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DRUG RELEASE PROPERTIES OF THE MICROCAPSULES OF ADRIAMYCIN HYDROCHLORIDE WITH ETHYLCELLULOSE PREPARED BY A PHASE SEPARATION TECHNIQUE

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ABSTRACT

Adriamycin hydrochloride was microencapsulated with ethylcellulose by a phase separation method to develop a prolonged release dosage form. Polyisobutylene (PIB) was used as a coacervation-inducing agent to control the particle size and drug release rate of the resultant microcapsules. With increasing the concentration of PIB (1 to 3 %) the average diameter of the microcapsules

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decreased, due to the fact that the microcapsules were discreted to a single microcapsule. At low concentration of PIB, the resultant microcapsules were agglomerated, which resulted in increasing the size. The microcapsules prepared with PIB 2 % prolonged desirably the drug release from the microcapsules. A little size effects of the microcapsules on the drug release rate was found for the microcapsules with PIB 2 % and 3 %.

INTRODUCTION

Many microencapsulation techniques have been developed in a various field including chemical, food, cosmetic, pharmaceutical industry and etc.[1] In the pharmaceutical field, this technique is accepted as a useful method for developing a new dosage form to improve the bioavailability, to reduce the adverse action, to prolong the action of the drug and etc.[2] One of the most attractive applications of the microcapsules is the use as a new drug delivery system for an anticancer agent. Kato et al [3-5] prepared the microcapsule of mitomycin C with ethylcellulose to apply for intra-arterial infusion chemotherapy.

In the present study, adriamycin hydrochloride was microencapsulated with ethylcellulose by a phase separation method for developing a controlled release dosage form. The aim of the study was to investigate the drug

release behavior in vitro of the resultant microcapsules. The elucidation of the effect of polyisobutylene (PIB) used as a coacervation-inducing agent on the micromeritic and the drug release properties of the microcapsules was a second objective.

EXPERIMENTAL

Preparation of the microcapsule ——The microcapsules were prepared by the phase separation method described by Koida et al [6] and Donbrow [7]. Three to nine grams of PIB (Vistanex MML-100, Esso Chemicals) divided into fine pieces was dissolved in 300 ml of cyclohexane with heating up to 70 ℃ and stirring at 250 rpm. After cooling the solution to 40 ℃, 1 g of ethylcellulose (100 cps, Nakarai Chemicals) was dissolved, thereafter 200 mg of adriamycin hydrochloride supplied from Kyowa Hakko Co. was dispersed in the solution. Adriamycin hydrochloride was comminuted and sieved with a 150 mesh (105 μm) screen prior to using. The system was gradually heated to 78 ℃ and held for 10 minutes at this temperature. Then the system was slowly cooled to room temperature, followed by cooling to 10 ℃ in a water bath in two hours. During cooling process, a phase separation occurred. A microscopic photograph of the resultant coacervates enclosing adriamycin hydrochloride particles is shown in Fig. 1. The supernatant of the system with the dispersed microcapsules was decantated. The microcapsules

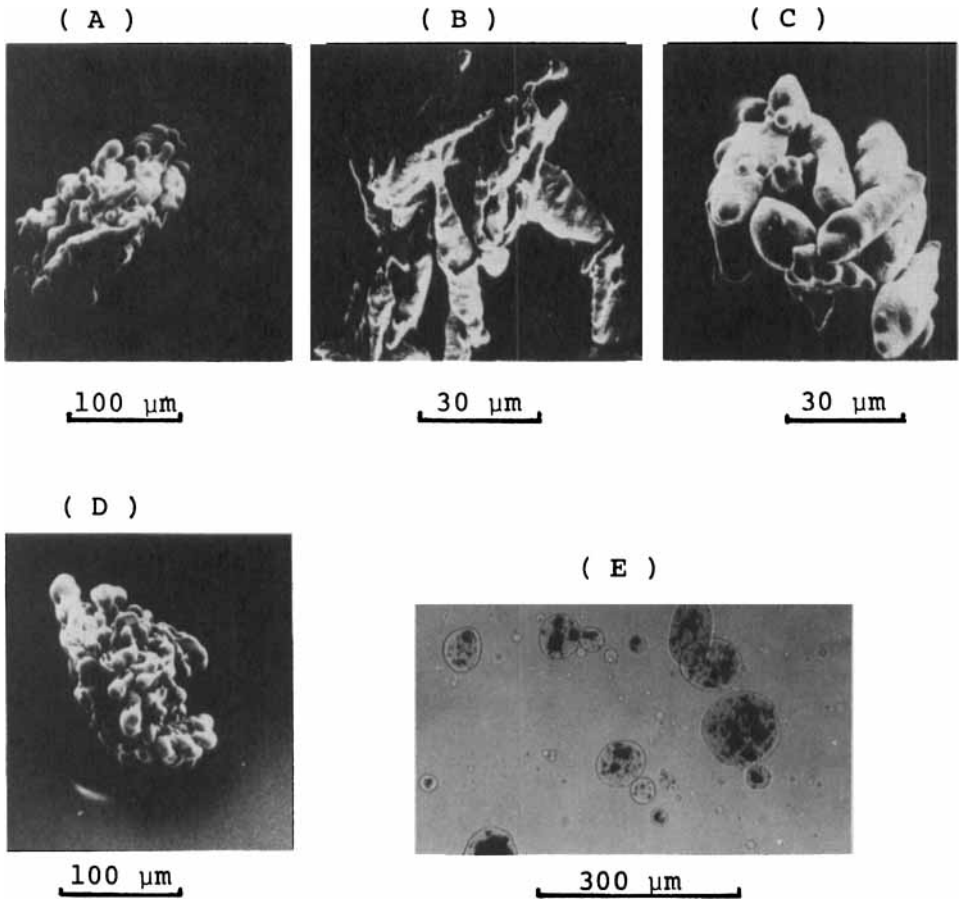

FIGURE 1

Scanning Electron Microphotographs of Adriamycin Hydrochloride Microcapsules prepared with Various Polyisobutylene Concentrations and Photomicrograph of Adriamycin Hydrochloride Coacervates

Key: (A), PIB 1%
(B), PIB 2%
(C), PIB 3%
(D), Polyethylene 1%
(E), Coacervates in cyclohexane

were washed with fresh cyclohexane and rinsed with the saturated one with hydrogenated castor oil (HCO-60, Nikkol Chemicals) alternatively in the vessel. The microcapsules were separated from the washing solvent and dried at 40 °C in vacuum for 24 hours.

Measurement of the micromeritic property of the microcapsules ——The surface topography of the microcapsule coated with gold was investigated by a scanning electron microscope (JMS-S1, Nihon Denshi). The particle size of the microcapsule was measured by a photographic counting method using a particle size analyzer (TGZ-3, Carl Zeiss).

Drug release test of the microcapsules ——The drug release test of the microcapsules was undertaken using the rotating basket specified in JP (X) attached with a propeller. Nine hundred milliliters of 0.9 % aqueous solution of sodium chloride thermally controlled at 37 °C was used as the dissolution medium. One hundred milligrams of the microcapsules was placed in the basket rotated at 100 rpm. Five milliliters of aliquot was sampled from the system and 5 ml of the fresh dissolution medium was added simultaneously to the system to keep the dissolution medium constant. Adriamycin hydrochloride in the sample was assayed spectrophotometrically with 233 nm.

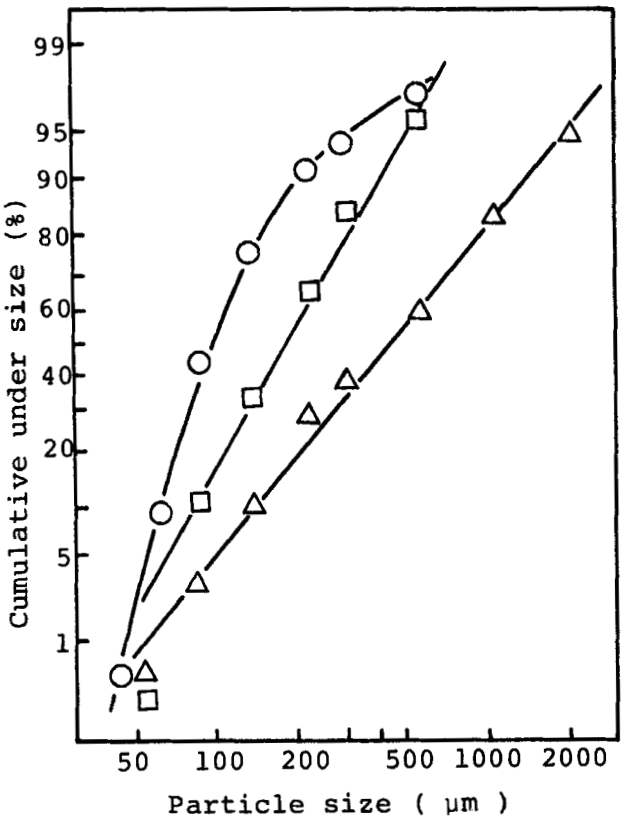

FIGURE 2

Particle Size Distribution of Microencapsulated Adriamycin Hydrochloride prepared with Various Polyisobutylene Concentrations

Key: △, PIB 1%
□, PIB 2%
○, PIB 3%

RESULTS AND DISCUSSION

Micromeritic properties of the microcapsules

The size distributions of the microcapsules of adriamycin hydrochloride prepared with various PIB concentrations are exhibited on a log-normal probability

graph as shown in Fig. 2. At lower concentration of PIB than 2 %, the size distribution was followed to a log-normal form. Whereas at 3 %, the size distribution deviated from a log-normal form. The geometric mean diameter of the microcapsules increased with decreasing the PIB concentration. At high PIB concentration, the dispersing medium became viscous, in which the movement of the coacervates was restricted resulting in less agglomeration of the coacervates.

In Fig. 1, the scanning electron microscopic photographs of the microcapsules prepared at various PIB concentration are displayed. At low concentration of PIB, e.g. 1 %, the microcapsule was an agglomerated form. The microcapsules prepared with PIB concentration 3 % were clearly discreted to a single microcapsule as exhibited in Fig. 1. As a reference, polyethylene was used as a coacervation-inducing agent at 1 %. The resultant microcapsule was agglomerated like the microcapsule prepared at PIB 1 % as shown in Fig. 1. The coacervation-inducing action of PIB was superior to that of polyethylene. Furthermore, it was found that PIB acted more effectively to induce the coacervation at the higher concentration.

The improved coacervation-inducing action of PIB with high concentration, e.g. 3 %, also might cause to decreasing the size of the resultant microcapsules as found in Fig. 2.

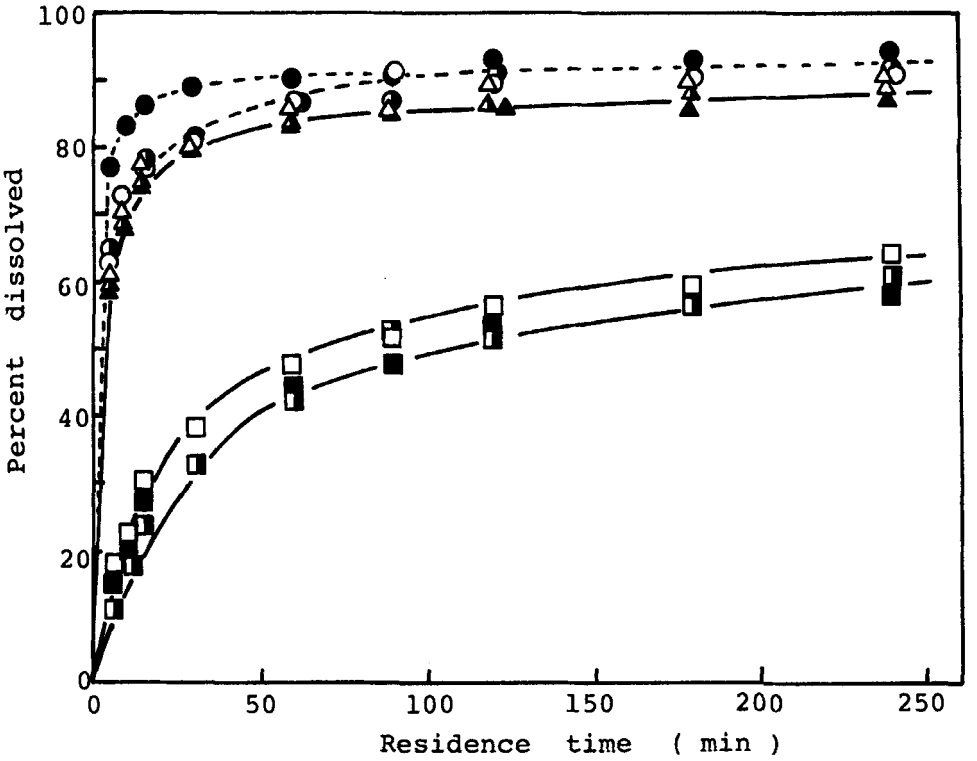

FIGURE 3

Dissolution Profile of Adriamycin Hydrochloride from Ethylcellulose Microcapsules prepared with Various Polyisobutylene Concentrations in 0.9% Sodium Chloride Aqueous Solution at 37°C

Key:
74- 105 μm: △, PIB 1%; □, PIB 2%; ○, PIB 3%
105- 177 μm: ▲, PIB 1%; ◨, PIB 2%; ◑, PIB 3%
177- 250 μm: ▲, PIB 1%; ■, PIB 2%; ●, PIB 3%

Drug release behavior of the resultant microcapsule

Drug release behaviors of the microcapsules fractionated to three size ranges in 0.9 % aqueous sodium chloride solution at 37°C are shown in Fig. 3. It was found that the microcapsules prepared with PIB 2 % effectively

prolonged the drug release rate compared with the microcapsules prepared with PIB 1 % and 3 %. The size effect of the microcapsule on the drug release rate appeared for the microcapsule with PIB 2 %. The smaller microcapsule released the drug more rapidly. For the microcapsules with PIB 1 %, the drug release rate was independent of the microcapsule size. The larger microcapsule with PIB 3 % released the drug rapidly compared with the smaller microcapsules. This reversed effect might be interpreted in terms of the wall thickness of the large microcapsule prepared with PIB 3 %. Donbrow [8] reported that the empty microsphere without the drug increased in number with increasing the amount of PIB exerted as a protected colloid. This phenomenon suggested a decrease in the wall thickness of the large microcapsules with the drug. Therefore the faster release of the drug from the microcapsules might result. At the later stage of the dissolution, the drug release rate was extraordinarily delayed.

The drug released percents are plotted against a square root of residence time to test the adaptability of the release data to Higuchi model [9] in Fig. 4. It was found that the drug release process for the microcapsules with PIB 2 % obeyed the Higuchi model up to reaching to 50 % of the drug released. For the small microcapsules, a burst effect was found as shown in Fig. 4. The microcapsules with PIB 1 % and 3 % did not obey the

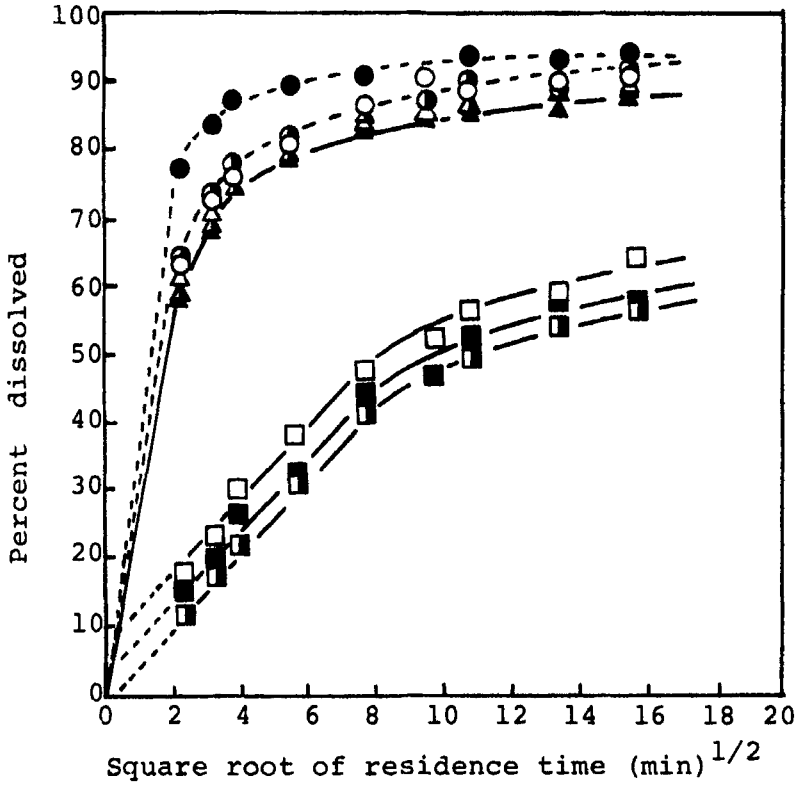

FIGURE 4

Drug Release Percent as a Function of Square Root of Residence Time

Key: see Figure 3

Higuchi model as shown in Fig. 4. The above findings indicated that the drug was reasonably encapsulated with PIB 2 % to exhibit a matrix type drug release.

The time required for 50 % of drug released from the microcapsules (T_{50}) is plotted as a function of the average diameter of the microcapsules fractionated in Fig. 5. Wagner[10] reported that T_{50} was the most reasonable parameter to explain the coating effect on the dis-

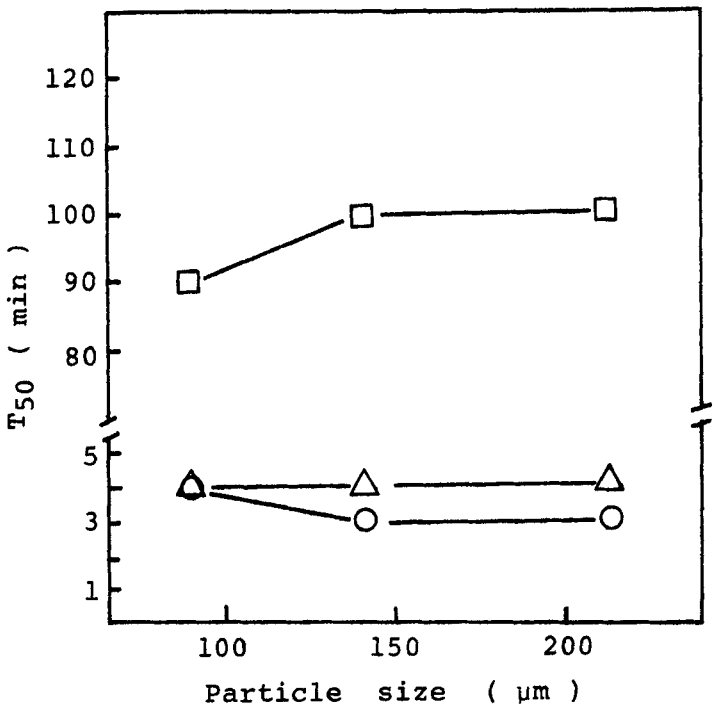

FIGURE 5

50% Dissolution Time (T_{50}) as a Function of Particle Size of Microcapsule

Key: see Figure 2

solution behavior of the coated solid dosage form. As indicated in Fig. 3 and 4, T_{50} of the microcapsules with PIB 2 % was longer than the other microcapsules. A little size effects of the microcapsules with PIB 2 % and 3 % on T_{50} were found. The microcapsules with PIB 2 % fractionated to 74 μm-105 μm reduced T_{50}, whereas T_{50} of the microcapsules with PIB 3 % fractionated to the same size range was prolonged a little.

In conclusion, it was found that the particle size and the drug release rate of the microcapsules were easily controlled by selecting a suitable concentration of PIB. In this study, it was desirable to use PIB 2 % for obtaining a fairly prolonged release of the drug.

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