Preparation of Microspheres with Microballoons Inside for Floating Drug-Delivery Systems

Zhenqiu Yang, Baozhen Song, Qiaoxia Li, Honglei Fan, Fan Ouyang

State Key Laboratory of Biochemical Engineering, Institute of Process Engineering, Chinese Academy of Sciences, P.O. Box 353, Beijing 100080, China

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ABSTRACT: The use of floating drug-delivery systems is one method that is used to achieve prolonged gastric residence times. We developed a novel, multiple-unit, floating drug-delivery system of microspheres with microballoons inside from xanthan gum (XG) and gelatin (GA) by a water-in-oil method. With theophylline as the model drug, four formulations (FI–FIV) with different ratios of the two polymers were prepared. The size distribution, drug-encapsulation efficiency, floating behavior, release characteristics, and morphological properties were investigated. The ratio of the two polymers influenced the size distribution, encapsulation efficiency, and drug release appreciably. With increasing amounts of GA, the percentage yield of the floating microspheres and the drug-encapsulation efficiency decreased from 100 and 84.5% to 31 and 56.2%, respectively. The drug-release rate also decreased with increasing GA content, which was attributed to an increase in the crosslinking extent. An initial burst was observed, and after that, the drug was released slowly by a near-zero-order pattern, which was attributed to the low solubility of theophylline and the possible complexes formed by XG and GA in the simulated gastric fluid (pH 1.2). © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 94: 197–202, 2004

Key words: polysaccharides; drug delivery systems; microencapsulation; particle size distribution

INTRODUCTION

In recent years, scientific and technological advancements have been made in the research and development of rate-controlled oral drug-delivery systems. However, to achieve more predictable and increased bioavailability of drugs, short gastric residence times, unpredictable gastric emptying times, and other physiological adverse conditions must be overcome.[1,2] These considerations have led to the development of oral, controlled release dosage forms possessing gastric retention capabilities, which help to retain the controlled drug-delivery system in the stomach for a longer and more predictable time. Additionally, this is more important for drugs with an absorption window in the stomach or the upper small intestine and drugs with stability problems.

Several techniques,[3–6] including bioadhesive drug-delivery systems, size-controlled drug-delivery systems, and gastric floating drug delivery systems, have been adopted for this purpose. However, there are some inherent problems associated with bioadhesive systems because they deliver a large amount of drug at a particular adhesive site of the gastrointestinal tract (GIT), which leads to local irritation. For the size-controlled drug-delivery system, when in contact with the gastric fluid, the matrix swells and expands the size, therefore retarding passage through the pylorus.[7–9] Another approach for improving gastric residence time is to incorporate the drug into a floating device that is less dense than the gastric fluid. Floating, single-unit dosage forms, also called *hydrodynamically balanced systems*, have been studied extensively.[6] These single-unit dosage forms have the disadvantage of a release all-or-nothing emptying process.[4] However, multiple-unit, particulate dosage forms do not have this problem. The uniform distribution of these multiple-unit dosage forms in the gastric content could result in more reproducible drug absorption and a reduced risk of local irritation than single-unit dosage forms.[10] These systems could also reduce intersubject variabilities and fluctuations in the plasma levels of drugs resulting from delayed gastric emptying.[6] Most of the multiple-unit systems are effervescent ones that use matrices prepared with swellable polymers and effervescent components, such as sodium bicarbonate, calcium carbonate, and citric or tartaric acid.[11] The disadvantage of these systems is their delayed response; gas generation takes some time.

Polysaccharides are very promising biomedical materials because of their perfect biocompatibility and biodegradable character. Many polysaccharides, such as pectin, cellulose and its derivatives, curdlan, guar

Correspondence to: Z. Yang (zhenqiuy@yahoo.com).

gum, dextran, cyclodextrin, chitosan, starch, and xanthan gum (XG), have been studied extensively as biomedical polymers.[12]

The objective of this study was to develop a new multiple-unit, floating drug-delivery system with natural polysaccharides, namely, XG and gelatin (GA), which have been used widely in the food industry. The physical properties, morphology, and size distribution were examined. Theophylline (TH) was chosen as the model drug because of its narrow therapeutic window. The therapeutic effects of TH require a plasma TH concentration of at least 5–10 mg/mL, and toxic effects become apparent at about 15 mg/mL and frequent above 20 mg/mL.[13–15] The drug release from the floating system and the effect of the ratio of the two natural polymers on physical properties, floating, and drug release were evaluated.

EXPERIMENTAL

Materials

Theophylline (National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China) was used as the model drug. GA (Beijing Chemical Co., Beijing, China), XG (Heilongjiang Huaguan Share Co., Ltd., Haerbin, China), glutaraldehyde (Beijing Chemical Co., Beijing, China), liquid paraffin, ethanol, ethyl ether, and hydrochloric acid were standard laboratory reagents and were used as received. All other chemicals and reagents were of the highest purity available from local sources. Simulated gastric and intestinal fluids were freshly prepared.

Microsphere preparation

The polymer solutions were prepared as described next.

GA (1.5 g) was hydrated in 10 mL of deionized water at 40°C for 12 h to form a 15% w/v solution.

XG (1.5 g) was hydrated in 100, 200, 300, and 750 mL of deionized water to form 1.5, 0.75, 0.5, and 0.2% w/v solutions, respectively. To obtain homogeneous solutions, these dispersions were stirred at 2000 rpm for 2 h and then filtered.

Microspheres were prepared by a water-in-oil emulsification technique modified from previously described methods.[16] A GA solution (10 mL of a 15% w/v solution) was mixed with 10 mL of a 1.5, 0.75, 0.5, or 0.2% (w/v) XG solution to form the aqueous phases (recorded as FI, FII, FIII, and FIV, respectively). The model drug (2 mL of 0.1*M* theophylline) was added into the aqueous phase to form a drug/polymer solution, which was then added into a round-bottom flask loaded with 100 g of liquid paraffin (outer oil phase). We then emulsified the aqueous phase into the oil phase by stirring the system at 500 rpm with a half-moon paddle blender. At the same time, the system was heated to 80°C and kept there for 30 min. After that, the system was cooled in an ice bath to harden the microspheres, and 20 mL of ethanol was introduced into the system. To further solidify the microspheres, the crosslinking agent [1 mL of glutaraldehyde (50% v/v)] was added slowly, and the system stirred for another 30 min in the ice bath. The microspheres were then separated from the oil phase by centrifugation, washed several times with hexane to remove excess oil, washed with deionized water to remove residuals on the surfaces of the microspheres, filtered, and freeze-dried. If the microspheres were divided into two parts (floatable and sunk) during centrifugation, we collected them separately and processed them as described previously. The top part was used for the floating drug-delivery system test.

Characterization

Surface morphology

The surface morphology of the microspheres was examined by scanning electron microscopy (SEM) with a Jeol instrument (model JSM-35CF, Japan) after the particles were vacuum-sputtered with gold. To view the inside structure, the selected microspheres were cut with a razor before gold-sputtering.

Determination of the floatable microsphere yield

During preparation, if the microspheres were divided into two parts (floatable and sunk) during centrifugation, we collected them separately and processed them as described previously. The percentage yield of floatable microspheres was determined by the following equation:

$$\% \text{ Yield} = \frac{\text{Weight of floatable microspheres}}{\text{Weight of total microspheres}} \quad (1)$$

Size of the microspheres

We determined the size distribution of the microspheres by sieving the floating microspheres in standard test sieves.[17] Particles that passed through one sieve but were retained by the other were collected and weighed, and the distribution was analyzed based on the weight fraction in each sieve. According to the diameters, the particles were further divided into four parts (<300, 300–600, 600–850, and >850 μm); the weight proportion of microspheres included in each size category was recorded.

Floating behavior of the microspheres

We performed floating behavior studies by placing 50 microspheres (600–850 or >850 μm) into 100-mL glass

beakers and subsequently adding 60 mL of preheated 0.1*N* HCl (pH 1.2) containing 0.02% w/v Tween 20 (37 ± 0.1°C) to exclude floating due to nonwetted surfaces. The beakers were shaken horizontally in a water bath at 37 ± 0.1°C (50 rpm). At predetermined time intervals, the flasks were allowed to stand for 5 min without agitation, and the number of settled particles was counted visually.

Drug content of the microspheres and the yield of floatable microspheres

Finely powdered theophylline microspheres (50–100 mg, accurately weighed) were suspended in distilled water (100 mL). The samples were placed in an ultrasonic bath for three periods of 30 min each with a resting period of 30 min between each ultrasonic treatment. After 12 h, the mixture was filtered through a 0.22-μm filter, and the drug content was determined in the filtrate.[16]

In vitro drug-release studies

We performed *in vitro* drug-release studies by placing a weight corresponding to 10–20 mg of drug as microspheres (accurately weighed) into 100-mL glass flasks, subsequently adding 60 mL of preheated release medium (0.1*N* HCl at pH 1.2 without additives, 37 ± 0.1°C), and then horizontally shaking the flasks (37 ± 0.1°C, 75 rpm). At predetermined time intervals, 1 mL of the solution was withdrawn and made up to 5 mL. Theophylline was detected with ultraviolet spectroscopy at 272 nm. An equal volume of the fresh medium (37 ± 0.1°C) was introduced into the container after each withdrawal to maintain a constant volume. All of the experiments were conducted in triplicate. The mean values are plotted as cumulative release (%) versus time in Figure 1.

We determined the mechanism of *in vitro* drug release from the microspheres by fitting a semiempirical model of Fickian and non-Fickian drug release from polymeric matrices to mean dissolution data as follows [18–20]:

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released after an infinite time, k is a constant that takes into account the structural and geometric features of the matrix, and n is a release exponent indicative of the mechanism by which drug is released. The values of n and k for each data set were determined from the slope and y intercept of a logarithmic plot of the percentage of drug released versus time.

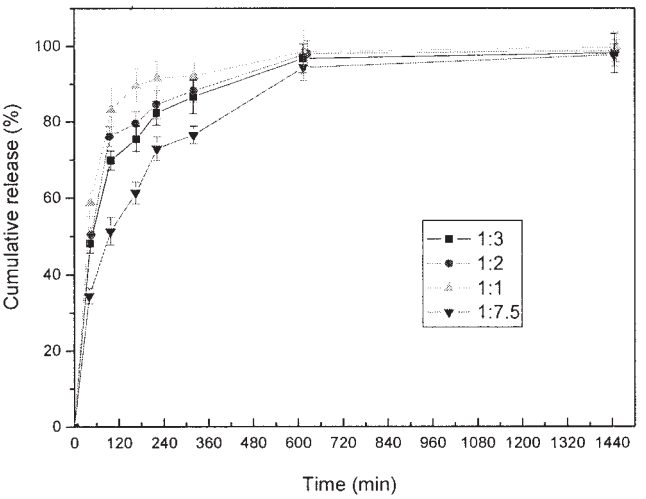

Figure 1 Release profiles of theophylline from microspheres FI–FIV with microballoons inside in simulated gastric fluid(pH 1.2).

RESULTS AND DISCUSSION

Morphology

SEM photographs of the floating microspheres are shown in Figure 2; the shape of the particles was spherical for all four of the formulations, but the sizes were different. As shown, there were some knobs in the surface of the microspheres; these knobs (microballoons) may have been caused by entrapped air. During the formation of the microspheres, gelation occurred after the cooling step. GA has been used widely as an emulsifier, and XG has been widely used as an emulsifier and a foaming agent.[21–24] It is reasonable to suggest that air bubbles introduced in the solution during the preparation process were emulsified by GA and XG up to the complete gelation of the polymer solution after cooling. Subsequently, the entrapped air expanded because of the ambient temperature increase, but it could not escape out because of the restriction of the formed polymer membrane. The number of entrapped air balloons in the microspheres and the size of the microspheres also decreased with increasing polymer ratio. In the cross-section, a porous structure was seen (Fig. 2). Microballoons were arrayed one by one, which led to a low density of microspheres and their floating ability. The number of microballoons decreased and the thickness of the wall of microballoons increased with increasing polymer ratio, which is also shown in Figure 2.

Percentage yield and size distribution of the floating microspheres

The percentage yields of floating microspheres determined by weighing after drying were 100, 74, 54, and 31% for FI–FIV, respectively. The size distributions are shown in Figure 3.

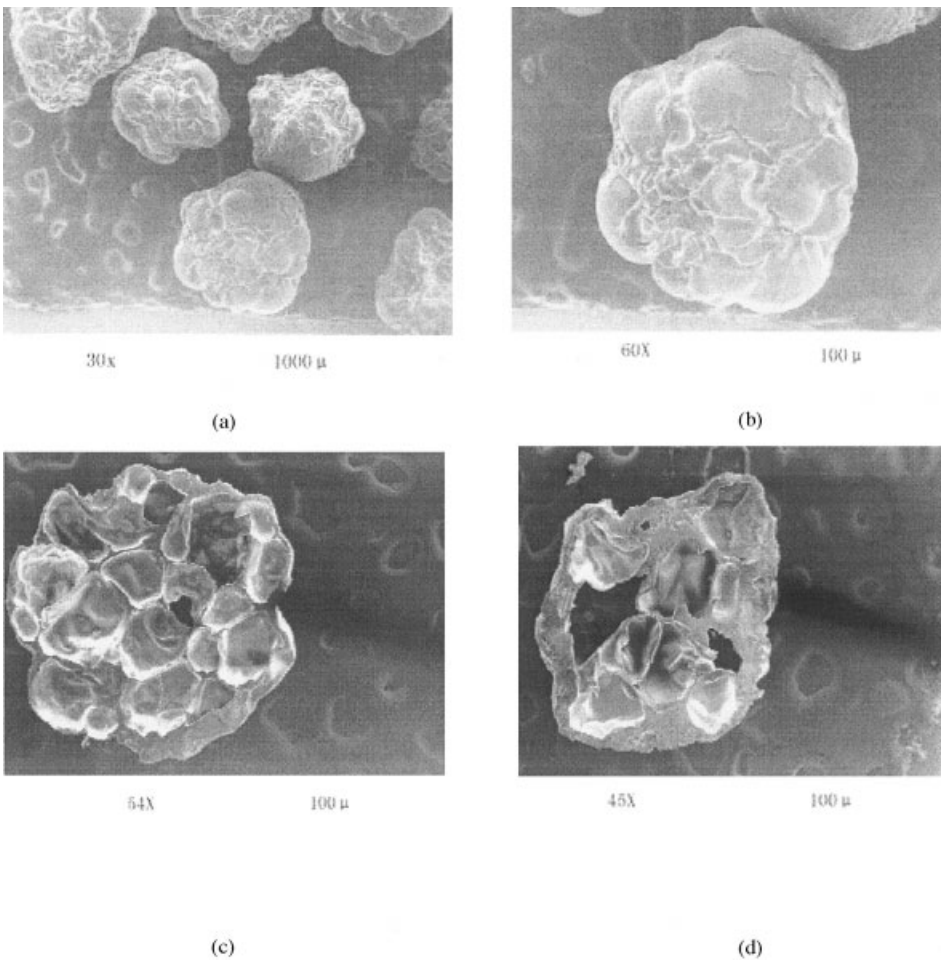

Figure 2 SEM micrographs of blank microspheres with microballoons inside: (a,b) photographs of FI, (c) cross-section photograph of FI, and (d) cross-section photograph of FIII.

As shown, the percentage yield of the floating microspheres and the mean diameter were remarkably affected by the polymer ratio. The increase of the ratio (decreasing the weight fraction of XG) led to a decreased percentage yield and a decrease in the mean diameter of the microspheres. This may have been due to the decrease in emulsifying ability with decreasing XG in the system; then, less air was entrapped into the microspheres, and subsequently, a more dense structure was formed. However, a high amount of XG increased the viscosity of the polymer solution, which led to the formation of large microspheres. The size of the microspheres also increased with decreasing stirring speed (data not shown). In addition to these factors, the size was affected by other factors, including the geometry of the apparatus, the volume ratio of the inner and outer phases, the viscosity of the dispersed phase, and the dispersion medium.[25] If the preparation parameters were optimized, it would be possible to obtain microspheres with expected sizes and size distributions.

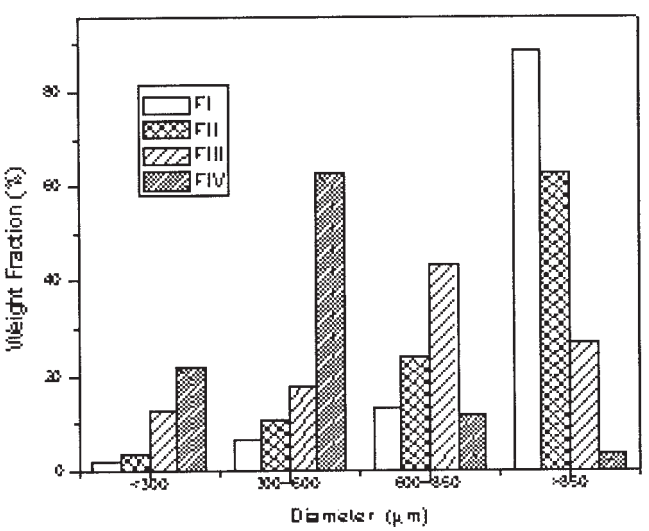

Figure 3 Size distribution of microspheres FI–FIV.

Floating ability

After centrifugation, as be mentioned previously, the top layer was collected for use as floating micro-

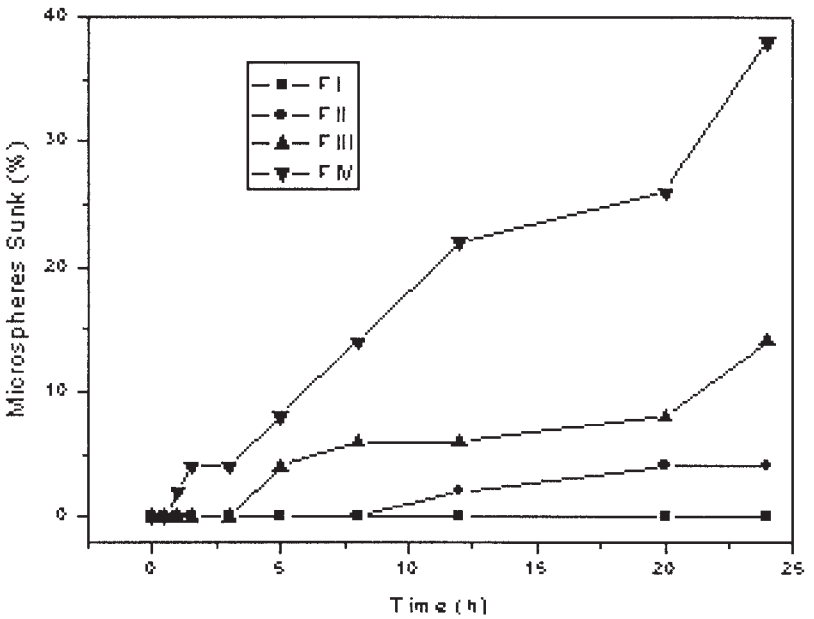

Figure 4 Floating behavior of microspheres FI–FIV.

spheres. As shown in Figure 4, all of the microspheres revealed good floating abilities. This was because of the low apparent density of the microspheres, which contained microballoons inside and formed porous structures. As time passed, water gradually penetrated into the microspheres and filled the microballoons and subsequently changed the densities, so some microspheres sunk into the bottom. As shown in Figure 2(c), the microballoons were arrayed one by one; thus, it would take a long time for water to permeate the multigrade membranes between microballoons and to fill most of the microballoons. The percentage of sunken microspheres also increased with decreasing XG content. This was probably because a larger relative surface area caused a faster water permeation rate per unit mass of the microspheres. However, a higher density and the presence of fewer microballoons inside also have influence on sinking.

Encapsulation efficiency

As shown in Table I, the encapsulation efficiency was high in all cases (56.2–84.5%), which probably resulted from the poor water solubility of the model drug in the external oil phase and water. However, with increasing polymer ratio, the encapsulation efficiency decreased. This might have been related to the size of the microspheres. The relative surface area increased with decreasing diameter of the microspheres. During the preparation process, some drug precipitated on the surface; when the system was cooled, this part of the drug was washed out in the following rinsing step. With a larger relative surface area, more drug precipitated on the surface, so the encapsulation efficiency varied with microsphere diameter; that is, it was probably affected by the drug remaining on the surface. After this part of drug was released, the residual drug within the microspheres was released more slowly, which may have been attributed to the low solubility of theophylline. In addition, in simulated gastric fluid (pH 1.2), XG and GA probably formed complexes because the —NH_2 groups of GA were protonated in acidic solution, and then, electrostatic attraction between the —NH_3^+ groups and carboxylic groups of the anionic polymer XG occurred. Thus, the diffusion of drug and water was hindered to some extent. In basic solution (pH 7.4), XG was dissolved and released from the microspheres (data not shown).

The values of n and k, obtained in each case from the slope and y intercept of a logarithmic plot of percentage of drug released versus time, are summarized in Table II. According to the model [eq. (2)], a geometry-dependent release exponent of 0.43 indicates release behavior governed solely by the diffusion of the drug through the sphere matrix. Conversely, a value of 1.0 indicates release behavior governed solely by dissolu-

TABLE I
Drug Encapsulation Efficiency of Microspheres FI–FIV

Formulation No.	Polymer ratio (GA:XG)	Drug encapsulation efficiency (%)
FI	1:1	84.5 (± 1.2)
FII	2:1	73.6 (± 0.9)
FIII	3:1	65.8 (± 1.5)
FIV	7.5:1	56.2 (± 1.1)

TABLE II
***k* and *n* Values Related to the Drug Released from Microspheres of Batches I–IV**

Batch No.	k (% h^{-n})	n	Regression coefficient (R)
FI	72.02	0.133	0.855
FII	63.18	0.176	0.892
FIII	59.44	0.195	0.929
FIV	44.04	0.298	0.962

tion kinetics. In the latter case, the drug may be released in pseudo-zero-order fashion, secondary to saturation of drug solubility within the pores of the matrix. Intermediate values of the release exponent (i.e., between 0.43 and 1.0) represent anomalous behavior characterized by a combination of diffusion and dissolution mechanisms. The values of n for FI–FIV were 0.133, 0.176, 0.195, and 0.298, respectively. Such values were consistent with a release mechanism governed by diffusion. The values of k were also large and relatively dependent on the ratio of the two polymers, which was probably caused by the different inner structures and crosslinking extents of the microspheres. Because of their complicated structures, a detailed interpretation of the drug-release mechanism requires further study.

CONCLUSIONS

A new type of multiple-unit, floating drug-delivery system based on microspheres with microballoons inside was developed. The effects of the ratio of the two polymers, GA and XG, on drug release, morphology, microsphere size, and other characteristics were studied. The system had good floating properties and high drug-encapsulation efficiency and sustained drug release over several hours after an initial burst. This system could be useful for the delivery of drugs with narrow absorption windows and/or for gastric-specific site delivery.

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