# Chitosan Microspheres: Modification of Polymeric Chem-Physical Properties of Spray-Dried Microspheres to Control the Release of Antibiotic Drug

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**ABSTRACT:** Antibiotic drug releasing from chitosan and acylchitosan microspheres was studied. The acylchitosan microspheres were prepared by modifying the microencapsulation process from spray-drying to spray in-liquid coagulating process for the improvement of chem-physical properties of polymer in controlling the release of antibiotic drug. A higher yield of microspheres was recovered by this improved process. Crystallinity, swelling ability, and the morphology of various microspheres were investigated by X-ray, water adsorption, and scanning electron microscopy studies. Results show that by modifying the microencapsulation process from spray-drying to spray in-liquid coagulating process, the chemical properties of the microsphere were varied from a hydrophilic chitosan microsphere to a hydrophobic acylchitosan microsphere, while the physical structure of the microsphere was varied from a porous chitosan microsphere to a dense acylchitosan microsphere. For the reasons, drug release rate of acylchitosan microspheres prepared by the novel spray microencapsulation method were apparently depressed, and the long-acting release of antibiotic drug was possible to be achieved.
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## INTRODUCTION

There has been considerable interest in recent years in developing controlled or sustained drug delivery systems by using biopolymers. Controlled-release drugs provide many advantages in comparison with conventional forms: reduced side-effects, drug concentration kept at affective levels in plasma, and improved utilization of drug and decrease the dosing times. Ideally, a delivery system might be developed to release a drug at precisely the rate it is required for different application. The drug release kinetics would be affected by coating materials, matrix density, and solubility of drugs, especially the encapsulating process. Oxytetracycline is a widely used antibiotic agent for treating many diseases induced by bacterial infection. Traditionally, they are administered in feeds, in drinking water, or by injection given several times a day. But, these modes of administration are not economic and sometimes induce of gastrointestinal side effects. It was recognized that, optimally, these drugs should be dosed once or twice a week, preferably as a long-acting injectable. For the reason, preparation of microspheres less than 50 $\mu$m by using biodegradable polymer for long-term release of the antibiotic drug should be investigated.

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Spray-drying has a wide range of application in the chemical industry, such as in food, ceramics, fertilizers, organic chemicals, polymeric resin, pharmaceuticals, and biological agents.[1] Recently, spray-drying has been developed to be used as a continuous process for producing microspheres, especially for the preparation of microspheres for pharmaceutical applications.[2] The feed, which consists of the coating polymer and pharmaceuticals, is fed to the atomizer, spray-dried, and collected. The advantage of spray-drying for application to microencapsulation is that it is reproducible, rapid, and easy to scale-up. Whereas, as an unfavorable factor, the spray-dried hydrophilic microspheres are usually porous and water-swellable, then lead to a quick releasing of encapsulated chemicals.[3] In the previous study, bioerodable hydrophobic polymer, such as polyanhydride or poly(L-lactic acid), has been employed as the coating materials to prepare spray-dried microspheres for the long-acting release of drugs.[4–7]

Chitosan [Poly(1,4)-$\beta$-D-glucopyranosamine], a polysaccharide produced from crab or shrimp shells, which is a copolymer combined of glucosamine and an *N*-acetyl glucosamine unit, is the second most plentiful natural biopolymers. Recently, chitosan has shown great potential in the development of inexpensive and versatile drug delivery systems due to its enzyme degradable ability and good biocompatibility.[8–10] Considering a continuous process for preparing chitosan microspheres, spray-drying would be a desirable method. However, in regard to the controlled release of drugs as a long-acting dosage, spray-dried chitosan microspheres seem not to be an adequate drug delivery system because of their quickly swelling ability. For the reason, the spray-drying technology has not yet been developed to prepare chitosan microspheres for long-term release of drugs.

The purpose of this study was to develop a novel spray technology by modifying the microencapsulation process from spray-drying to a spray in-liquid coagulating process, to transform the prepared hydrophilic chitosan microspheres to hydrophobic acylchitosan microspheres with depressed swelling ability in controlling the release of the oxytetracycline, a widely used antibiotic agent. An additional aim was to evaluate the effect of the preparation process on the release kinetics of various microspheres and on the polymer properties, such as crystallinity, morphology, and swelling ability of the microspheres.

## EXPERIMENT SECTION

### Materials

Chitosan, derived from crab shell, was purchased from Fluka. The molecular weights of the chitosan are $7 \times 10^4$, $7.5 \times 10^5$, $2 \times 10^6$, respectively. Acetic anhydride and methanol were purchased from Fisher. Oxytetracycline and oxytetracycline hydrochloride were obtained from Sigma.

### Preparation of Chitosan–Antibiotics Microspheres by the Spray-Drying Process

Chitosan was dissolved in 0.5% (w/v) acetic acid to prepare chitosan solution (0.1 to 2.0 w/v %). Oxytetracycline hydrochloride powder was dissolved in the polymeric solution to be sprayed. The spray-drying process encompasses the following 4 stages:

1. Atomization of the feed into a spray;
2. Spray-air contact;
3. Drying of the spray;
4. Separation of the dried microspheres from the drying gas.

The scheme of a two-fluid cocurrent spray dryer is shown in Figure 1(a). The fed polymer–drug fluid and atomizing were passed separately to the nozzle, where they mix, and the air caused the feed to break up into a spray, which was a microdroplet containing polymer and drugs. The spray and drying air passed through the dryer in the same direction, evaporating the solvent and forming the microspheres. The final step in the spray-drying process was accomplished by means of a cyclone separator through which the air and product passed after exiting the drying chamber. Several operating parameters that can affect the preparation and characteristics of the microspheres were investigated, such as inlet, outlet temperature, spray rate of feed, and air flow rate. The inlet temperatures were varied between 110 and 180°C, which are higher than the boiling point of the polymer solvent and outlet temperatures, depending on the value of inlet temperature chosen, which are automatically set by the apparatus. The spray rate of feed represents the

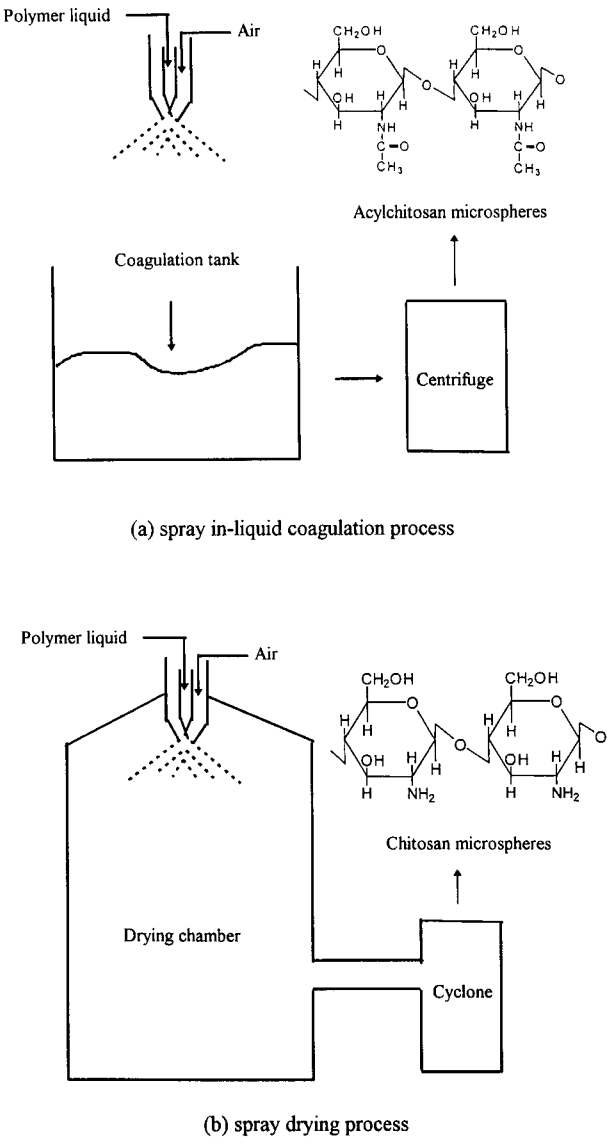



**Figure 1** Spray microencapsulating process: (a) scheme of a spray dryer process; (b) scheme of a spray in-liquid coagulation process.

rate of drug–polymer mixed solutions sprayed through the nozzle by a peristaltic pump, and the spray rate varied among 5–20 mL/min, which could insure the narrow dispersed size of the microspheres. Next, the molecular weight and concentration of polymer were considered as independent variables. The molecular weight and concentration of chitosan were varied from 70,000 to 2,000,000 $M_w$ and 0.1 to 2.5%, respectively. Microspheres collected from the spray dryer cyclone were used for physical properties' analysis.

## PREPARATION OF CHITOSAN–ANTIBIOTICS MICROSPHERES BY SPRAY IN-LIQUID COAGULATING PROCESS

Chitosan was dissolved in 0.5% (w/v) acetic acid to prepare chitosan solution (0.1 w/v % to 2.0 w/v %). Oxytetracycline hydrochloride or oxytetracycline powder was dissolved or suspended in the polymeric solution, respectively, to be sprayed. The spray in-liquid coagulating process was modified from the spray-drying process. The process encompasses the following stages:

1. Atomization of the feed into a spray;
2. Spray-coagulating agent contact;
3. Hardening of the sprayed droplets in coagulating agent;
4. Separation of the coagulated microspheres from the coagulating agent

The scheme of the spray in-liquid coagulating apparatus is shown in Figure 1(b). The feed polymer–drug fluid was sprayed into the coagulating liquid through the two-fluid nozzle and then coagulated in acetic anhydride by acylating chitosan droplets throughout. The finally formed product, the acylchitosan microspheres, were separated from acetic anhydride by centrifugation at 5000 rpm for 10 min using a high-speed centrifuge (Hermle, IK 365), washed with ethyl ether, and then dried in oven for 1 h. The operation parameters of this process were all kept the same with the process of spray-drying, except for removing the inlet and outlet temperature set.

### Physical Tests

#### *Particle Size Analysis*

The particle size of microspheres prepared by spray-drying and spray in-liquid coagulating methods were detected by a light scattering particle size analyzer (Galai, CIS-1).

#### *Morphology Study*

The spray-dried and spray in-liquid coagulated microspheres were gold-coated to about 500 $\times 10^{-8}$ cm thickness using a Hitachi coating unit IB-2 coater under a high vacuum, (0.1 Torr) and high voltage (1.2 kV and 50 mA). Coated samples were examined using Hitachi S-2300 electron scanning microscopy.

The cross section morphology of the microsphere prepared by spray-dried or spray in-liquid coagulated method is not easy to detect because the particle size of microspheres prepared by spray-drying or the spray in-liquid coagulating method is too small to be cut. In order to simulate the cross section structure of microspheres prepared by spray-drying and the spray in-liquid coagulating method, the polymer solution of chitosan was dispersed into the oil phase by stirring to form a water in oil (w/o) suspension. Then, the acetic anhydride was added into suspension gradually to prepared the acylchitosan microsphere, which could be employed as a simulated spray-dried microsphere for the cross section. Besides, the suspensions were instantly heated to 150°C to prepare the chitosan microsphere that could be employed as spray in-liquid coagulated microsphere. Thus, prepared microspheres with a larger particle size (200–500 $\mu$m) but an intraparticle structure similar to spray-dried or spray in-liquid coagulated microsphere were cut by a razor, and the morphologies of cross section were analyzed by scanning electron microscopy (SEM) study, as described previously.

### *Crystallinity Analysis*

The crystallinity forms of the original polymer, chitosan microsphere prepared by spray-drying, and acylchitosan microsphere, prepared by the spray in-liquid coagulation method, were all determined by an X-ray diffractometer (Simadzu, XD-5, Japan).

### *Swelling Ability*

The dynamic swelling properties of the chitosan microspheres were determined. Microspheres of a known weight (100 mg) without containing drug were placed in distilled water for a required period of time. The swollen microspheres were collected by a centrifuge, and the wet weight of the swollen microspheres was determined by first blotting the particles with filter paper to remove adsorbed water on surface and then weighing immediately on an electronic balance. The weight of the swollen microspheres was recorded at a predetermined time period. The percentage of swelling of microspheres in the media was then calculated from the formula,

$$E_{SW} = \left(\frac{W_t - W_o}{W_o}\right) \times 100$$

where $E_{SW}$ is the percentage of swelling of microspheres, $W_t$ denotes the weight of the microspheres at time $t$, and $W_o$ is the initial weight of the microspheres.

### *Yield of Microspheres*

The yields of preparation were determined by weighing the product of spray-dried microspheres or spray in-liquid coagulated microspheres with respect to the weight of the initial polymer and the drug used.

### *Drug Release Test*

Microspheres (50 mg) were suspended in 250 mL of PBS buffer. The drug containing microsphere suspensions were kept at 37°C in a glass bottle within a shaking water bath. At predetermined intervals, 1 mL of microsphere suspensions were collected at 5000 rpm by a centrifuge. Aliquots 0.5 mL of the supernatant were withdrawn, and the suspensions were replaced with fresh PBS. The amounts of oxytetracycline in the supernatant were analyzed spectrophotometrically at 354 nm.

## RESULTS AND DISCUSSION

### Particle Size Distribution

Particle size distributions of microsphere prepared by the spray-drying process or spray in-liquid coagulating are affected by process conditions, such as the mass ratio of air to polymer liquid, relative velocity of air to polymer liquid, and the viscosity of polymer liquid. The theoretical droplet size could be analyzed by the Kim—Marshall equation,[1] as follows:

$$D_{\text{mean}} = k_1\left[\frac{\eta_1^{0.32}\sigma^{0.4}}{(\rho_a V_{\text{rel}}^2)^{0.57} A_G^{0.36} \rho_1^{0.16}}\right] + \left[\left(\frac{\mu_1^2}{\rho_1\sigma}\right)^{0.17} \times \left(\frac{1}{V_{\text{rel}}^{0.54}}\right) \times \left(\frac{1}{M_R}\right)^m \times k_2\right]$$

where $M_R$ is the air-to-liquid mass flow rate, $M_{\text{air}}/M_{\text{liq}}$; $\sigma$ is the surface tension; $\mu_1$ is the liquid viscosity; $V_{\text{rel}}$ is the relative air liquid velocity at the nozzle; $\rho_a$ and $\rho_1$ are the air and liquid density respectively; and $A_G$ is the annular cross sectional area of air leaving nozzle.

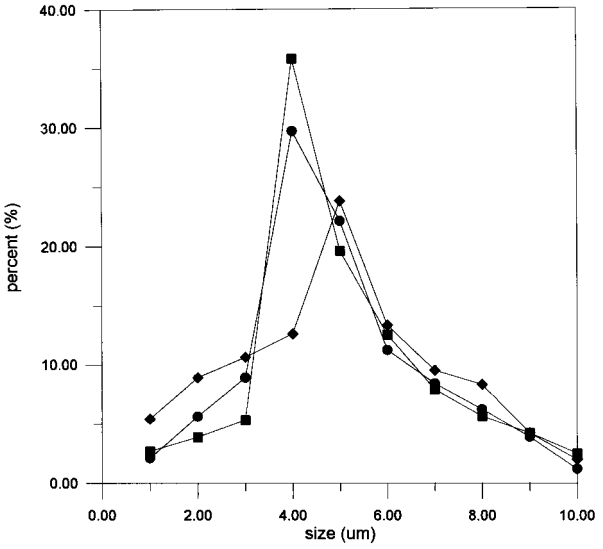



**Figure 2** Effect of the air-to-liquid ratio on the mean size of microspheres: (■) polymer solution without drug containing, (●) drug to polymer = 1 : 1, and (◆) drug to polymer = 2 : 1. Preparation conditions: air flow, 600 L/h; liquid flow, 10 mL/min; inlet temperature, 140°C; $M_w$, 70,000; 1.5 w/v %.

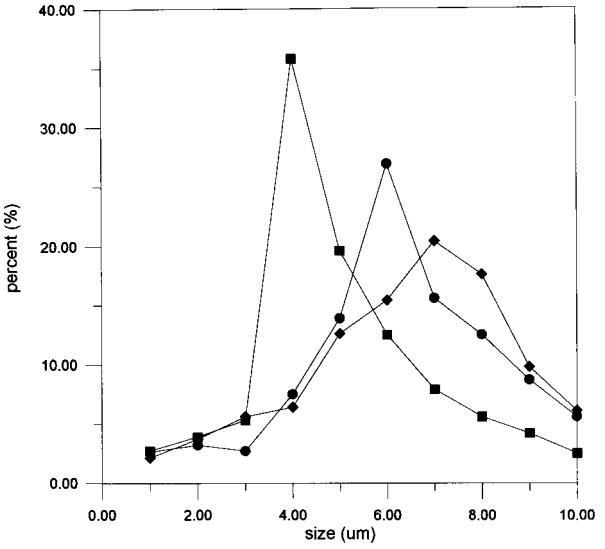



**Figure 3** Effect of the relative velocity on the mean size of microspheres. Air flow rate (■) 800, (●) 600, and (◆) 300 L/h. Preparation conditions: liquid flow, 10 mL/min; inlet temperature, 140°C; $M_w$, 70,000; 1.5 w/v %.

### *Effect of Air-to-Liquid Ratio*

As shown in Figure 2, keeping constant the air and liquid rate, the effect of the air-to-liquid mass ratio was examined by adding a drug into the polymer solution to vary the mass of liquid. The mass ratio is one of the most important variables to affect mean droplet size. The air-to-liquid ratio could be regulated by varying the feed and air flow rate. An increase in the mass ratio means that the polymer solution ejected out through inner tube could be more uniformly dispersed into the air ejected out through outer tube of the two-fluid nozzle. So, the size of the sprayed polymer droplet decreased with an increase in the air-to-liquid ratio.

### *Effect of Relative Velocity*

As shown in Figure 3, keeping the feed rate constant, the effects of relative velocity were examined by regulated the air flow rate from 200 to 800 L/h. Mean droplet size decreased with an increase in relative velocity. Increasing the relative velocity between air and liquid at the point of constant increases the air dynamic force, and more energy is available.

### *Effect of Viscosity*

An increase in viscosity increases the mean droplet size (Fig. 4). The viscosity of chitosan solution increases with increasing the molecular weight and concentration of polymer (Table I), so the mean particle size of spray-dried chitosan microsphere was apparently affected by the concentration and molecular weight of the polymer.

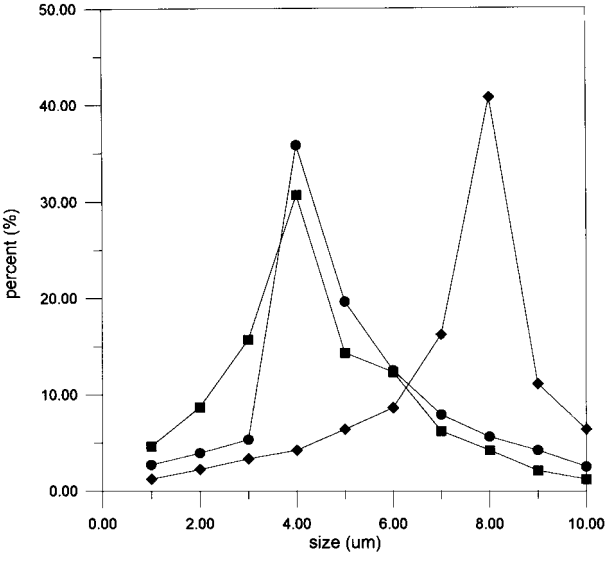



**Figure 4** Effect of viscosity on the mean size of microspheres: (■) 290, (●) 690, and (◆) 1250 cp. Preparation conditions: air flow, 600 L/h; liquid flow, 10 mL/min; inlet temperature, 140°C.

**Table I Viscosity of Chitosan Solutions**

| $M_w$ | Concentration (% w/v) | Viscosity ($c_p$) |
|---|---|---|
| 70,000 | 0.1 | 6 |
| 70,000 | 0.5 | 28 |
| 70,000 | 1.0 | 289 |
| 70,000 | 1.5 | 690 |
| 70,000 | 2.0 | 1250 |
| 70,000 | 2.5 | 1680 |
| 750,000 | 1.5 | 1360 |
| 2,000,000 | 1.5 | 2480 |

## Morphology Study

The microspheres prepared by the spray-drying process show mostly good sphericity, except for some shrinkage. The operation parameters of the spray microencapsulation process induced no remarkable change in the morphology of microspheres. The effect of the concentration of polymer solution to be sprayed in the study was that the concentrated solution generated well-formed spherical particles [Fig. 5(a) and (b)], whereas the diluted solution generated shrunk particles [Fig. 5(c)]. Microspheres prepared on the condition of a lower inlet temperature and air flow rate were easily aggregated [Fig. 5(d) and (e)] due to a slower solvent evaporating rate of the sprayed polymer droplet. The morphology of microspheres prepared by spray in-liquid coagulating process are different from those prepared by the spray-drying process (Fig. 6). Many pores formed on the surface of the microspheres, which might be caused by the residual acetic anhydride that was quickly diffusing out of the bead during drying in the oven. The microspheres prepared from low-molecular-weight polymer (70,000 $M_w$) tended to aggregate because of the slower coagulating rate of chitosan droplets during acylating in acetic anhydride, so the polymer droplets could not easily retain their original shape. The presence of oxytetracycline crystals on the surface of microspheres with high drug loading had the ability to prevent further sticking of the microspheres by forming a physical barrier to the adjacent microsphere, touching one another as they acylating through the matrix before final coagulation.

Considering the observation of inner structure of various microspheres prepared by the method of water in oil (w/o) suspension, which are simulated as spray-drying or the spray in-liquid coagulation method, the intraparticle structure of spray-dried or spray in-liquid coagulated microsphere could be inferred and depicted schematically in Figure 7. The spray-dried microsphere is a very denser outer layer supported by a porous inner structure [Fig. 5(f)]. As soon as the polymer droplets were sprayed out from the nozzle into a heat chamber, the dense phase-inversion skin was formed on the surface of the droplets because of the quick evaporation of the unprotected solvent outer layer. An inner porous matrix was formed after a delayed time by evaporation of the inside solvent out through the initially formed rigid skin of microsphere. Whereas, the microspheres prepared by the in-liquid coagulation method were acylated homogeneously throughout the polymer droplets, and more dense matrices of microspheres were formed [Fig. 6(f)].

## Crystallinity Analysis

X-ray analyses of the spray-dried or spray in-liquid coagulated microspheres were performed in order to characterize the physical state of the polymers. The crystallinity of the chitosan microsphere or acylchitosan microsphere was lower than the crystallinity of the original polymer (Fig. 8). The crystallinity of the chitosan unit was almost destroyed, and the typical diffraction of the spray-dried chitosan microspheres disappeared; but the crystallinity of acylchitosan unit prepared by in-liquid coagulation was not destroyed, and the typical diffraction of the acylchitosan microsphere was still retained. The result indicated that spray-drying may be too fast a phase inversion process for the polymer to allow crystallization. So, an amorphous loose-structure microspheres was prepared by using the spray-drying method.

## Swelling Ability

The swelling experiments were conducted at distilled water. The results plotted as the percentage of swelling versus time are given in Figure 9. The microspheres prepared by the spray-drying process had a higher equilibrium percentage swelling value as compared to the original polymer. The result indicated that the increasing porosity and decreasing crystallinity of the spray-dried chitosan microspheres en-

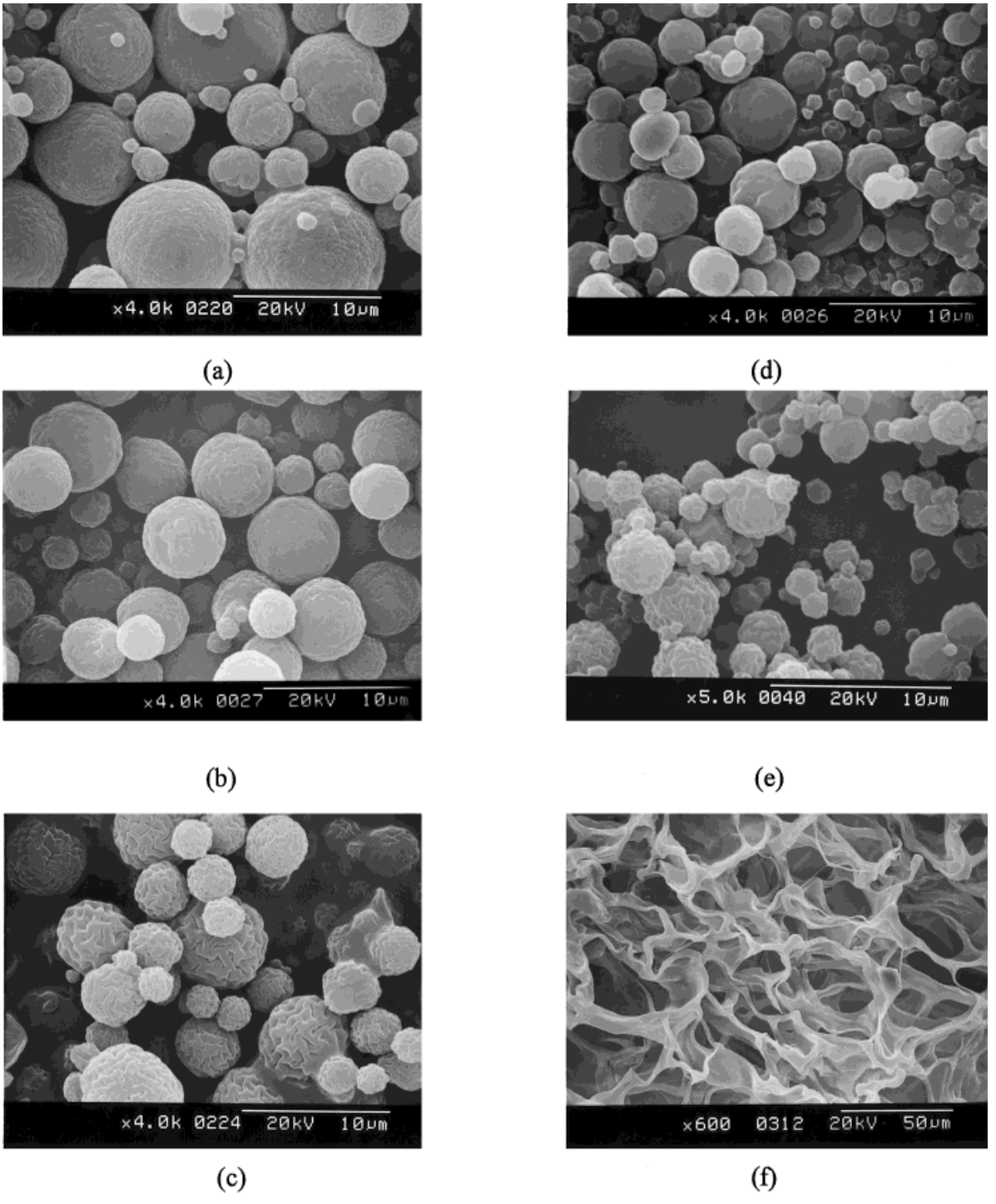



**Figure 5** Scanning electron micrography morphology of chitosan microspheres prepared by spray drying: (a) 2,000,000 $M_w$, 1.5% w/v; (b) 70,000 $M_w$, 1.5 % w/v; (c) 70,000 $M_w$, 1.0% w/v, prepared on the condition of an inlet temperature of 140°C and an air flow rate of 600 L/h; (d) 70,000 $M_w$, 1.5% w/v, prepared on the condition of an inlet temperature of 110°C and an air flow rate of 600 L/h; (e) 70,000 $M_w$, 1.5% w/v, prepared on the condition of an inlet temperature of 140°C and an air flow rate of 200 L/h; (f) cross section of the microsphere.

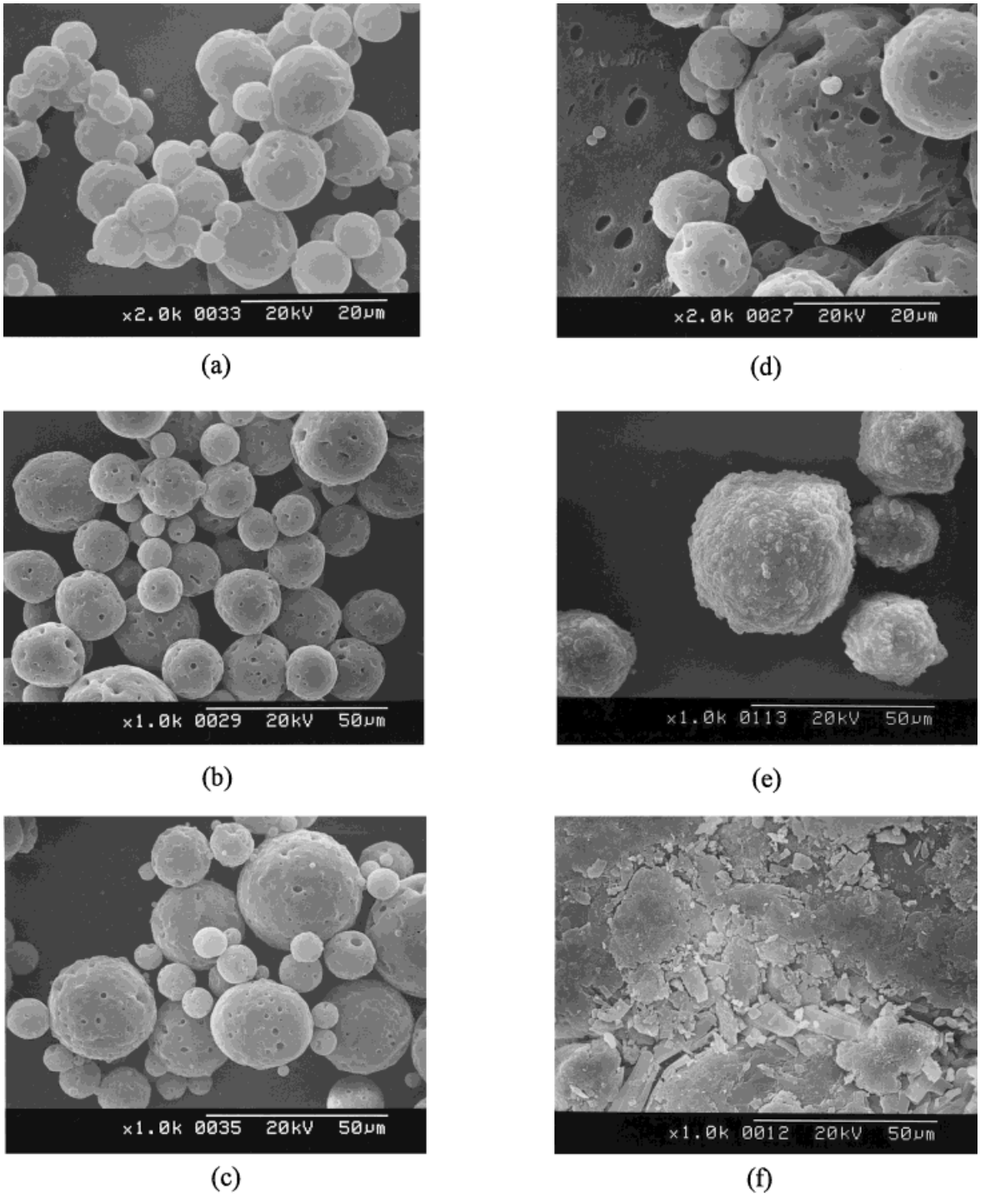
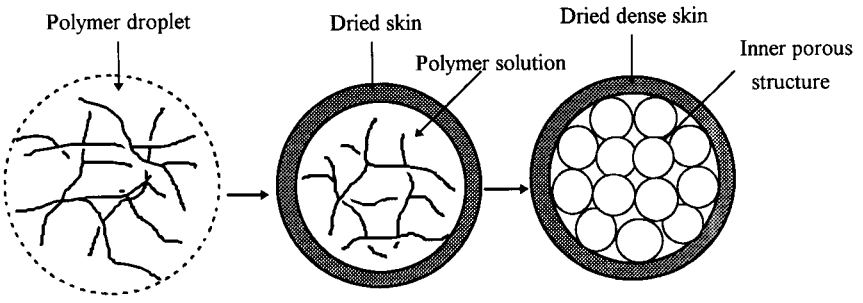
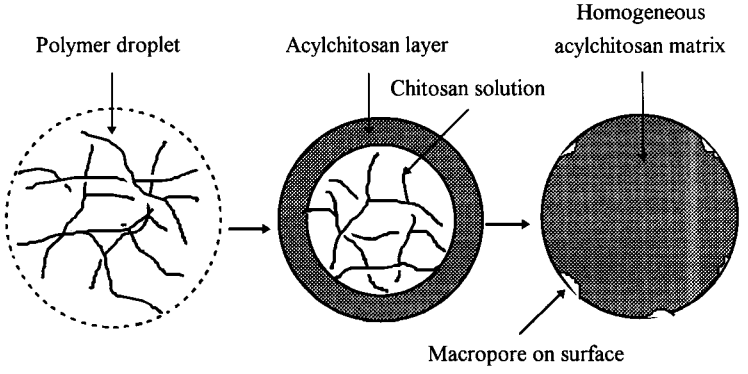



**Figure 6** Scanning electron micrography morphology of acylchitosan microspheres prepared by spray in-liquid coagulation: (a) 70,000, (b) 750,000, (c) 2,000,000 (×1000), (d) 2,000,000 (×2000), and (e) 70,000 $M_w$, with drug loading; (f) cross section of microsphere.

hances the swelling ability of the polymer. The swelling ability of the spray-dried microspheres increased with an increase in the molecular weight of chitosan. This is apparently due to the higher chain-relaxation ability in high-molecular-weight chitosan as a result of increasing the




(a) Process for the formation of porous spray dried microsphere




(b) Process for the formation of dense spray in-liquid coagulated microsphere

**Figure 7** Schematic description of preparing porous chitosan microsphere and dense acylchitosan microsphere: (a) formation of porous spray-dried chitosan microspheres; (b) formation of dense spray in-liquid coagulated acylchitosan microspheres.

entanglement of the polymeric chain. The modified acylchitosan microspheres show only slightly swelling because the transformation of hydrophilic amine to hydrophobic amide groups on the polymer side-chain of chitosan reduces the water uptake to the polymer.

### Yield of Microsphere

As shown in Table II, there are remarkable differences in yield between products prepared by spray-drying and the spray in-liquid coagulation method. The lower yield of microspheres prepared by the spray-drying process is due to the residence of microspheres in the spray chamber or to loss of the microspheres to the surroundings during collection from cyclone. Increasing the concentration of polymer solution increases the yield of product because the more dense a structure of microsphere could be prepared to decrease the loss of the microsphere during collection from the cyclone.

## DRUG RELEASE

### Drug Release from Microspheres Prepared by Spray-Drying Process

The releasing behavior of oxytetracycline hydrochloride from chitosan microspheres could be de-

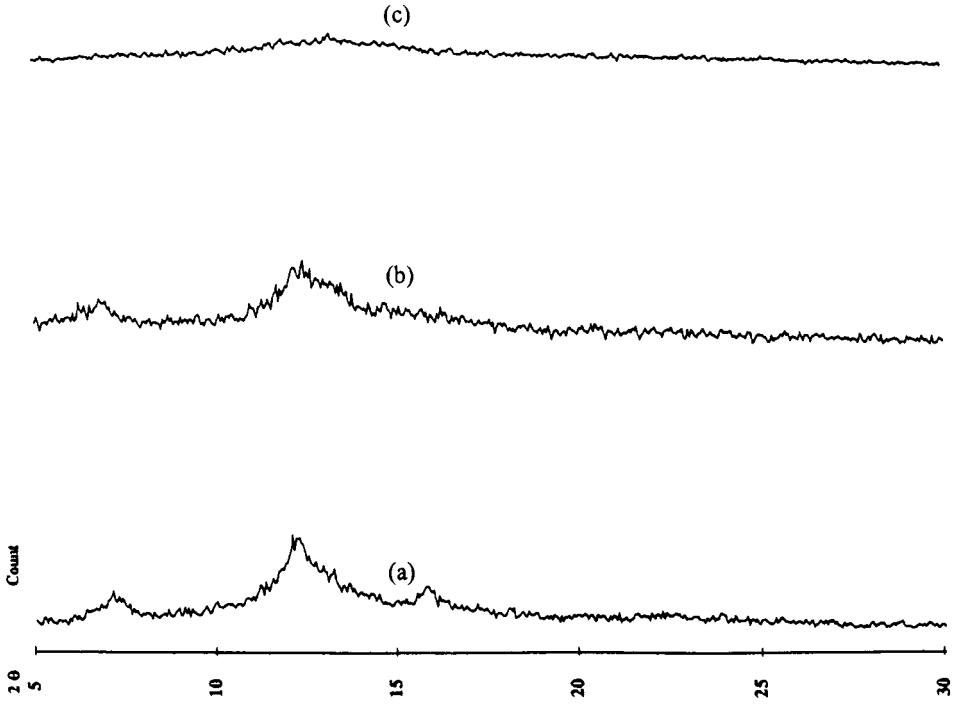



**Figure 8** Crystallinity analysis of chitosan and acylchitosan microspheres: (a) original chitosan powder; (b) spray in-liquid coagulated acylchitosan microspheres; (c) spray-dried chitosan microspheres.

scribed by the swelling-controlled release model derived by Peppas.[11–13] Chitosan is a hydrophilic polymer that could swell by absorbing large quantities of water. The volume phase transition in gels occurs because of the penetrant diffusing into the glassy region and forming a swollen gel phase in the wetted region.[14–16] The transition from the glassy to the rubbery state increases the permeability of the polymer to the drug, permitting the latter to diffuse outward. The fast release of drug is due to the easy penetration of water into porous chitosan microspheres, quickly inducing the swelling behavior of the polymer. About 90% of the oxytetracycline hydrochloride released from the spray-dried chitosan microsphere in 30 min. Slightly lower release rates could be observed from microspheres prepared by higher-molecular-weight chitosan due to a slower chain-relaxation rate of polymer.

### Drug Release from Microspheres Prepared by the Spray In-Liquid Coagulating Process

Compared to spray-dried chitosan microspheres, the acylchitosan microspheres gave significantly lower drug release rates (Fig. 10). Increasing the density of the polymer matrix and transformation of the hydrophilic amine to hydrophobic amide groups on the polymeric side chain of chitosan significantly reduced the swelling ability of acylchitosan microspheres, finally decreasing the drug release rate. This relationship suggested that the main mechanism of oxytetracycline diffusion through the polymeric matrix was that of diffusion through the water-filled pores. The drug concentration in the matrix is a decisive parameter influencing the rate of drug releasing from microspheres. The porosity and the tortuosity are directly related to the concentration of the drug in the microspheres. A higher drug concentration in the initial polymer solution increased the porosity of microspheres due to an increase in the crevice between the drug crystal and the polymer interface. It is obvious that when the concentration of drug in matrix increased, the release rate increases markedly in comparison to microspheres with a low drug concentration. It could be demonstrated by the Higuchi model, described by the following relationship:[17]

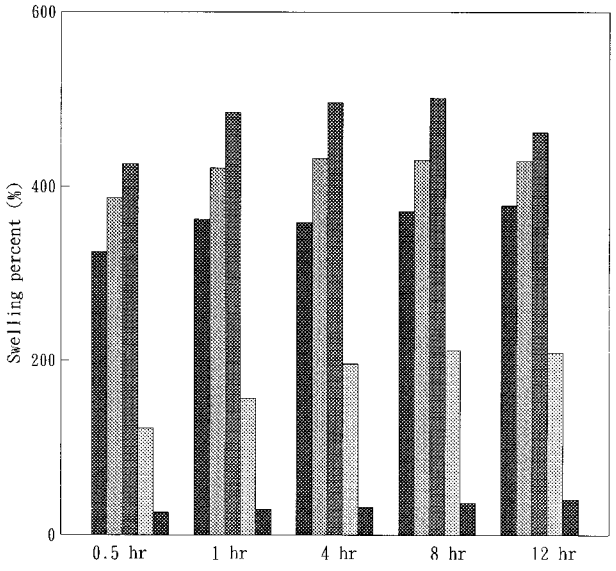



**Figure 9** Swelling ability of chitosan and acylchitosan microspheres: (▩) chitosan microsphere (70,000 $M_w$), (▤) chitosan microsphere (750,000 $M_w$), (▨) chitosan microsphere (750,000 $M_w$), (▣) original chitosan powder (70,000 $M_w$), (▦) acyl-chitosan microspheres (70,000 $M_w$).

$$Q = S \bullet [D_S \bullet \varepsilon (2A - \varepsilon C_S) C_S \bullet t/\tau]^{1/2}$$

where $D_S$ is the diffusion coefficient of the drug, $\varepsilon$ and $\tau$ are the porosity and tortuosity of the matrix, and $Q$ is the amount of drug release from insoluble porous matrix and depends on terms $\varepsilon$ and $\tau$. The increase of drug content in microsphere led to a decrease of $\tau$ and an increase of $\varepsilon$, then increased the release rate of the drug (Fig. 11).

Apparently, different release rates were observed between spray in-liquid coagulated acylchitosan microspheres containing hydrophobic oxytetracycline and hydrophilic oxytetracycline hydrochloride. The poor wetting ability of hydrophobic oxytetracycline in microspheres was difficult to dissolve by the external fluid penetrating into the polymer matrix, and the rate of subsequent diffusion of oxytetracycline through the chitosan matrix was reduced (Fig. 12).

## CONCLUSION

In this study, a sustained release of antibiotic drug from acylchitosan microspheres was successfully prepared by modifying the spray microencapsulating process from spray-drying to the spray in-liquid coagulating process. Different release patterns were observed from the chitosan microspheres prepared by spray-drying and acylchitosan microspheres prepared by the spray in-liquid coagulating method. For chitosan microspheres having good swelling ability, immediate and relatively rapid release of antibiotic drug through the swollen region occurs,

**Table II Yield and Drug Content of Chitosan or Acylchitosan Microspheres**

| Type | $M_w$ | Concentration | Inlet Temperature | Air Flow | Yield (%) |
|---|---|---|---|---|---|
| Chitosan | 70,000 | 0.5 | 140 | 600 | 24.3 |
| Chitosan | 70,000 | 1.0 | 140 | 600 | 32.7 |
| Chitosan | 70,000 | 1.5 | 140 | 600 | 41.8 |
| Chitosan | 70,000 | 1.5 | 120 | 600 | 40.4 |
| Chitosan | 70,000 | 1.5 | 160 | 600 | 49.6 |
| Chitosan | 70,000 | 1.5 | 180 | 600 | 52.2 |
| Chitosan | 70,000 | 1.5 | 140 | 400 | 39.5 |
| Chitosan | 70,000 | 1.5 | 140 | 800 | 44.6 |
| Chitosan | 2,000,000 | 1.5 | 140 | 800 | 46.9 |
| Acylchitosan | 70,000 | 0.5 | — | 600 | 89.4 |
| Acylchitosan | 70,000 | 1.0 | — | 600 | 92.3 |
| Acylchitosan | 70,000 | 1.5 | — | 600 | 94.0 |
| Acylchitosan | 70,000 | 1.5 | — | 400 | 93.1 |
| Acylchitosan | 70,000 | 1.5 | — | 800 | 92.9 |
| Acylchitosan | 2,000,000 | 0.5 | — | 600 | 89.9 |
| Acylchitosan | 2,000,000 | 1.0 | — | 600 | 90.4 |
| Acylchitosan | 2,000,000 | 1.5 | — | 600 | 93.2 |
| Acylchitosan | 2,000,000 | 1.5 | — | 800 | 93.8 |

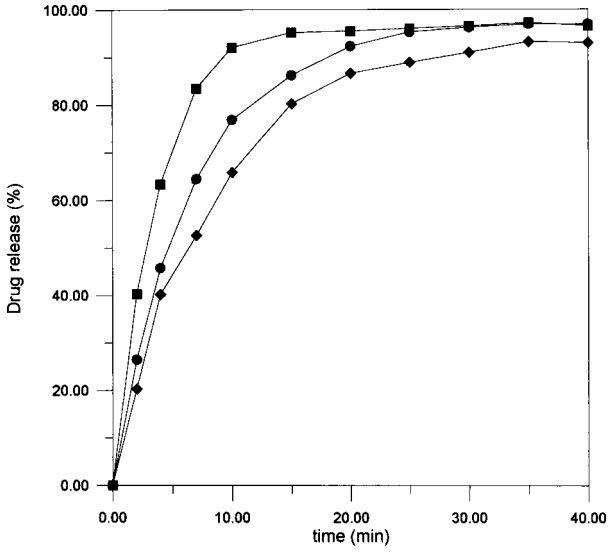



**Figure 10** Oxytetracycline hydrocholoride releasing from spray-dried chitosan microspheres: (■) 70,000, (●) 750,000 and (◆) 2,000,000 $M_w$. Preparation condition: drug to polymer = 1 : 1.

while for acylchitosan microspheres prepared by the modified spray microencapsulation process having a depressed swelling ability could achieve the goal for the long-acting release of antibiotic drug.

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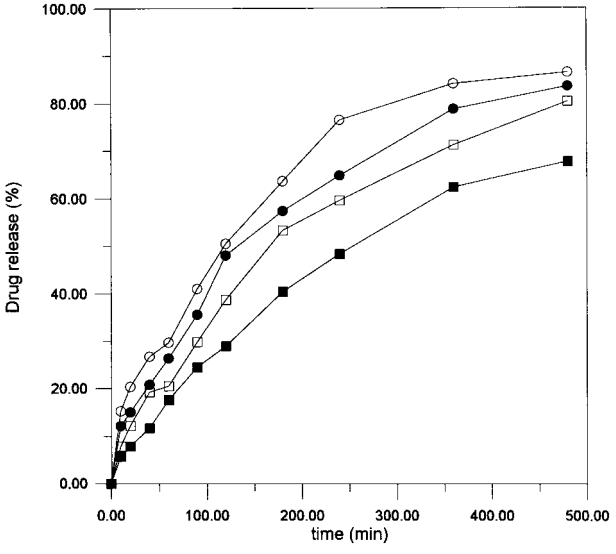


**Figure 11** Oxytetracycline hydrocholoride releasing from spray in-liquid coagulated acylchitosan microspheres: (■) drug to polymer = 1 : 1, (□) 2 : 1, (●) 3 : 1, and (○) 4 : 1. Preparation condition: 70,000 $M_w$.

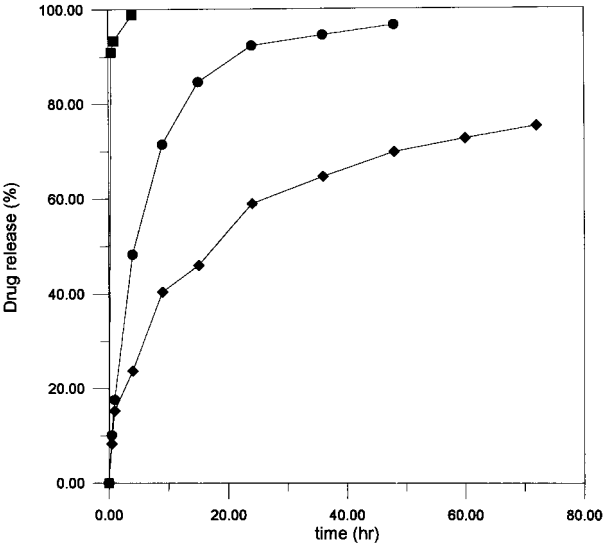


**Figure 12** Oxytetracycline hydrocholoride or oxytetracycline releasing from spray in-liquid coagulated acylchitosan microspheres: (■) oxytetracycline hydrocholoride releasing from spray-dried chitosan microspheres; (●) oxytetracycline hydrocholoride releasing from spray in-liquid coagulated acylchitosan microspheres; (◆) oxytetracycline releasing from spray in-liquid coagulated acylchitosan microspheres. Preparation condition: 70,000 $M_w$ drug to polymer = 1 : 1.

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