Preparation, characterization and in vitro release properties of ibuprofen-loaded microspheres based on polylactide, poly(ε-caprolactone) and their copolymers

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Abstract

In this paper, ibuprofen was encapsulated into microspheres by oil-in-water (o/w) emulsion solvent evaporation method. Biodegradable polymers with certain compositions and characteristics such as polylactide (PLA), poly(ε-caprolactone) (PCL) and their block copolymer were used to prepare the microspheres. The results indicate that, under the same processing conditions, the drug entrapment efficiency was similar (~80%) for microspheres prepared with PLA and P(LA-b-CL) (78.7/21.3 by mole), but it was only 25.4% for PCL microspheres. The in vitro drug release rate decreased in the order of PCL, P(LA-b-CL) (78.7/21.3 by mole) and PLA microspheres. PCL microspheres showed more serious burst release during the first day (almost 80%) than P(LA-b-CL) (50%) and PLA microspheres (18%). The complete ibuprofen release duration from the last two kinds of microspheres exceeded 1 month. Characterization of the microspheres by differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and polarized optical microscope (POM) revealed that ibuprofen was amorphous in PCL microspheres and partially crystalline in P(LA-b-CL) and PLA microspheres. The different release behaviour of ibuprofen from the three kinds of microspheres could be attributed to the different crystallinity of the studied polymers and drug dispersion state in polymer matrices. All the above results suggest that the copolymer with a certain ratio of lactide to ε-caprolactone could have potential applications for long-term ibuprofen release.

Keywords: Ibuprofen, microspheres, microencapsulation, crystallization, controlled release

Introduction

Ibuprofen is a non-steroid drug commonly used in the treatment of post-operative, epidural, arthritis, arthragra, dysmenorrhea and dental pain. It is α-aryl propionic acid drug, shows poor water dissolution and tableting behaviour due to its hydrophobic substituted isobutyl benzene. Additionally, its high coalescence results in low flowability and processibility (Rasenack and Müller. 2002). The drug can be easily absorbed from the gastrointestinal tract and the peak plasma concentrations occurs ~1-2h after ingestion (Filippo et al. 1999). As its duration of action is fairly short, repeated administration of the same single dose is necessary during 24 h (Cox et al. 1999). In addition, like many other non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen can also produce gastrointestinal adverse effects, such as diarrhea, nausea, vomiting, ulcers, abdominal pain and gastric irritation. To overcome these problems, as well as fulfill its therapy for some chronic disorders such asankylosing spondylitis, osteoarthritis and rheumatoid arthritis, the preparation of a long-acting, single-dose formulation is becoming one of the most widely discussed topics in pharmaceutical field.

In the last two decades, many studies have been undertaken to obtain controlled-release systems for ibuprofen, such as tablets (Majid Khan and Zhu 1998a, b, 1999), gels (Paavola et al. 1998, 2000), osmotic pumps (Özdemir and Sahin 1997), beads (Sipahigil and Dortunc 2001), spherical crystal agglomerates (Kachrimanis et al. 1998), microspheres and microcapsules (Kawashima et al. 1992, Gallardo et al. 1998, Perumal et al. 1999, Tamilvanan and Sa 2000) and nanoparticles (Pignatello et al. 2002). Loading materials mostly based on polystyrene, polymethylmethacrylate and biodegradable aliphatic polyesters, such as poly(lactide) (PLA) and its glycolide copolymers (PLGA). However, serious burst release of ibuprofen from PLGA-based formulations was frequently reported (Leo et al. 2000) and the longest period was no more than 20 days (Sivakumar and Rao 2002). In this study, a series of ibuprofen-loaded microspheres composed of PCL, PLA and their block copolymer were prepared. It was expected to prolong ibuprofen release and reduce burst release through regulating the composition of system (monomeric units, crystallity, etc.). The results demonstrated that the copolymerization of lactide with a small amount of ε-caprolactone (21.3%) yielded satisfactory products, which could be successfully utilized for extending and modulating the release of ibuprofen.
Materials and methods

Materials

Ibuprofen was obtained from Xin Hua Pharmaceutical Factory (Shandong, China) and used as supplied. Polylactide (PLA) and P(LA-b-CL) were prepared in Yasuda lab. (Hiroshima University, Japan), poly(ε-caprolactone) (PCL) was supplied from Jerome lab. (Liege University, Belgium). All samples were purified by extraction with hydrochloric acid (0.1 M) to ensure removal of trace catalyst residuals, followed by washing with distilled water and dried. The characteristics of all samples are presented in Table I.

### Table I. Characteristics of homo- and copolymers of LA/ε-CL.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Monomer composition (wt%)</th>
<th>Mₙ</th>
<th>Mₘ/Mₙ</th>
<th>Tₕ (°C)</th>
<th>Tₘ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>100</td>
<td>0</td>
<td>28 300</td>
<td>1.45</td>
<td>46.8</td>
</tr>
<tr>
<td>P(LA-b-CL)</td>
<td>78.7</td>
<td>21.3</td>
<td>30 000</td>
<td>1.62</td>
<td>nd</td>
</tr>
<tr>
<td>PCL</td>
<td>0</td>
<td>100</td>
<td>21 000</td>
<td>1.25</td>
<td>54.2</td>
</tr>
</tbody>
</table>

-Monomer composition, Mₙ, and Mₘ/Mₙ were calculated from ¹H-NMR.
-  
- Tₕ and Tₘ were determined by DSC.
- nd = not detectable.

Poly(vinyl alcohol) (PVA, MW 120,000, degree of hydrolysis 88%) was purchased from Aldrich Chemical Company (Saint Louis, MO, USA). All the other solvents and chemicals were of analytical grade and used as received.

Preparation of microspheres

Microspheres were prepared using the oil-in-water (o/w) solvent evaporation method (O’Donnell and McGinity 1997). Briefly, a certain amount of polymers and ibuprofen were dissolved in 5 ml of methylene chloride (DMC) at room temperature and then the organic phase was emulsified into 50 ml of aqueous phase containing a certain amount of PVA. After the complete evaporation of DMC under magnetic agitation (~3 h, at room temperature), microspheres were collected by centrifugation at 4000 rpm, washed three times with double-distilled water and dried in vacuum. The experiment was repeated by varying ibuprofen loading from 10–20% in the organic phase, PVA concentration from 0.1–1% w/v and polymer concentration from 4–10% w/v. Each formulation was prepared in triplicate.

Determination of drug content in the microspheres

About 10 mg of the microspheres were weighed accurately and dissolved in 0.5 ml of DMC, then 9.5 ml of phosphate buffer solution (PBS, pH 7.4) was added and the mixture was stirred for at least 2 h with a magnetic stirrer. Finally, the system was centrifuged to separate the aqueous phase. The ibuprofen concentration in the organic layer was assayed spectrophotometrically (Cary 100 UV-VIS-NIR Spectrophotometer, λ = 222 nm, n = 3). This method was proved to be credible by conducting recovery analysis using known amounts of ibuprofen with or without polymer. Recovery analysis averaged 95.46 ± 1.32%.

Particle size analysis

The particle size and size dispersion of the microspheres were measured by the laser light scattering technique using a Coulter LS-230 Particle Size Analyser (Miami, FL, USA). The microspheres were first dispersed in 100 ml of double-distilled water containing 0.05% Tween 80 and sonicated for 15 s to redisperse the microspheres. The particle size at 60% of the total volume fraction was taken as the average particle size (n = 3).

DSC analysis

To investigate the physical state of ibuprofen and polymers in the microspheres, the thermal analysis was performed by differential scanning calorimetry (Pyris 1 DSC, Perkin Elmer Corp., UK). All the samples were heated in crimped aluminum pans and the first scan was measured at a heating rate of 10°C/min from room temperature to 200°C, subsequent scan was from —60°C to 100°C followed by cooling the sample to —60°C.
Characterization of the microspheres by SEM

Dried microspheres were firstly mounted onto stubs using double-sided adhesive tape without being gold-coated, then were directly observed using a scanning electron microscope (JSM-5501LV, Tokyo, Japan) at an accelerating voltage of 15kV and 20kV, respectively.

Observation of the microspheres by POM

In order to study the crystalline structure of the microspheres and further investigate drug dispersion in polymer matrices, polarized optical microscopy (Olympus BX-50, Japan) equipped with a video camera and a computerized image analyser was utilized to observe the morphology of ibuprofen containing films. All samples containing the same amount of ibuprofen as in microspheres were prepared by a solvent casting method as reported in earlier publications (Tsuij and Ikada 1996, 1998). Briefly, methylene chloride solutions of the same drug content as that in microspheres were prepared at a total polymer concentration of 1.0gL⁻¹, then cast onto flat glass plates, followed by very slow solvent evaporation at room temperature for ~1 week. The resulted films were dried in vacuum for 1 week and stored at room temperature for more than 1 month to allow equilibrium to be reached. The morphology study was performed on films of 25 µm thickness.

In vitro release study

Approximately 10 mg of microspheres were incubated in 4.5 ml of 0.1MPBS at pH 7.4 and 37°C. The samples (3 ml) were withdrawn at pre-determined time intervals and centrifuged for 10 min at 4000 rpm, the supernatant was collected for UV analysis at 222 nm and replaced by the same amount of fresh buffer solution.

Diffusion coefficient measurements

In order to understand release kinetics, the diffusion coefficients of ibuprofen in the four different polymers were measured. At first, the polymer films were prepared by dissolving certain polymers in DMC and casting on a PE plate. After the solvent evaporated without forming any air bubbles at room temperature, the films were dried at 30°C under vacuum and the disk samples with ~10mm in diameter and 4 mm in thickness were punched from the films.

The diffusion coefficients of ibuprofen in different polymers were determined by measuring the absorption kinetics of ibuprofen aqueous solution to the polymer disks at 37±0.1°C and calculated according to the below equation (Shen et al. 2000).

\[ 3V/(2KAa) \ln(X + 0.5/A^2 - 0.5) = 4 \cdot Dta^2 \]  

(1)

where V is the volume of ibuprofen solution, K stands for the dispersion coefficients of polymer-aqueous phase in equilibrium, A is the one side area of the disk, a is the disk’s half thickness and X is the ibuprofen fractional amount in the aqueous phase at time t. This experiment was repeated three times for each measurement.

Results and discussion

Microsphere preparation

The O/W emulsion solvent evaporation method has been successfully used to incorporate poorly water-soluble drugs into polymers. Although extensive study about the effect of formulation variables on the physical characteristics of ibuprofen microspheres based on different polymer matrices, such as Eudragit® RS 100 (Perumal et al. 1999), polystyrene (Tamilvanan et al. 1999) have been reported, the drug release time was still too short. As a first step, the effect was investigated of preparation parameters such as polymer concentration, theoretical ibuprofen loading and PVA concentration on the entrapment efficiency of ibuprofen in the microspheres composed of PLA, PCL and their copolymers.
Table II. Effect of PVA concentration, polymer content and drug-loading on drug entrapment efficiency and particle size of microspheres made from PLA (n = 3, mean ± SD).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PLA concentration (%, w/v)</th>
<th>Theoretical ibuprofen loading (%, w/w)</th>
<th>PVA concentration (%, w/v)</th>
<th>Stirring speed (rpm)</th>
<th>Ibuprofen entrapment efficiencya (%)</th>
<th>Mean diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4.02</td>
<td>20.14</td>
<td>0.50</td>
<td>900</td>
<td>88.25 ± 0.93</td>
<td>38.24 ± 2.48</td>
</tr>
<tr>
<td>b</td>
<td>4.14</td>
<td>19.67</td>
<td>0.25</td>
<td>900</td>
<td>71.54 ± 0.84</td>
<td>40.84 ± 3.78</td>
</tr>
<tr>
<td>c</td>
<td>4.01</td>
<td>19.92</td>
<td>0.10</td>
<td>900</td>
<td>67.60 ± 1.08</td>
<td>44.31 ± 1.20</td>
</tr>
<tr>
<td>d</td>
<td>4.04</td>
<td>19.26</td>
<td>0.10</td>
<td>600</td>
<td>76.54 ± 0.18</td>
<td>46.82 ± 3.01</td>
</tr>
<tr>
<td>e</td>
<td>4.02</td>
<td>15.06</td>
<td>0.10</td>
<td>600</td>
<td>80.31 ± 0.27</td>
<td>47.13 ± 2.46</td>
</tr>
<tr>
<td>f</td>
<td>4.00</td>
<td>10.18</td>
<td>0.10</td>
<td>600</td>
<td>87.14 ± 0.46</td>
<td>47.09 ± 2.01</td>
</tr>
<tr>
<td>g</td>
<td>5.04</td>
<td>10.19</td>
<td>0.10</td>
<td>600</td>
<td>87.40 ± 0.12</td>
<td>48.16 ± 1.80</td>
</tr>
<tr>
<td>h</td>
<td>9.94</td>
<td>10.05</td>
<td>0.10</td>
<td>600</td>
<td>88.62 ± 0.23</td>
<td>48.87 ± 1.80</td>
</tr>
</tbody>
</table>

*entrapment efficiency was calculated by the ratio of the actual drug loading to theoretical drug loading.

The representative results of using PLA as polymer matrix are listed in Table II. It can be seen from formulation d, e and f that when other parameters remained constant, the drug entrapment efficiency gradually increased (from 76.54% to 87.14%) with a decrease in the theoretical ibuprofen loading (from 19.26% to 10.18%). It was reported that the solubility of ibuprofen in pH 7.4 phosphate buffer solution at 37 ± 1°C could be up to 27.3 mg/ml⁴ (Leo et al. 2000). Therefore, the higher drug loading would allow a greater partition of ibuprofen into the aqueous phase. When keeping ibuprofen loading and PVA concentration constant at ~10% and 0.1%, respectively, it was found from formulation f, g and h that the entrapment efficiency and particle size was almost independent of PLA concentration (~88% and 48 µm, respectively). A simple comparison of two stirring speed (600 and 900 rpm) was also listed in Table II, suggesting that an increase in stirring speed leads to a decrease in particle size. The results were consistent with those reported in literatures (Perumal 2001). Among all the examining factors, PVA concentration seems the most important. As formulation a, b and c shows, ibuprofen entrapment efficiency greatly decreased from 88.25% to 67.60%, when PVA concentration decreased from 0.5% to 0.1% w/v. Since PVA used in this experiment is a high molecular weight polymer, the increase in PVA concentration leads to the increase in viscosity of external aqueous phase, which makes it easier to form a film-like surface over the droplets. During the process of microspheres solidification, the formation of such a layer prevented ibuprofen diffusion from oil phase towards external aqueous phase. It also can be seen that increasing PVA concentration from 0.1 to 0.5% w/v results in a decrease in particle size (formulation c, b and a). The above results are in agreement with those reported by Tamilvanan et al. (1999).

The results of Ibuprofen entrapment in PCL and P(LA-b-CL) microspheres are listed in Table III. All samples were prepared under the same conditions as formulation g. It can be seen that the entrapment efficiency of ibuprofen in microspheres decreased with the increase in the amount of e-CL segments (ca. 70 ~ 80% for the copolymer and 25.38% for PCL microspheres). It is well known that PCL is in the rubber state at room temperature with Tg around —60°C. Therefore, PCL chains possess more flexibility than those of PLA and its crystallinity is less affected by solvent evaporating rate or the addition of ibuprofen. Table IV shows a similar regular of PVA concentration on PCL microspheres as shown in Table II. During the process of solvent evaporation, high Ibuprofen diffusion coefficient value in PCL (see Table V) would lead to the low entrapment efficiency of ibuprofen entrapped in PCL microspheres.

Table III. Entrapment efficiency and particle size of four kinds of microspheresd (n = 3, mean ± SD).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Entrapment efficiency (%)</th>
<th>Mean diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>81.21 ± 0.31 (PVA: 0.1% w/v)</td>
<td>48.16 ± 1.80</td>
</tr>
<tr>
<td>P(LA-b-CL)</td>
<td>74.15 ± 2.13 (PVA: 0.1% w/v)</td>
<td>40.43 ± 1.38</td>
</tr>
<tr>
<td>PCL</td>
<td>25.38 ± 0.67 (PVA: 0.1% w/v)</td>
<td>51.14 ± 2.64</td>
</tr>
</tbody>
</table>

*All microspheres were prepared under the same experimental condition as formulation g: polymer concentration: 5% w/v; theoretical ibuprofen-loading: 10% w/w; PVA concentration: 0.1% w/v; stirring speed: 600 rpm.
Table IV. Effect of PVA concentration on entrapment efficiency and particle size of PCL microspheres\(^a\) \((n = 3, \text{mean} \pm SD)\).

<table>
<thead>
<tr>
<th>PVA concentration (% w/v)</th>
<th>Entrapment efficiency (%)</th>
<th>Mean diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1%</td>
<td>25.38 ±0.67</td>
<td>51.14±2.64</td>
</tr>
<tr>
<td>0.5%</td>
<td>37.78 ±0.32</td>
<td>32.81±3.10</td>
</tr>
<tr>
<td>0.75%</td>
<td>42.21 ±0.16</td>
<td>19.67±3.41</td>
</tr>
</tbody>
</table>

\(^a\)Microspheres were prepared under conditions as: polymer concentration: 5% w/v; theoretical Ibu-loading: 10% w/w; stirring speed: 600 rpm.

Table V. Ibuprofen diffusion coefficient \((D)\) in different polymer matrices \((n = 3, \text{mean} \pm SD)\).

<table>
<thead>
<tr>
<th>Sample</th>
<th>(D \times 10^8 (\text{cm}^2/\text{S}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>1.03±0.81</td>
</tr>
<tr>
<td>P(LA-b-CL)</td>
<td>8.24±0.56</td>
</tr>
<tr>
<td>PCL</td>
<td>23.48±0.62</td>
</tr>
</tbody>
</table>

Microsphere characterization

SEM studied the shape and surface morphology of the microspheres. It can be observed from Figure 1 that the microspheres prepared from PLA and P(LA-b-CL) are generally spherical, while most PCL microspheres are irregular. In addition, PLA microspheres shows rough surface, covered with many small openings. The surface of P(LA-b-CL) microspheres is smooth with few concaves. Big holes and defects can be observed on the surface of PCL microspheres.

Considering the possibility of partial ibuprofen crystallization in the outer aqueous phase during microsphere preparation process and/or on the microspheres surface (Leo et al. 2000), thermodynamic properties of the microspheres were studied by DSC. From Figure 2(A), it can be seen that the thermogram of ibuprofen showed an apparent endothermic peak at 71.6°C, corresponding to its melting temperature (curve a). This endothermic peak can be detected in the thermograms of P(LA-b-CL) and PLA microspheres (curves c and d), but it didn’t appear in the case of PCL microspheres (curve b). The above results indicates that ibuprofen was uniformly dispersed in the PCL matrix, but partial drug loaded in P(LA-b-CL) and PLA matrices was in crystalline state. It could also be found that \(T_m\) of CL segments in P(LA-b-CL) decreased from 54 to 48°C when ibuprofen was incorporated according to results shown in Figure 2(A) and (B), which indicates that the presence of ibuprofen had a certain hindering effect on the crystallinity of P(LA-b-CL).

In order to further investigate drug dispersion throughout the polymer matrices, the films composed of three types of the polymers were prepared by solvent casting method for polarized optical microscopy observation. All specimens were prepared as the reports in previous publications (Tsujii and Ikada 1996, 1998). Figure 3 reveals that the addition of ibuprofen into the films has an evident effect on the polymer crystallization through comparing polarized optical micrographs of films before and after adding ibuprofen. For PCL films, the size of PCL spherulites showed an obvious decrease after the addition of ibuprofen (shown in Figure 3(A)), which indicates that ibuprofen has a hindering effect on PCL crystallization.

In addition, the results shown in Figure 2(A) (curve b) also reveal that PCL segments prevent the crystallization of ibuprofen in the microspheres. In the case of P(LA-b-CL) film, relatively less crystalline region can be seen in Figure 3(B), indicating that the e-CL sequences could form a crystalline structure at the monomer ratio of 21.3/78.7 to LA sequences. It also could be seen that some crystalline ibuprofen scattered in the crystalline region reflected by the bright dot in Figure 3(A) (b). As for PLA film, it is amorphous in macroscopic scale, benefiting for the formation of large number of drug micro-crystals (appeared in Figure 3(A) (c)). All these results were in accordance with those obtained from DSC thermograms.

The different amount of amorphous ibuprofen appeared in different polymers could be attributed to the different hindering effect of polymer chains on the drug crystallization. Many researchers (Leo et al. 2000, Tamilvanan et al. 2000) have found the contemporaneous presence of the amorphous and crystalline drug fraction in different types of polymer matrices and Castelli et al. (2002) reported that ibuprofen is homogeneously dispersed in Eudragit RS matrix in a microcrystalline form, without polymorph changes and transition phenomena into an amorphous form. Owing to the distinctly flexible chains of PCL, ibuprofen crystallization would encounter more inhibition or retardation. In the case of P(LA-b-CL) and PLA films, it has to be taken into account that the crystallization of polymer also has some effect on drug dispersion, a small quantity of microcrystalline ibuprofen.
was allowed to form and co-existed with the amorphous ibuprofen.

Figure 1. Scanning electron micrographs of ibuprofen-loaded microspheres made from (a) PCL; (b) P(LA-b-CL); (c) PLA.
Figure 2. DSC thermograms of (A) ibuprofen-loaded microspheres; (B) blank polymers. a-plain ibuprofen crystals, b-PCL, c-P(LA-b-CL) and d-PLA.
Figure 3. Polarized optical micrographs of films: (A) containing 10% w/w ibuprofen, (B) not containing ibuprofen, a-PCL, b-P(LA-b-CL) and c-PLA.

Figure 4. Ibuprofen released from three microspheres in (a) pH 7.4 phosphate buffer solution and (b) pH 6.0 phosphate buffer solution. (■) Ibu-PCL; ( ●) Ibu-P(LA-co-CL); (▲) Ibu-PLA.
In vitro release behaviour

The in vitro release profiles of ibuprofen from four kinds of microspheres are shown in Figure 4. In general, the drug release rate decreased in the order of PCL, P(LA-b-CL) and PLA. PCL microspheres showed more serious burst release during the first day (almost 80%) than P(LA-b-CL) microspheres (~50%) and PLA microspheres (18%); thereafter, ibuprofen release continued at a reduced rate and almost completely released in 30 days. In the case of P(LA-b-CL) and PLA microspheres, the ibuprofen release is characterized with two different steps. The first one corresponded to a period of 15 days, with 45–75% ibuprofen released. There was an acceleration of the drug release in the second step, which reached 90% and 75% in 30 days for P(LA-b-CL) and PLA microspheres, respectively.

From the results of ibuprofen diffusion coefficient (D) in different polymer matrices, SEM, DSC and POM, it was concluded that the in vitro release of ibuprofen from these three microspheres was strongly dependent on polymer crystalline behaviour and drug dispersion state in different matrices. It is apparent that ibuprofen release rate decreased as the increase of polymer crystallization tendency and the decrease of ibuprofen crystallization in different matrices.

It can also be concluded from the comparison between Figure 4(a) and (b) that the release of ibuprofen is pH dependant; the release is gradually slower in pH 6.0 PBS than in pH 7.4 PBS due to the acidic characteristics of ibuprofen. Similar phenomena has also been mentioned by Arida et al. (1999), who pointed out that the more sustained-release characteristics of ibuprofen in the acidic medium may reduce the irritation possibility of ibuprofen toward stomach and other side effects.

Conclusions

A series of ibuprofen-loaded microspheres comprising PLA, PCL, as well as their block (with monomer composition of LA/CL: 78.7/21.3) copolymer have been prepared by the solvent evaporation method. The drug entrapment efficiency decreased with an increase in the amount of ε-CL segments in the polymers. The in vitro release rate decreased in the order of PCL, P(LA-b-CL) and PLA microspheres. The results obtained from DSC, SEM and POM indicated that the drug release was significantly affected by the crystallization characteristics of polymer matrices and ibuprofen dispersion state in the microspheres. The copolymers of lactide and ε-caprolactone are promising materials to prepare ibuprofen-loaded microspheres for prolonging ibuprofen release.

Acknowledgements

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References


excipients on release rate of the drug. Journal of Controlled Release 57:197-203.


