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RESEARCH PAPER

# Release Profiles of Theophylline from Microspheres Consisting of Dextran Derivatives and Cellulose Acetate Butyrate: Effect of Polyion Complex Formation

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## ABSTRACT

The objective of this study was to evaluate the utility of mixtures among oppositely charged dextran derivatives as constituents of a controlled release microsphere. Carboxymethyldextran (CMD) and dextran sulfate (DS) were used as polyanions, and [2-(diethylamino) ethyl] dextran (EA) and [2-hydroxypropyltrimethylammonium] dextran (CDC) as polycations. The microspheres consisting of hydrophilic and hydrophobic polymers were prepared by emulsion-solvent evaporation method. The mixtures, CMD/EA, CMD/CDC, DS/EA, and DS/CDC, were used as hydrophilic polymers, because they can interact with each other to form polyion complexes for the improvement of sustained-release performances. Cellulose acetate butyrate and theophylline were used as a model hydrophobic polymer and a model drug, respectively. The yield of microspheres was excellent (more than 95%). According to observation, by scanning election microscopy (SEM) microspheres were spherical with a rough surface. The in vitro drug release from microspheres was examined in the JP XIV first fluid, pH 1.2, and second fluid, pH 6.8, at 37°C, and 100 rpm. In the DS/CDC system, drug release was depressed by formation of a polyion complex and not affected by pH of dissolution medium. The release rate was modulated by the ratio of hydrophilic and hydrophobic matrix. This particulate system, in which the polyion complex matrix is strengthened by a hydrophobic polymer, is a promising formulation for drug delivery.

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*Key Words:* Dextran derivatives; Microspheres; Controlled release; Polyion complex; Theophylline; Cellulose acetate butyrate.

## INTRODUCTION

The use of natural polymers in formulation design of dosage forms has received considerable attention, especially from the viewpoint of safety. Among these polymers, dextran has been used clinically for more than 50 years as a plasma volume expander. Hydrophilic dextran derivatives are also used clinically. For instance, [2-(diethylamino) ethyl] dextran is an anion-exchange resin that is used as a hypolipidaemic agent, and dextran sulfate is used as an anticoagulant and as a hypolipidaemic agent.[1]

Recently, dextrans have been investigated as macromolecular carriers for delivery of drugs, proteins, and imaging agents. Another application of dextrans as drug carriers has been for targeting drugs to specific sites of action via passive or active targeting.[2] However, few studies have reported the potential of dextrans for delivery of drugs via the oral route. The main limitation of dextrans for the preparation of oral sustained release systems arises from its rapid dissolution in aqueous environments, leading to fast drug release at body temperature. In order to overcome this problem, chemical cross-linking procedures (e.g., epichlorohydrin, glutaraldehyde) giving rise to the formation of nonsoluble networks, have been considered.[3] However, the use of cross-linkers can lead to toxic side effects, due to the presence of a residual cross-linking agent or to an unwanted reaction between drug and cross-linker. Thus, an appropriate alternative method to obtain insoluble or partially soluble devices would be preferable. For instance, the use of hydrophobic dextran derivatives or physical cross-linking of hydrophilic polymers could be used for long-term drug release.

On the other hand, hydrophilic dextran derivatives have been proposed as useful excipients for a sustained-release matrix tablet.[4] The mixtures of oppositely charged dextran derivatives react with each other to form polyion complexes when swollen. The formation of the complex reduced the drug-release rate from hydrophilic matrix tablets. From a clinical viewpoint, particulate systems are considered useful because they have less variation in gastrointestinal transit times of preparation and bioavailability of the drug than single-unit dosage forms. In the case of microparticles prepared from mixtures of oppositely charged dextran derivatives, however, the higher surface area should lead to a more rapid release of drug due to its rapid swelling. Therefore, a particulate hydrophilic matrix consisting of dextran derivatives was not sufficient for a sustained-release system. In addition, when physical cross-linking by electrostatic interaction instead of chemical cross-linking is applied to avoid possible toxicity of reagents and other undesirable effects, the mechanical strength of these dextran microparticles is very poor, so its usage in oral administration is still limited. In this article, we propose a hydrophilic matrix, consisting of a mixture of hydrophilic polymers that formed a polyion complex, strengthened by a hydrophobic polymer.

The objectives of this study were the production and characterization of microspheres consisting of oppositely charged dextran derivatives and cellulose acetate butyrate, and the investigation of controlled release behavior of theophylline from these microspheres. Theophylline was chosen as a suitable drug for investigation of the formations showing sustained release characteristics because some dosage forms with slow release are commercially available. Cellulose acetate butyrate was chosen as a model hydrophobic polymer because it has been used frequently in matrices or coating membranes of slow release dosage forms.

## MATERIALS AND METHODS

### Materials

Carboxymethyldextran (CMD, Mw 1,000,000) and [2-hydroxypropyltrimethylammonium] dextran (CDC, Mw 1,000,000) were donated from Meito Sangyo Co. Ltd. (Nagoya, Japan). Dextran (Mw 513,000), dextran sulfate (DS, Mw 500,000), [2-(diethylamino) ethyl] dextran (EA, Mw 500,000) and theophylline (TH) were purchased from Sigma Chemical Co. (St. Louis, MO). Dextran, dextran derivatives, and TH were used after sieving through a 100-mesh sieve (less than 150 μm). Cellulose acetate butyrate (CAB, Mw 30,000) was obtained from Fluka Chemical Co. (Buchs, Switzerland). Sugar ester DK F-10 used as a surfactant was kindly supplied by Daiichi Kougyou Seiyaku Co. Ltd. (Kyoto, Japan). All other chemicals were reagent grade and used as received.

### Preparation of Microspheres

Microspheres were produced by emulsion-solvent evaporation method, and described as follows. Theophylline and hydrophilic polymers were dispersed in 15 mL of acetone containing 10% w/v CAB, and then poured into 150 mL of liquid paraffin containing 0.5% w/v of sugar ester, at 20°C under agitation (400 rpm). The mixture was mechanically stirred under atmospheric pressure to form a w/o emulsion. After 30 min, the solution was heated to 50°C to evaporate acetone. Then the solution was gradually cooled at 20°C and then decanted off. The removal of residual oil was performed by washing the microspheres with 50 mL of n-hexane three times. The microspheres were dried under vacuum at room temperature.

### Particle Size Analysis

Particle size analysis was performed on dried microspheres by sieving through a set of the pharmacopoeia of Japan, 14th edition (JP XIV) standard sieves. Sieving was conducted by an electromagnetic shaking sifter (M-2 model, Tsutsui Rikagaku Kikai Co., Ltd., Tokyo, Japan) for 3 min. Weight median diameter was calculated from the cumulative distribution curve, which was plotted cumulative to above the size percent as a function of diameter of sieve.

### Drug Content Determination

Drug content of microspheres sieved at 1000–1180 μm was determined. Approximately 10 mg (accurately weighted) of microsphere was dissolved (or dispersed) in 50 mL of methylene chloride. The solution was subjected to sonication at room temperature for 30 min. The resultant solution was filtered through a 0.2 μm membrane filter and analyzed spectrophotometrically at 274 nm. All drug content determinations were performed in triplicate.

### Morphological Characterization of Microspheres

The surface and cross-sectional morphologies of the microspheres were evaluated by scanning electron microscopy (SEM, JSM-5600LV, JEOL Ltd., Tokyo, Japan). The samples were mounted on metal grids, using double-sided adhesive tape, and coated with gold under vacuum before observation.

### Evaluation of TH Release from Microspheres

Release experiments were conducted at 37°C by a paddle method (100 rpm). Typically, 250 mg of microspheres was placed into a dissolution vessel filled with 900 mL of the JP XIV 1st fluid (pH 1.2, 0.07 M HCl and 0.0342 M NaCl). The JP XIV 2nd fluid (pH 6.8, 0.05 M $H_2KPO_4$ and 0.0236 M NaOH) was used in the study for effect of pH on drug release. Five mL samples were withdrawn at appropriate intervals and filtered with a membrane filter (pore size 0.45 μm). The filtrate was analyzed spectrophotometrically for TH content at 274 nm. An equal volume of the same dissolution medium was added to maintain a constant volume.

## RESULTS AND DISCUSSION

### Evaluation of Microspheres Containing Dextran or Dextran Derivative

Microspheres were prepared by using each of the dextran derivatives in order to investigate the effect of individual dextran derivative on drug release. Typical formulation of microspheres was 20% of TH, 25% of CAB, and 55% of hydrophilic polymer. Dextran and dextran derivatives were used separately as hydrophilic polymers. The effects of dextran and dextran derivatives on particle characteristics and drug release properties were evaluated. The particle data are summarized in Table 1. The mean diameter

***Table 1.*** Particle characteristics of microspheres containing dextran or its derivative as a hydrophilic polymer.

| Sample name | Yield (%) | Mean diameter (μm) | Drug content[a] % (w/w) |
|---|---|---|---|
| Dextran-MS | 96.5 | 1014 | 19.4 ± 1.6 |
| CMD-MS | 101.0 | 682 | 21.7 ± 0.9[b] |
| DS-MS | 88.8 | 938 | 2.0 ± 1.5 |
| EA-MS | 96.3 | 1013 | 22.2 ± 2.4 |
| CDC-MS | 95.2 | 1016 | 21.1 ± 1.0 |

[a] The results are expressed as the mean ± S.D. ($n = 3$).
[b] Drug content of microsphere sieved at 850–1000 μm.

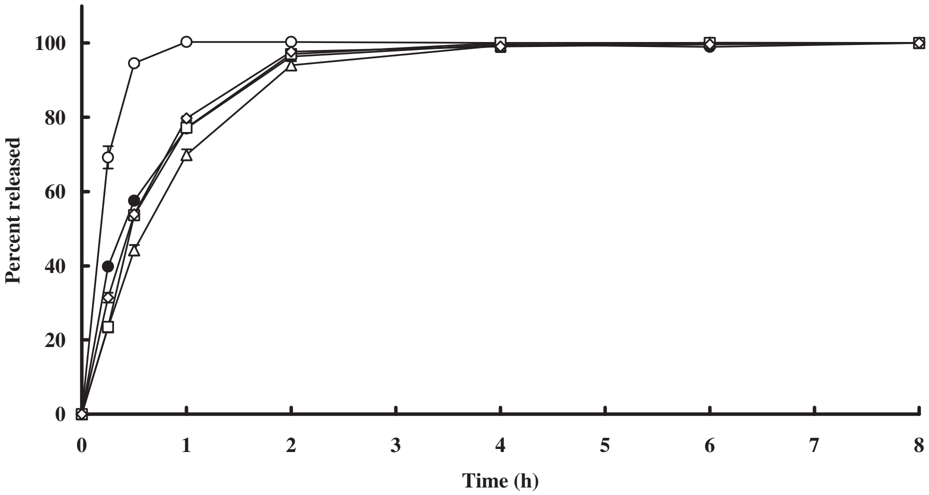

***Figure 1.*** Drug release profiles from microspheres containing dextran or its derivative. The experiments were performed using the JP XIV 1st fluid at 37°C. Each point represents the mean ± S.D. ($n = 3$). Key: (●) Dextran-MS, (○) CMD-MS*, (△) DS-MS, (□) EA-MS, (◇) CDC-MS. *Microspheres sieved at 850–1000 μm.

of Dextran-MS, EA-MS, and CDC-MS were almost the same, at about 1000 μm, but that of CMD-MS was slightly smaller than the others. The yield and drug content were good.

Figure 1 shows the release profiles from microspheres listed in Table 1. The microspheres sieved at 1000–1180 μm were used for the drug release study. In CMD-MS, the microspheres sieved at 850–1000 μm were used because of lack of fraction at 1000–1,180 μm. Percent released was calculated by comparing the released amount after 8 h to 100% released, because the precise drug content of the microspheres was not equal. Dextran-MS, EA-MS, and CDC-MS showed similar release profiles, with more than 95% of drug released 2 h after the release test started. The CMD-MS showed most rapid release of TH. The release from DS-MS was slightly delayed, but TH release from all types of microspheres finished within 4 h.

The release rate was evaluated by in vitro mean dissolution time (MDT), defined as the first moment of the dissolution rate-time curve. Mean dissolution time (MDT) is a model-independent parameter proposed for evaluating in vitro dissolution time.[5] Figure 2 shows the comparison of MDT of TH from the microspheres. Mean dissolution time values were calculated to be about 0.7 h for Dextran-MS, DS-MS, EA-MS, and CDC-MS. These results demonstrate that the dextran derivatives affected release rate to the same extent compared with dextran, although their substitutes were different. The value of MDT for CMD-MS was 0.22 h, indicating about one-third of the other. This might be due to the physicochemical property of CMD and also the particle-size effect. The particle size of CMD-MS used for the drug release study was slightly smaller than the others. Dextran derivatives are water-soluble polymers, and are dissolved in the 1st fluid. Generally, water-soluble polymers incorporated into the microsphere formed channels on dissolution and allowed the release of drug from the microsphere.[6,7] Dextran derivatives played the role of pore-forming agents.

## Effect of Polyion Complex Formation

The effects of polyion complex formation on particle characteristics and drug release behavior were investigated by changing the mixing ratio of DS/CDC in the microsphere. The formulation of microspheres was 20% of TH, 25% of CAB, and 55% of DS/CDC. It is known that DS reacts CDC in dilute solutions and they form polyion complexes.[8] The maximum complexation has been reported to occur at weight ratio, 25:75 of DS/CDC mixture. So, we used mixing ratios of DS/CDC at 15:85, 25:75, and 35:65. Table 2 shows the effect of DS/CDC mixing ratio on particle characteristics. The yield, mean diameter, and drug content were not affected by the mixing ratio of DS/CDC. The particle shapes of M2, M3, and M4 were nearly spherical, but the surface was not smooth (data not shown).

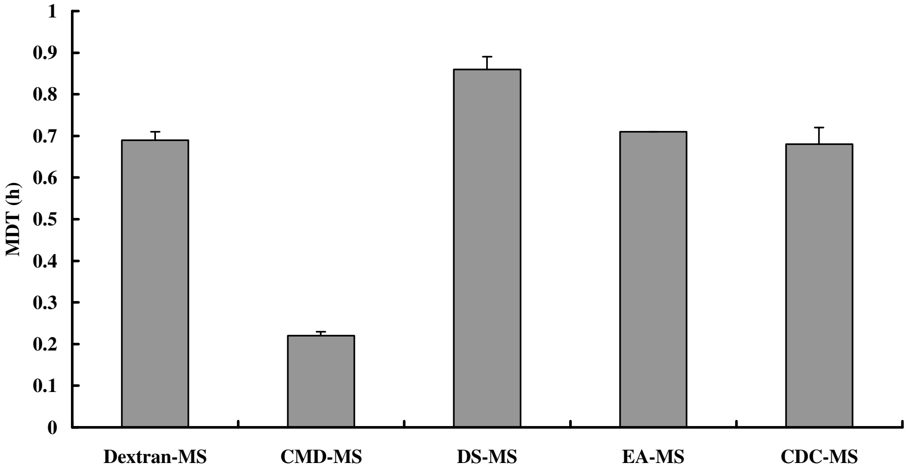

***Figure 2.*** Comparison of MDT of TH from microspheres containing dextran or its derivatives. Data shown are the mean ± S.D. ($n = 3$).

***Table 2.*** Effect of DS/CDC mixing ratio on yield and particle characteristics of microspheres.

| Sample name | CAB (g) | TH (g) | DS (g) | CDC (g) | DS/CDC ratio | Yield (%) | Mean diameter (μm) | Drug content[a] % (w/w) |
|---|---|---|---|---|---|---|---|---|
| M1 (= CDC-MS) | 1.5 | 1.2 | — | 3.3 | 0:100 | 95.2 | 1016 | 21.1 ± 1.0 |
| M2 | 1.5 | 1.2 | 0.165 | 2.805 | 15:85 | 96.5 | 1091 | 20.6 ± 2.8 |
| M3 | 1.5 | 1.2 | 0.825 | 2.475 | 25:75 | 96.8 | 1028 | 20.2 ± 1.3 |
| M4 | 1.5 | 1.2 | 1.155 | 2.145 | 35:65 | 95.5 | 1057 | 20.6 ± 1.5 |
| M5 (= DS-MS) | 1.5 | 1.2 | 3.3 | — | 100:0 | 88.8 | 938 | 22.0 ± 1.5 |

[a] The results are expressed as the mean ± S.D. ($n = 3$).

The effect of DS/CDC mixing ratio on drug release properties was evaluated by use of MDT. The release test was conducted in JP XIV 1st fluid, using microspheres sieved at 1000–1180 μm. Figure 3 shows the comparison of MDT of TH from the microspheres from M1 to M5. Among them, MDT of M3 was longer than the other microspheres. This is believed to be due to the formation of a polyion complex in M3, and as a result, a hydrophilic network was formed in the microsphere, which influenced drug release. From these results, the mixing ratio of polyanion to polycation is a very important factor for controlling drug release.

### Microspheres Consisting of Combination of Oppositely Charged Dextran Derivatives

Four kinds of microspheres were prepared with various combinations of oppositely charged dextran derivatives. The compositions and particle characteristics are listed in Table 3. Derivatives CMD, DS, EA, and CDC were used as a weak polyanion, a strong polyanion, a weak polycation, and a strong polycation, respectively. The ratio of polyanion to polycation was 35:65 in CMD/EA-MS and CMD/CDC-MS, and 25:75 in DS/EA-MS and DS/CDC-MS, in order to obtain maximum effect of complex formation.[8] In spite of variations in the physicochemical properties of dextran derivatives, all microspheres were obtained under the same conditions. The yield and drug content were very good, and mean diameter was not affected by the kind of combination of polyanion and polycation. Scanning electron micrographs of the microspheres prepared with various combinations of oppositely charged dextran derivatives are shown in Fig. 4. The microspheres were almost spherical in shape and had a rough surface with large craters. These may be due to insolubility of dextran derivatives in acetone. Cross-sectional analysis of microspheres indicated that all microspheres had a densely packed monolithic structure.

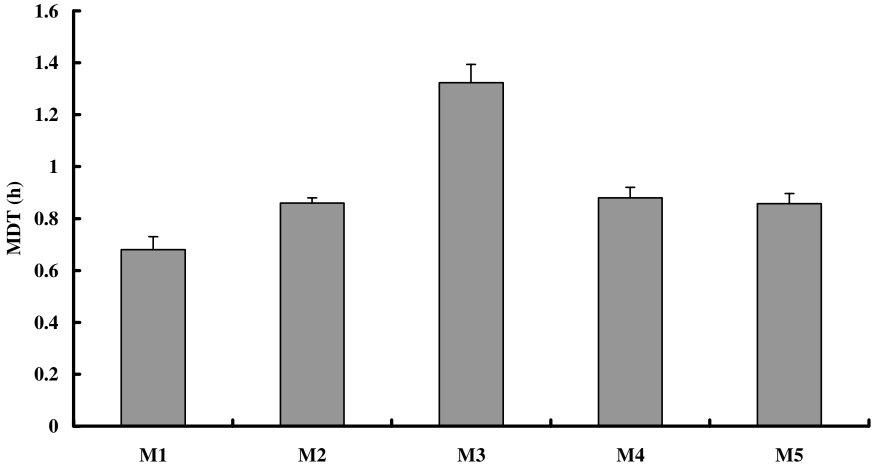

*Figure 3.* Influence of the DS/CDC mixing ratio on MDT of TH from microspheres. Data shown are the mean ± S.D. ($n = 3$).

*Table 3.* Particle characteristics of microspheres prepared from various combinations of polyanions and polycations.

| Sample name | CAB (g) | TH (g) | CMD (g) | DS (g) | EA (g) | CDC (g) | Yield (%) | Mean diameter (μm) | Drug content[a] % (w/w) |
|---|---|---|---|---|---|---|---|---|---|
| CMD/EA-MS | 1.5 | 1.2 | 1.155 | — | 2.145 | — | 99.1 | 1005 | 19.5 ± 0.7 |
| CMD/CDC-MS | 1.5 | 1.2 | 1.155 | — | — | 2.145 | 98.7 | 1015 | 18.9 ± 1.8 |
| DS/EA-MS | 1.5 | 1.2 | — | 0.825 | 2.475 | — | 97.6 | 1001 | 20.6 ± 0.8 |
| DS/CDC-MS | 1.5 | 1.2 | — | 0.825 | — | 2.475 | 96.8 | 1028 | 20.2 ± 1.3 |

[a] The results are expressed as the mean ± S.D. ($n = 3$).

### Effect of Combination of Oppositely Charged Dextran Derivatives on Drug Release

Release profiles of microspheres with diameters of 1000–1180 μm prepared from four combinations of oppositely charged dextran derivatives are shown in Fig. 5. Furthermore, comparisons of MDT are shown in Fig. 6 to clarify the differences among combinations of polyanions and polycations. Theophylline was rapidly released at CMD/EA-MS and CMD/CDC-MS, as shown in Fig. 5. Polyion complexes formed between CMD and the polycation were considered to be not rigid enough to decrease TH release rate. The TH release from DS/EA-MS was most suppressed among these microspheres both in JP XIV 1st and 2nd fluid (Fig. 6).

In order to examine the effect of pH on drug release property, a release test was also performed using JP XIV 2nd fluid. The results, when compared with those obtained by the test in 1st fluid, showed that the TH release was decreased in the 2nd fluid, while the release profiles almost overlapped in the case of DS/CDC-MS [Fig. 5(d)]. The similarity between the released profile in the 1st fluid and that in the 2nd fluid was evaluated using the similarity factor.[9] The application of conventional mathematical models to these profiles seems to be not suitable because drug release mechanisms from these microspheres are more complex than expected. The similarity factor can be used to characterize drug release profiles regardless of the theoretical dissolution model.[10] The similarity factor ($f_2$) is a function of the reciprocal of mean square-root transformation of the sum of square distances at all points, and is a measure of the similarity in the present rate of drug release between two dissolution profiles. The value of $f_2$ ranges between 0 to 100 with a higher $f_2$ value indicating more similarity between the two profiles. The $f_2$ values in DS/EA-MS and DS/CDC-MS were 58.0 and 70.4, respectively, indicating that the released profiles in the 1st fluid were closely similar to that in the 2nd fluid. It is considered that pH-independent release was obtained in DS/EA-MS and

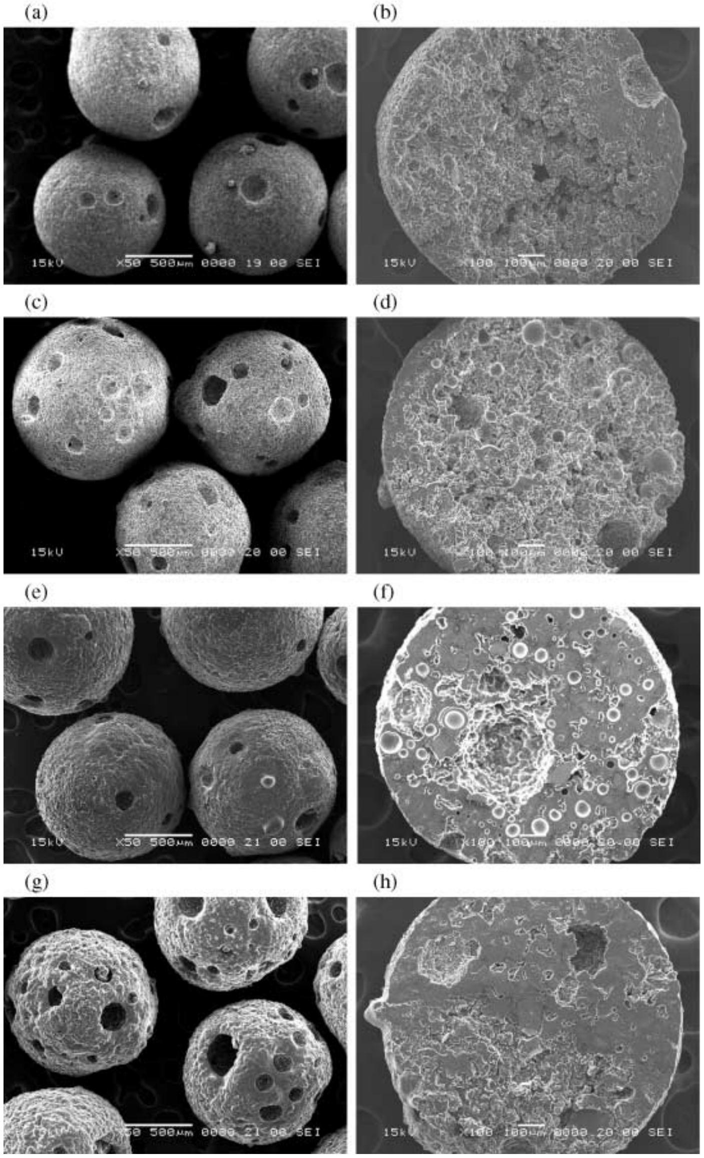

***Figure 4.*** Scanning electron micrographs of microspheres (a, c, e, g) and their cross-sections (b, d, f, h). Key: (a) and (b), CMD/EA-MS; (c) and (d), CMD/CDC-MS; (e) and (f), DS/EA-MS; (g) and (h), DS/CDC-MS.

DS/CDC-MS. On the other hand, the $f_2$ values were calculated at 40.8 and 49.7 for CMD/EA-MS and CMD/CDC-MS, respectively. These values indicated that drug release was affected by pH of the dissolution medium in CMD/EA-MS and CMD/CDC-MS. DS, EA, and CDC are a strong polyacid, weak polybase, and strong polybase, respectively. So, their substituted groups were fully dissociated in both fluids. Therefore, these polymers can react in the 1st fluid the same as in the 2nd fluid. However, CMD is a weak polyanion and its carboxymethyl groups are not dissociated in the 1st fluid. Thus, the rapid release from CMD/EA-MS and CMD/CDC-MS in the 1st fluid was caused by an absence of polyion complex formation despite using a mixture of oppositely charged polymers. The change of the release pattern at pH 6.8 could be caused by an increase in the complexation due to an increase in the ionization of carboxymethyl groups with pH increase. As a result, the drug release from microspheres in pH 6.8 was more depressed than that at pH 1.2. From these results, it is important to select a polymer that is fully dissociated in the environmental pH to form a polyion complex.

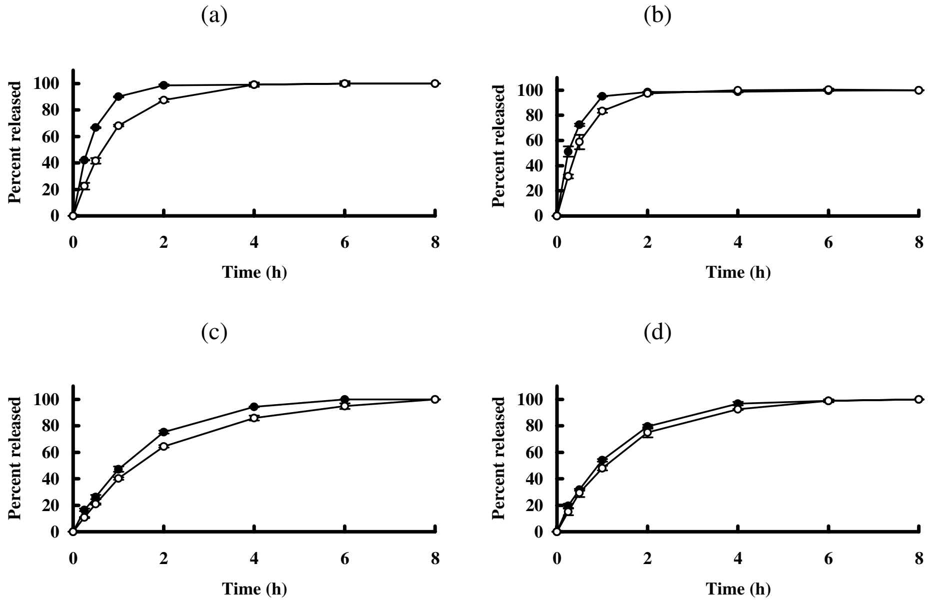

*Figure 5.* Drug release profiles from microspheres. The experiments were performed using the JP XIV 1st (●) and 2nd fluid (○) at 37°C. Each point represents the mean ± S.D. ($n = 3$). Key: (a) CMD/EA-MS, (b) CMD/CDC-MS, (c) DS/EA-MS, (d) DS/CDC-MS.

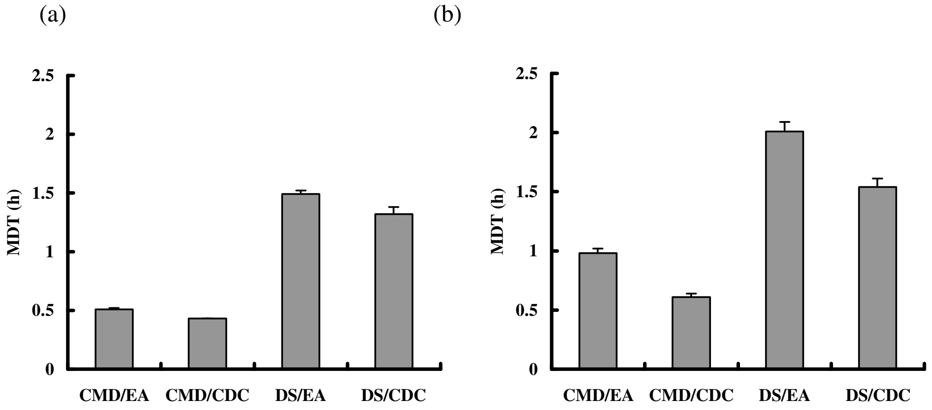

*Figure 6.* Comparison of MDT of TH from microspheres prepared from various combinations of polyanions and polycations. Data shown are the mean ± S.D. ($n = 3$). Key: (a) JP XIV 1st fluid, pH 1.2, (b) JP XIV 2nd fluid, pH 6.8.

## Effect of Hydrophilic/ Hydrophobic Matrix Ratio

The effect of changing the ratio of hydrophilic/hydrophobic matrix in the microsphere on drug release behavior was investigated in order to modulate drug release. The formulations and particle characteristics of microspheres are summarized in Table 4. It was possible to prepare microspheres from various hydrophilic/hydrophobic ratios. All microspheres obtained were spherical and free-flowing. As the ratio of hydrophilic/hydrophobic matrix was raised, the yield and mean diameter were increased, and drug content was decreased. The explanation is that generation of larger emulsion droplets was caused by the increase in viscosity within the internal phase in the microencapsulation process, resulting in the formation of larger microspheres. Shukla and Price reported that changes in the drug to polymer ratio within the internal phase of the emulsion influenced the particle size distribution of resulting microspheres.[11] In the present study, the mean diameter tended to be increased in order of increasing amount of drug and hydrophilic polymers in the dispersed phase.

***Table 4.*** Effect of hydrophilic/hydrophobic polymer ratio on particle characteristics of microspheres.

| Hydrophilic/ hydrophobic ratio | CAB (g) | TH (g) | DS/CDC (g) | Yield (%) | Mean diameter (μm) | Drug content[a] % (w/w) | Formation |
|---|---|---|---|---|---|---|---|
| 3:5 | 1.5 | 0.6 | 0.9 | 78.4 | 559 | 21.0 ± 1.0[b] | A1 |
| 5:5 | 1.5 | 0.75 | 1.5 | 77.7 | 999 | 25.8 ± 1.3 | A1.5 |
| 7:5 | 1.5 | 0.9 | 2.1 | 84.9 | 964 | 25.0 ± 1.2 | A2 |
| 11:5 | 1.5 | 1.2 | 3.3 | 96.8 | 1028 | 20.2 ± 1.3 | A3 |
| 15:5 | 1.5 | 1.5 | 4.5 | 98.3 | 1049 | 18.6 ± 0.7 | A4 |
| 19:5 | 1.5 | 1.8 | 5.7 | 99.7 | 1081 | 19.5 ± 0.2 | A5 |

[a] The results are expressed as the mean ± S.D. $(n = 3)$.
[b] Drug content of microspheres sieved at 500–600 μm.

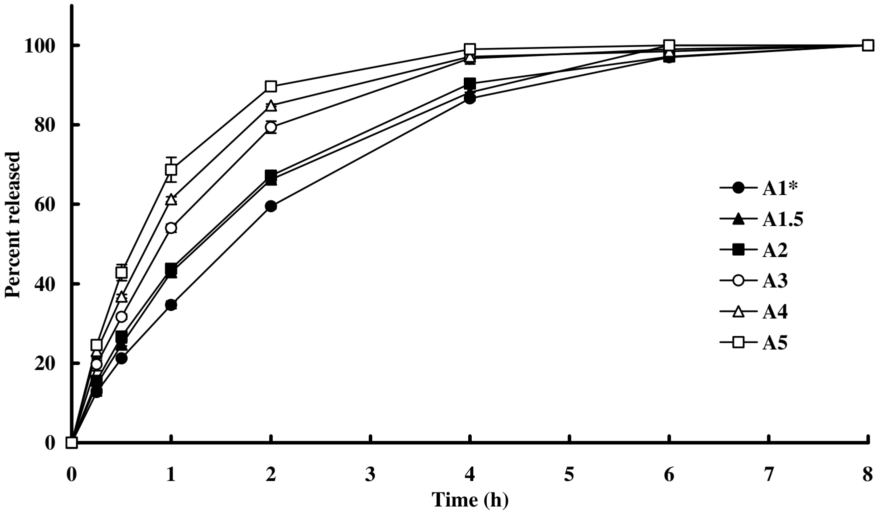

***Figure 7.*** Drug release profiles from microspheres consisting of DS/CDC. The experiments were performed using the JP XIV 1st fluid, pH 1.2, at 37°C. Each point represents the mean ± S.D. $(n = 3)$. *Microspheres sieved at 500–600 μm.

The release profiles from microspheres, A1–A5, in the JP XIV 1st fluid are shown in Fig. 7. The A1 obtained with a ratio of hydrophilic/hydrophobic matrix, 3:5, showed delayed drug release, and TH was released almost completely 8 h after the start of the release test. As the ratio of hydrophilic/hydrophobic matrix was raised, the release rate increased. For A5, prepared with a ratio of hydrophilic/hydrophobic matrix, 19:5, TH was released completely 4 h from the start of the release test. The drug release from A1 was still slow, although the particle size of A1 used for the drug release study was smaller than the other. It is possible that a high concentration of CAB in A1 led to a decrease in the surface area for drug release conversely.

The effect of the hydrophilic/hydrophobic matrix ratio was evaluated by using MDT. Mean dissolution time was plotted against the ratio of hydrophilic/hydrophobic matrix, as shown in Fig. 8. Mean dissolution time decreased with increasing hydrophilic polymer in microspheres. This suggested that most of TH in the microsphere was released after diffusing in the hydrophilic matrix. Moreover, the linear correlation was observed $(r^2 = 0.97)$. The rate of drug release is considered to be modulated by the ratio of hydrophilic/hydrophobic matrix.

## CONCLUSIONS

A study of the development of hybrid microspheres has been performed in order to demonstrate the utility of mixtures of oppositely charged dextran derivatives for the particulate-controlled release delivery system. The most gradual release was shown with the combination of DS/EA, a strong polybase, and a weak polyacid. Moreover, their release profiles in the JP XIV 1st and 2nd fluids were similar, indicating

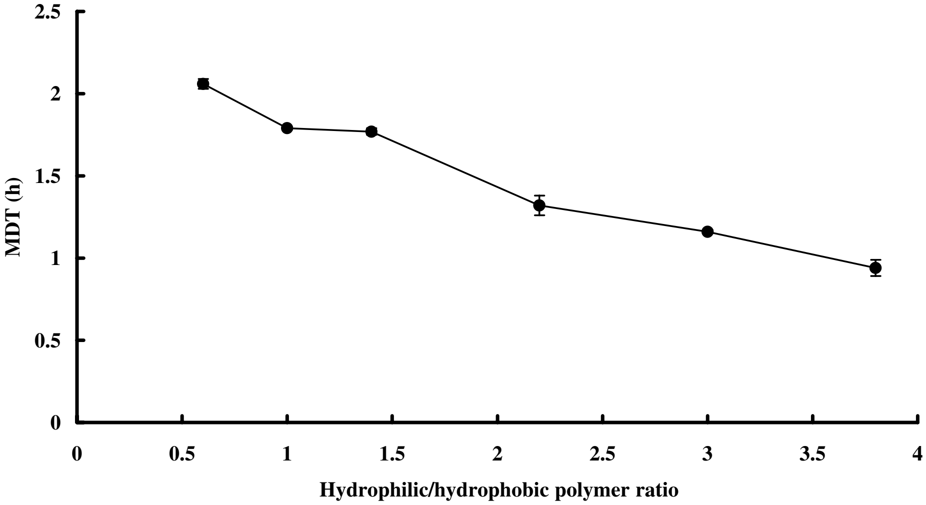

***Figure 8.*** Influence of hydrophilic/hydrophobic polymer ratio on MDT in DS/CDC system. Each point represents the mean ± S.D. ($n = 3$).

pH-independence. The release rate was modulated by the ratio of hydrophilic/hydrophobic matrix. The results have shown that formation of polyion complex made possible an application of dextran derivatives for oral sustained-release preparations.

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