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Microwave-assisted Polymerization of ε-Caprolactone with Maleic Acid as Initiator and Drug Release Behavior of Ibuprofen-Poly(ε-caprolactone) System

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Abstract: Poly(ε-caprolactone) (PCL) with weight-average molar mass over 10000 g/mol was synthesized by microwave-assisted ring-opening polymerization of ε-caprolactone (ε-CL) with maleic acid (MA) as initiator (2.45 GHz, 360 W, 85 min). Ibuprofen-PCL controlled release system was prepared directly by the ROP of ε-CL in its mixture with ibuprofen. The release of ibuprofen from the system was sustained and steady.

Keywords: Microwave, ring-opening polymerization, poly (ε-caprolactone), maleic acid, ibuprofen, drug release.

Poly(ε-caprolactone) (PCL) is one of the well-known synthetic polymer carriers for drug controlled release system and is prepared by ring-opening polymerization (ROP) of ε-caprolactone (ε-CL) with stannous octanoate as catalyst.

It has been proved that ROPs of ε-CL and lactide as well as polycondensation of L-2-hydroxy-3-phenylpropanoic acid were significantly enhanced by microwave irradiation in our previous study[1-3]. Cationic ROP of ε-CL could take place in the presence of organic acids by conventional thermal method[4,5]. To avoid using metallic catalysts, we investigated microwave-assisted ROP of ε-CL with organic binary acids such as maleic acid (MA), succinic acid and sebacic acid as initiators and thus a new method was developed to fabricate well-mixed drug release system. In this paper, the results of MA initiated ROP of ε-CL under microwave irradiation, the preparation of ibuprofen-PCL controlled release system by the new method and the release behavior of ibuprofen from the system are presented.

Experimental

The mixture of 1.14 g (10 mmol) ε-CL and 0.058 g (0.5 mmol) maleic acid was subjected to reduced pressure (50 Pa) for 0.5 h and the sealed tube was irradiated by microwave (2.45 GHz) from 25 to 195 min with various power levels (270-720 W).

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The reprecipitate PCL from dichloromethane/methanol was dried in vacuum and its Mw was determined by GPC. As to ROP of the mixture of ε-CL with ibuprofen, the ratio of ε-CL and ibuprofen was 95:5 (in weight) and the polymerization procedure was similar to above. Ibuprofen controlled release system with PCL as matrix was obtained. The release of ibuprofen from the system *in vitro* was performed in pH7.2 phosphate buffer at 37°C.

Results and Discussion

The ROP was carried out with microwave power from 270 W to 720 W for 25 min. The weight-average molar mass (Mw) of PCL was in range from 4000 to 8300 g/mol (**Table 1**). When the irradiation time lasted 135 min (360 W), Mw of PCL increased to 12000 g/mol. However, by conventional method, Mw of PCL from ROP of ε-CL initiated by organic acids was below 3000 g/mol (230°C, over 3 h)[4,5]. Obviously, the rate of ROP of ε-CL and Mw of PCL were both improved. Decreasing in Mw (10500 g/mol) was observed after the reaction mixture was irradiated for 195 min, which may be induced by a transesterification between PCL and remaining maleic acid[6].

Table 1 Results of MA initiated ROP of ε-CL under microwave irradiation*

Entry	Power (W)	Time (min)	Mw	Mw/Mn
1	270	25	4000	1.2
2	360	25	5100	1.2
3	450	25	5300	1.4
4	540	25	6300	1.4
5	630	25	7400	1.4
6	720	25	8300	1.5
7	360	40	7100	1.3
8	360	55	9100	1.4
9	360	85	11000	1.5
10	360	135	12000	1.8
11	360	165	11700	1.8
12	360	195	10500	1.8

*MA:CL (Molar ratio) = 1:20

Ibuprofen is a non-steroidal anti-inflammatory drug. In the presence of ibuprofen, PCL with Mw of 4500 g/mol obtained by the ROP of ε-CL (450 W, 20 min, MA/CL=1:20), while Mw of PCL was 5300 g/mol under the same conditions without ibuprofen. The results indicated that the presence of ibuprofen had no significant influence on the ROP. Thus, the PCL-based ibuprofen controlled release system could be prepared directly by the ROP of ε-CL in its mixture with ibuprofen.

Figure 1 SEM image of PCL-ibuprofen

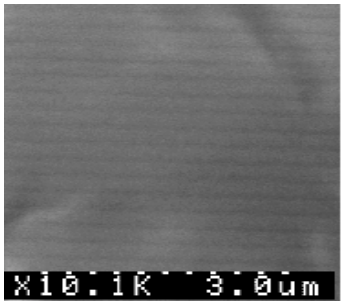
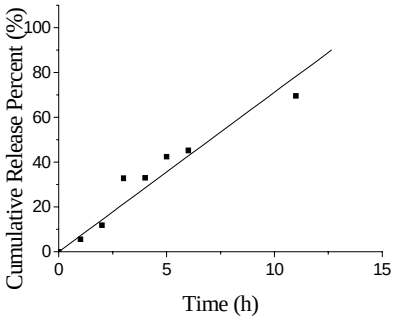


Figure 2 The release rate of ibuprofen



Neither ibuprofen particles nor microphase separation was observed from the surface of the ibuprofen-PCL controlled release system by scanning electron microscopy (SEM) (**Figure 1**). Within 12 h, 70% of ibuprofen was released out in zero-order without burst release, which was generally observed in the release systems by mixing drug and polymers powder together. The cumulative release curve was plotted as **Figure 2**.

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