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COMMUNICATION

Preparation and Some Physicochemical Properties of Cross-Linked Poloxamer Hydrogel Spheres

Hui Xu,* Pingtian Ding, Gang Wei, and Junmin Zheng

Department of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110015, People's Republic of China

ABSTRACT

The principal purpose of this paper is to report the preparation of cross-linked poloxamer hydrogel spheres in an aqueous two-phase system without the use of organic solvent and additional emulsifier and physicochemical properties related to drug release. Poloxamer 188 was modified with methacryloyl chloride to obtain the polymerizable derivative (macromer). The aqueous solution of the macromer was mixed with dextran/magnesium sulfate aqueous solution to form a water-in-water emulsion system. After polymerizing the macromer in the dispersion phase, nonporous particles with a mean diameter of micron level were prepared. Both the mean diameter and swelling ratio of spheres can be tailored by varying the starting composition of the preparations. The drug release experiments indicate that the release of vitamin B_{12} entrapped in the spheres follows first-order kinetics.

KEY WORDS: Aqueous two-phase system; Hydrogel spheres; Poloxamer; Sustained release.

INTRODUCTION

Hydrophilic polymer microspheres have been under intensive investigation as a matrix for the delivery of drugs, especially for proteins and peptides. The preparation of such spheres is generally based on the water/oil emulsion technique (1–3). However, as is well known, it is difficult to eliminate the residual organic solvent and surfactant, which were introduced into the particles during the preparation. Recently, Franssen et al. (4) described a completely aqueous emulsion technique for the preparation of certain cross-linked hydrophilic polymeric microparticles.

Poloxamer, a series of poly(oxyethylene)-poly (oxypropylene)-poly(oxyethylene) block copolymeric surfactant, is widely used as hydrophilic matrix material in pharmaceutical dosage forms. Florence et al. (5)

*To whom correspondence should be addressed. E-mail: Xuhuimail@21cn.com

developed the cross-linked hydrogels of poloxamer diacryloyl derivative. Here, we described the emulsification of dimethacryloyl derivative of poloxamer 188 in dextran/magnesium sulfate aqueous solution and the preparation of cross-linked poloxamer spheres. Vitamin B_{12} was selected as model drug to study the release of solute form such spheres.

METHODS

Materials

Pluronic® F68 was obtained from SERVA (Heidelberg, Germany). Vitamin B_{12} and dextran 40 were from Huabei Pharmaceutical Co. (Shijiazhuang, China). All other reagents were from commercial sources.

Preparation of the Macromer

The macromer was prepared according to the method described by Florence (5). The final product was characterized by UV–vis spectrophotometry (UV 2201, Himadzu, Japan), FTIR (IFS 55, Bruker) and ^{1}H NMR (ARX 300, Bruker, Germany).

Preparation of the Spheres

Deoxygenated aqueous solution of macromer (20% w/w) and dextran 40-magnesium sulfate solution were mixed by magnetically stirring for a fixed amount of time under nitrogen atmosphere. The resulting emulsion was allowed to stabilize for 10 min, and subsequently a 50:50 (v/v) mixture of ammonium persulfate and sodium metabisulfite solution was added as a redox initiator in the amount of 1 wt.-% of the macromer. The mixture was incubated without stirring for 30 min at $37 \pm 1^{\circ}$C. The cross-linked spheres were purified with multiple washing and centrifugation steps. The spheres were observed under scanning electron microscope (1000B, Amary, Japan), and particle size and size distribution were measured with an image analysis system (IMG 500, IBAS, Germany).

Swelling Experiments

Swelling studies were performed in deionized water, and the particle size was determined under photomicroscope with scale. The swelling ratio was defined as the ratio of the volume of the equilibrium-swollen samples to that of dried samples, and was calculated from at least 10 samples.

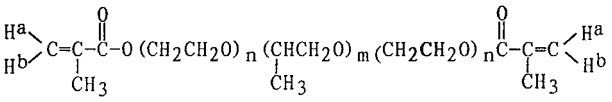
Drug Loading and In Vitro Release

Water-soluble drug, VB_{12} (1 in 90 water, MW = 1355.38), was selected as model drug for the release experiments. VB_{12}-loaded spheres were achieved by equilibrating the dried spheres in concentrated aqueous solution of VB_{12} at 37°C for 2 days. After rinsing and centrifuging, the drug-loaded spheres were air dried. The amount of drug loading was determined spectrophotometrically after complete extraction of drug-loaded spheres in water. The drug release experiments were carried out using a dialysis method. VB_{12}-loaded spheres were put into a dialysis tube (D45 mm, MW = 8,000 to 10,0000), and 1 mL deionized water was added. 1 mL VB_{12} solution was used as control. The dialysis tube was then placed into 100 mL of deionized water kept at $37 \pm 1^{\circ}$C in a water bath with constant stirring. At certain time intervals, 5 mL of release media was removed and replaced by the same amount of pure solvent. The absorption of the solution was analyzed as a function of time using UV-vis spectrophotometry at 361 nm.

RESULTS AND DISCUSSION

Characterization of Macromer

The macromer was characterized by UV-vis (λ_{max}, 206 nm for the methacryloyl group), FTIR (KBr, the stretching vibration absorption of carbonyl group at 1719 cm^{-1} and vinyl group at 1638 cm^{-1}), and ^{1}H NMR ($CDCl_3$, $\delta = 5.58$, 6.13 for protons of methylene). The yield was approximately 85%. The conversion of methacrylate per poloxamer molecule was estimated from integral values of proton signals in ^{1}H NMR spectrum. The efficiency of methacrylation of poloxamer is 93.3%, which indicates that one poloxamer molecule carries two polymerizable functional group.



Chemical structure of poloxamer macromer

The Preparation of Hydrogel Spheres

Many combinations of water-soluble polymers and or inorganic salt, such as PEG/dextran, PEG/PVA, PEG/sulfate, PVP/phosphate, etc., can form aqueous two-phase system (6). From a thermodynamic point of view, phase separation in these systems occurs when the

change in the Gibbs free energy of mixing is positive, i.e., $\Delta G_{mix} = \Delta H_{mix} - T \cdot \Delta S_{mix} > 0$ (7). Depending on the concentration of dextran and macromer, polymer immiscibility many occur. After the mixture was magnetically stirred, a water-in-water emulsion can be obtained. To prepare spheres with such an emulsion, a relatively high concentration of dextran 40 must be used (4), thus magnesium sulfate was introduced into the system to reduce the amount of dextran used. In all experiments, 0.2% (w/w) CMC-Na was also added to stabilize the emulsion. When the concentration of dextran, magnesium sulfate, and macromer were 10–20, 4–10, and 0.7–3% (w/w), respectively, a relatively stable emulsion can be easily formed. At the same time, the viscosity of the emulsions was <40 mPa s (NDJ-I rotary viscometer), so the mixture was easy to handle.

After the resulting emulsion was stabilized for 10 min, the polymerization was carried out without further stirring to prevent the aggregation of the particles.

Analysis by SEM (Fig. 1) shows that regular-shaped, nonporous spheres were prepared. Figure 2 shows a typical size distribution of spheres prepared in the study. The effects of concentration of dextran, magnesium sulfates, macromer and dispersion time, etc., on the particle size was also studied, and the results are listed in Table 1. The mean diameter of the particles increases with increasing the concentration of magnesium sulfate and dextran 40 or with decreasing the concentration of macromer. For an aqueous two-phase system, it is known that in equilibrium state the volume ratio of dispersion phase to continuous phase and concentrations of polymers in both phases are different from those of the starting composition. Depending on the starting composition of the reaction mixture, the viscosity of the two phases differed, and the resulting spheres had various number mean diameters and various equilibrium water content. Increasing the dispersion time can narrow the size distribution but has little effect on mean particle size.

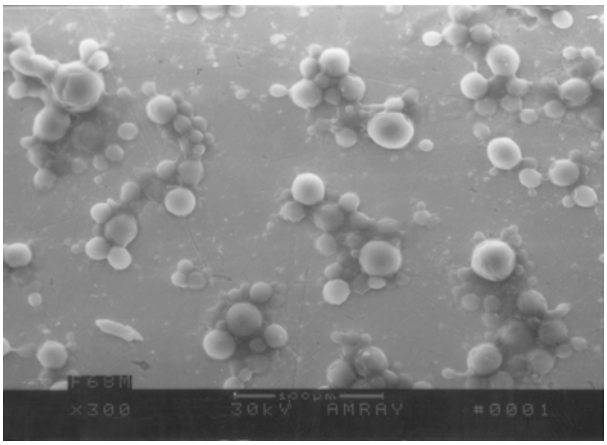


Figure 1. SEM picture of cross-linked poloxamer hydrogel spheres.

Swell and Drug Release

During the swelling process, no high-viscosity gel layers occurred. The spheres reach equilibrium swelling within seconds after contact with water. The experimental results (Table 1) showed that when the concentration of $MgSO_4$ increased from 4 to 8%, the swelling ratio decreased significantly ($P < 0.01$), whereas changing the concentration of dextran did not significantly change the swelling ratio. As diffusion occurs primarily through water-filled pores or channels in the hydrogel networks, the diffusion of solute may be decreased by decreasing the swelling ratio (8).

Table 1.

Effect of Starting Composition on the Size and Swelling Ratio of Spheres[a]

Starting Composition (%, w/w)			Viscosity of Suspension Medium (mPa s)	Average Diameter (μm)	Swelling Ratio
Macromer	Dextran 40	$MgSO_4$			
1	14	4	26.1	34.51	7.14 ± 0.50
1	14	6	29.0	51.16	6.78 ± 0.45
1	14	8	30.4	52.82	6.32 ± 0.34
1	11	6	26.7	41.51	6.89 ± 0.28
1	17	6	32.5	56.09	6.76 ± 0.38
1.5	14	6	29.0	55.24	6.69 ± 0.32

[a] In each preparation, 0.2% w/w CMC-Na was added.

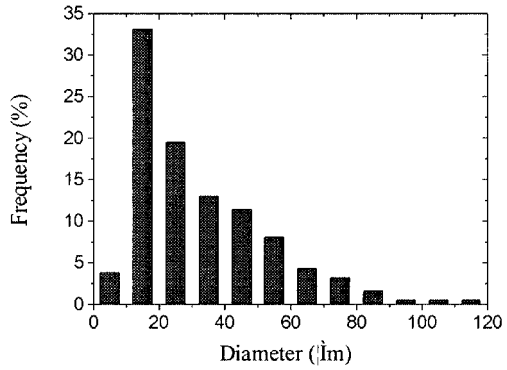


Figure 2. Typical size distribution of hydrogel spheres (starting composition: dextran, 11; $MgSO_4$, 4; macromer, 1; and CMC-Na 0.2% w/w, respectively).

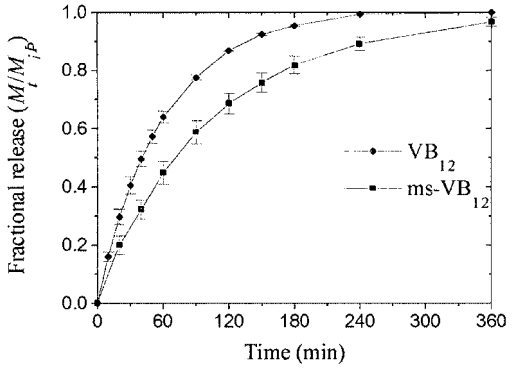


Figure 3. Fractional release of VB_{12} from poloxamer hydrogel spheres (drug loading: 3.6 wt.-%; starting composition: dextran, 11; $MgSO_4$, 4; macromer, 1; and CMC-Na 0.2% w/w, respectively).

Figure 3 shows the fractional drug release profile of VB_{12}-loaded spheres. The results indicated that the hydrogel spheres sustained the release of entrapped VB_{12}. The rate of release of VB_{12} from cross-linked gel spheres was well described with first-order kinetics model ($1 - M_t/M = 0.9789\,e^{-0.0094t}$) with $R^2 = 0.9996$.

CONCLUSION

Amphiphilic polymer (poloxamer 188) spheres with different particle sizes and swelling ratios could be prepared in completely aqueous emulsion. The spheres were easy to purify. The resulting easily purified hydrogel spheres are candidates for loading and delivering water-soluble drugs.

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