation. As an additional experiment, X-ray determinations of ibuprofen and the inert microspheres prepared with PLGA (Mw = 34,000) were developed.

3. Results

3.1. Additive-free microspheres

Microspheres (ME) prepared with polymers of different molecular weights and without oil addition encapsulated between 30 and 85% of the initial drug. Nevertheless, the ibuprofen release rate from microspheres was too rapid, with percentages of 14–21% of the encapsulated drug released during the first hour and between 63 and 82% within the first 24 h. After 24 h, the release rate of the drug in all formulations was lower than 8 μg/ml (theoretical release rate of ibuprofen to achieve "therapeutical" concentrations). In order to extend the release of the drug as well as to diminish the initial burst, Labrafil was included as an additive in the formulation.

3.2. Evaluation of oil (Labrafil) addition to the formulation

The effect of Labrafil addition was evaluated by preparing microspheres (ME) from PLGA of Mw 48,000 Da. The (ibuprofen: Labrafil: polymer) ratio was (2:2:10). Therefore, the formulation prepared was: 27.6 mg ibuprofen; 27.6 μl Labrafil; and 138 mg PLGA, Mw = 48,000 Da. As control, the same formulation was prepared without additive.

No significant differences were obtained between formulations with particle size 38.36±1.3 and 39.13± 0.6 μm, with percentages of encapsulated ibuprofen of 69.34 ± 2.6 and 68.25 ± 1.2% for formulations with and without additive, respectively. Nevertheless, the results obtained indicate that the presence of Labrafil significantly reduced the initial burst from 15.81±2.6 to 5.34±0.9% and lowered the release rate for ibuprofen, as shown in Fig. 1. Furthermore, the release rate resulted as more controlled for microspheres including the oil.

3.3. Optimisation of the formulation

In light of the results obtained in the preliminary assays, the optimisation of formulation was carried out to reach a constant ibuprofen release rate (24 μg/h) with a lower initial burst. The experimental design (2^3) was performed with six replicates (formulation R) at the central design level.

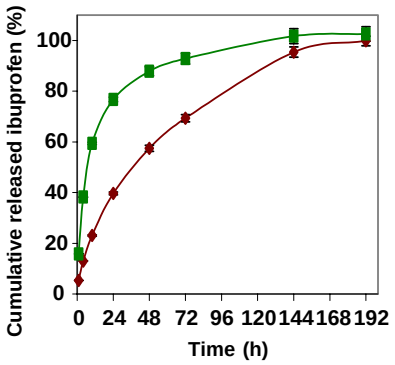

Fig. 1. Cumulative percentage of ibuprofen released from microspheres made from Resomer 504 PLGA (Mw = 48,000 Da), without Labrafil (■) and with Labrafil (◆).

As cited previously, the responses evaluated were encapsulation efficiency of ibuprofen (percentage) (Y_1) and quantity of drug encapsulated per milligram of microspheres (Y_2), because the highest proportion of ibuprofen drug with the lowest amount of excipient is always suitable. To quantify the initial burst, the percentage of dose released over first hour (Y_3) was calculated in all formulations. Table 2 summarises the different responses obtained from the formulations tested.

For the percentage of ibuprofen encapsulated (response Y_1), the variable molecular weight (X_1) was

Table 2
Results obtained for ibuprofen encapsulated (%), quantity of ibuprofen (μg) encapsulated per mg of microspheres and percentage of ibuprofen released in the first hour of the release assay

F	Encapsulation efficiency (%), Y_1	Amount of ibuprofen (μg/mg ME), Y_2	Burst 1 h (%), Y_3
1	84.46	110.15	3.14
2	46.04	60.0	5.15
3	79.89	159.9	5.09
4	36.17	68.7	8.94
5	70.84	91.7	3.2
6	30.07	39.2	7.35
7	79.16	158.3	5.55
8	30.56	61.1	13.49
RA	73.57	122.6	5.60
RB	67.37	112.2	4.46
RC	68.25	113.6	5.37
RD	65.15	108.7	5.89
RE	71.09	118.4	5.75
RF	60.07	100.1	5.85

significant ($P < 0.001$). If molecular weight increased the percentage of ibuprofen, loading into microparticles decreased. The quantity of ibuprofen encapsulated per milligram of microspheres (response Y_2) did not fit to the selected model.

Determining the percentage of ibuprofen dose released within the first hour (response Y_3), the molecular weight (variable X_1, $P < 0.001$) and initial ibuprofen:polymer ratio (variable X_2, $P < 0.022$) were significant. The percentage of ibuprofen released increased with increasing molecular weight and initial ibuprofen:polymer ratio.

The percentage of Labrafil (variable X_3) in the formulations tested in the factorial design promoted different release rate profiles. Nevertheless, the responses (Y_1–Y_3) were not significantly affected by this variable.

These findings show that, under our study conditions, larger quantities of ibuprofen were encapsulated and lower initial bursts were observed when decreasing the molecular weight of PLGA and the initial ibuprofen:polymer ratio. Furthermore, the addition of Labrafil in the range (10–30%) promoted a more controlled release in all the formulations. As shown in Table 2, microspheres elaborated with PLGA Mw = 34,000 Da show a higher encapsulation efficiencies with low initial burst. For these reasons, formulations 1, 3, 5 and 7 were initially chosen.

3.4. Comparison with the theoretical release profile

In order to select the most appropriate release rate the ibuprofen release profiles observed for the different formulations prepared with PLGA 34,000 Da (formulations 1, 3, 5 and 7) were compared with the theoretical release profile ($K_0 = 24\,\mu g/h$). Different quantities of microspheres (ME) for each formulation were chosen to find the closest fits between the experimental release profiles and the theoretical ones by means of the differential factor (f_1). The resulting values for formulations 1, 3, 5 and 7 were the following: 40 mg ME, $f_1 = 14.92$; 16 mg ME, $f_1 = 44.23$; 49 mg ME, $f_1 = 14.48$ and 16 mg ME, $f_1 = 42.94$, respectively.

Only formulations 1 and 5 yielded satisfactory f_1 values. Both formulations contained the same initial percentage of ibuprofen (ibuprofen:polymer ratio, 1.5:10). The only difference between them was the proportion of the oil, 10% in formulation 1 and 30% in formulation 5. Therefore, amounts of 40 mg of formulation 1 and 49 mg of formulation 5 would be sufficient to achieve theoretical "therapeutic" levels. Taking into account that formulation 1 provided a best fit with lower amount of microparticles, this formulation was selected for further studies. Fig. 2 shows the release patterns of formulation 1 (Mw = 34,000 Da, 15% ibuprofen, 10% Labrafil) and the theoretical pattern.

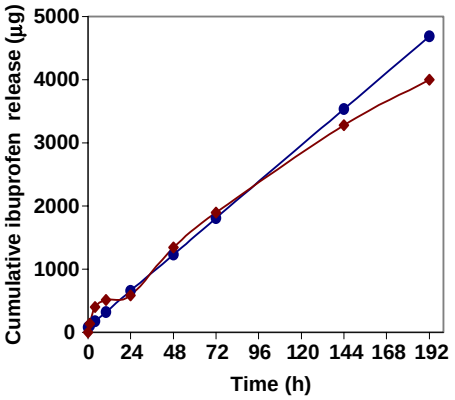

Fig. 2. Quantity of ibuprofen (μg) released from microspheres of formulation 1 (40 mg) (◆) and the theoretical release profile ($K_0 = 24\,\mu g/h$) (●).

3.5. Characteristics of the selected formulation

The selected formulation (Mw = 34,000 Da, 15% ibuprofen and 10% Labrafil) had a mean particle size of $39.69 \pm 1.5\,\mu m$ and a high percentage of encapsulation efficiency ($84.46 \pm 1.9\%$ referred to theoretical). Fig. 3 shows the microspheres as they appeared under the electron microscope, being spherical in shape and with uniform size distribution. No clumping was observed among particles.

Differential scanning calorimetry (DSC) of ibuprofen showed a characteristic melting point at 74.62 °C (Passerini et al., 2002). Thermal analysis of PLGA 50:50 (MW = 34,000 Da) revealed its characteristic glass transition temperature (T_g) at 45.49 °C. The T_g value was the same for the inert microspheres, which indicates that dichloromethane had completely evaporated and the microencapsulation method employed did not alter the thermal characteristics of the polymer. The DSC curve for the microspheres loaded with ibuprofen was also endothermic showing a lower T_g

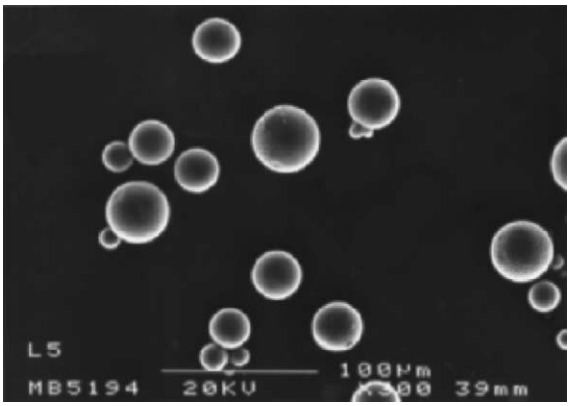

Fig. 3. Electron micrographs of microspheres made from Resomer 503 polymer (×300 magnification).

for PLGA (42.54 °C), but the thermogram did not show the characteristic ibuprofen peak, indicating a change in the crystallinity of the drug.

The powder X-ray diffraction of the ibuprofen samples yielded a typical pattern of crystalline substances (Fig. 4). X-ray diffraction patterns obtained for inert microspheres PLGA (Mw = 34,000 Da) were also consistent with an amorphous polymer. However, the X-ray patterns of the microspheres loaded with ibuprofen were found to be dissimilar, not exhibiting that of a crystalline substance like ibuprofen. This was in agreement with the results observed by DSC analysis. This fact confirmed an interaction between polymer and ibuprofen, when the latter was dissolved in the polymeric matrix.

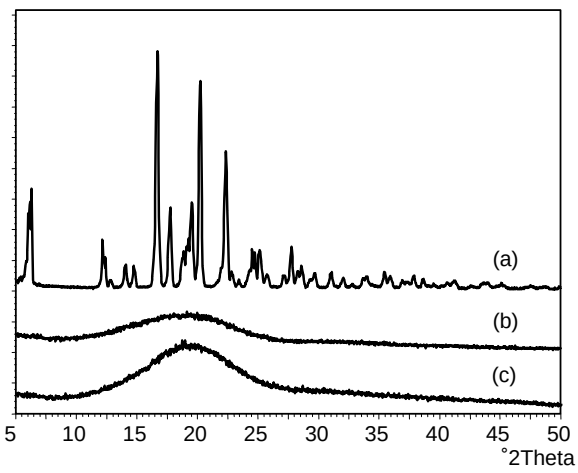

Fig. 4. X-ray powder diffraction patterns of: (a) ibuprofen; (b) inert microspheres; and (c) loaded microspheres.

4. Discussion

It is well known that additives are able to modify the release rate of drugs from microspheres. The effect of these substances can be different (Urata et al., 1999; Sansdrap and Moës, 1998). While additives such us fluorosilicone oil (FsiO) have demonstrated to diminish the rate of diffusion of a guanosine derivative (ganciclovir) from PLGA microspheres (Herrero-Vanrell et al., 2000), addition of fructose and PEG (Mn = 2000) promoted higher release of a sparingly soluble drug (piperazine) from PLA particles (Mallard et al., 2000b). The authors explained the increase of the drug dissolution rate via open pores and percolation channels formed by the PEG employed.

Nevertheless, in our case, Labrafil retarded the release rate of ibuprofen. Although Labrafil is a PEG derivative, the presence of fatty acids (mainly oleic acid) in the non-ionic amphiphilic compound granted hydrophobic properties to the molecule. Furthermore, Labrafil is soluble in methylene chloride being dissolved in the organic solvent at the same time than PLGA, resulting in its more homogeneous distribution into the particles. For this reason, we consider that the oil, contrary to PEG, promotes an obstruction of channels, resulting in a slow release rate of the drug. Nevertheless, the increase of the Labrafil concentration above 10% did not promote a significant change on ibuprofen release rate. Probably, the range of Labrafil assayed (10–30%) in the factorial design was too elevated to observe differences between the formulations tested. This result has been already commented by other authors after using others additives to modulate the release rate from PLA microparticles (Mallard et al., 2000a).

The factorial design employed in this work was used for two purposes. By one hand, it allowed the evaluation of the effects of the variables (polymer molecular weight [X_1]; percentage of ibuprofen:polymer ratio [X_2]; percentage of Labrafil:polymer ratio [X_3]) on the ibuprofen loading and release rate behaviour. On the other hand, we could make an initial selection of the formulations with optimal responses (higher encapsulation efficiencies with the low initial burst).

Molecular weight of the polymer affected the encapsulation efficiency of ibuprofen. In fact, if the molecular weight of the PLGA decreased, the ibuprofen encapsulation efficiency increased. Taking into account that precipitation of the polymer occurred at the same rate in all experiments (the viscosity of the inner phase was held constant in all formulations), this effect could be associated with the increasing number of carboxylic acid end groups in low-molecular-weight polymers, compared to the ones with high molecular weight, that probably allows forming hydrogen bonding with the acidic drug. It is well know that ibuprofen is a donor–acceptor substance and may interact with acidic and basic components (Bustamante et al., 2000). Furthermore, the interaction between PLGA and ibuprofen is confirmed by the alteration of the thermal behaviour in the DSC evaluation and confirmed by the X-ray pattern.

Once the effects of variables were evaluated, we initially selected formulations 1, 3, 5 and 7. These preparations were elaborated with the low-molecular-weight PLGA (34,000 Da).

In order to select the most appropriate release rate of ibuprofen, the release rate of each formulation was compared with the theoretical release pattern (K_0 = 24 μg/h). To find the closest fit between both profiles, we calculated the lowest value of the differential factor (f_1). For this purpose, we had to select the amount of microspheres that provided the lowest value of f_1. Using this criteria, the resulting f_1 values and the amounts of microparticles for formulations 1, 3, 5 and 7 were: $f_1 = 14.92$, 40 mg ME; $f_1 = 44.23$, 16 mg ME; $f_1 = 14.48$, 49 mg ME; and $f_1 = 42.94$, 16 mg ME, respectively (an f_1 value between 0–15% was considered indicative of overlapping curves (Polli et al., 1996)).

From these previous results, we proposed amounts of 40 mg of formulation 1 and 49 mg of formulation 5 to achieve appropriates levels in vitro. The difference between these formulations could be explained by the fact that the quantity of drug encapsulated was slightly lower when the highest proportion of oil was used. In consequence, formulation 1 was selected as the most suitable to deliver therapeutical amounts of drug for 8 days.

Several reports have described the use of additives to modulate the drug release rate from microspheres. However, no data are available regarding the benefits of using Labrafil to improve the release rate from PLGA microparticles of a donor–acceptor substance, such as ibuprofen, used in this work.

5. Conclusions

The addition of Labrafil in the PLGA microspheres loaded with ibuprofen modified the release profiles of the drug by controlling its release rate and reducing its initial burst. In this study, the selected microspheres (formulation 1), prepared with PLGA of Mw = 34,000 Da, ibuprofen (15%) and Labrafil (10%), yielded a suitable release profile. Forty milligrams of this formulation, containing 4.4 mg of ibuprofen, resulted enough to achieve in vitro "therapeutic" concentrations of ibuprofen (8 μg/ml) for 8 days.

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