Negatively Thermosensitive Release of Drug from Microcapsules with Hydroxypropyl Cellulose Membranes Prepared by the Wurster Process

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A negatively thermosensitive drug-release microcapsule with hydroxypropyl cellulose (HPC) coat was designed and its preparation was carried out by using an air suspension coating technique (the Wurster process). The microcapsule had a core of calcium carbonate, a drug layer of carbazochrome sodium sulfonate (model drug), a subcoat of temperature-insensitive, water-insoluble ethylcellulose (EC), a thermosensitive layer of HPC having a lower critical solution temperature (LCST) and an overcoat of EC. Three different grades of commercial HPC were used. No significant thermosensitivity of drug release was found in the microcapsules (MCs) without the overcoat of EC. However, MCs having the overcoat showed a negative thermosensitivity: the release rate suddenly decreased at temperatures close to the spectrophotometrically determined LCST of each dilute HPC solution. These results demonstrated that by simply constructing an LCST polymer layer sandwiched between EC membranes, devices exhibiting negatively thermosensitive drug-release could be obtained in the form of fine microcapsules and the temperature dependence of release could be altered depending on the solution properties of the polymers used.

Key words thermosensitive drug release; hydroxypropyl cellulose; microcapsule; ethylcellulose; lower critical solution temperature; the Wurster process

Stimulus-sensitive controlled-release is a new method of drug delivery.[1] This type of delivery system regulates the rate and mode of drug release in response to an external stimulus such as temperature,[2—5] pH,[6,7] light,[8] magnetic[9] or electrical fields[10] and chemical substances.[11] In particular, temperature-sensitive controlled-release systems have attracted much attention in view of potential applications to various industrial products in the pharmaceutical field, and also in the agricultural, chemical and biomedical fields.[12,13] In many cases, thermosensitive polymeric materials including linear polymers and hydrogels, which can alter their configurations in response to external temperature change, are often utilized to construct such systems. Typical configuration changes include precipitation of a polymer in water or collapse of a hydrogel with expulsion of a large fraction of the gel pore water at a phase transition temperature, the so-called lower critical solution temperature (LCST).[13] The use of such unique properties provides release of the contents from the products in a thermally controlled way.

Highly functional drug delivery devices, including thermosensitive controlled-release systems, generally require the use of newly synthesized materials in their preparation. However, a potential problem with these synthetic materials is that they have to pass the regulatory approval process, as is true for all novel materials. This often results in a long delay for their practical or clinical use. Alternatively, the use of well-established materials may have an advantage in this context, provided that their specific properties can lead to desirable properties as delivery devices without any chemical modification.

The majority of studies involving application of thermosensitive polymeric systems for responsive drug delivery have concentrated on the use of devices in the form of discs, slabs, cylinders or large beads. Due to their large dimensions, however, some biomedical applications of these devices are restricted. From this perspective, particulate devices such as microspheres and microcapsules seem to have potential advantages over conventional devices in terms of wider applications,[14—17] provided that they can be designed to display thermosensitive release characteristics. In addition, such miniaturization of the systems may make it possible to realize a more rapid response to external temperature change, providing improved sharpness of thermosensitivity.

In a previous study,[18] as an application of the fine particle coating technology developed by the present authors,[19—22] the design of negatively thermosensitive controlled-release microcapsules (MCs) consisting of a thermosensitive polymer, hydroxypropyl cellulose (HPC), was proposed and preliminarily prepared by means of an air suspension coating technique known as the Wurster process. HPC exhibits an inverse solubility-temperature behavior; that is, there is phase separation on heating above the LCST, typically around 41—45 °C in water,[23—26] leading to thermosensitive controlled-release from the MCs prepared using HPC.

Special attention in this study was paid to how the grade or molecular weight of HPC could affect the negatively thermosensitive drug release. The temperature dependence of the transmittance of HPC aqueous solutions was determined with three types of commercial HPC and its relation to the drug release properties of the MCs was investigated. A possible mechanism of the thermosensitive release was then discussed by taking account of temperature- and concentration-dependent mesophase formation in the phase separation behavior of HPC.

Experimental

Materials All materials were used as purchased or supplied without any purification. Calcium carbonate (08 Jyutan, Maruo Calcium Co., Ltd., Hyogo, Japan) fractionated into 75—90 μm by sieving was used as a core material. Carbazochrome sodium sulfonate (CCSS), a water-soluble model drug, was supplied by Kanebo Ltd., Osaka, Japan. Three types of HPC, HPC-L, HPC-SL and HPC-SSL, were the generous gifts of Nippon Soda Co., Ltd., Tokyo, Japan. Ethylcellulose pseudolatex (EC, Aquacoat®, FMC Corporation) was obtained from Asahi Chemical Industries Co., Ltd., Tokyo, Japan. Anhydrous silica (Aerosil #200, Nippon Aerosil Co., Ltd., Tokyo, Japan) was used as an antiadherent when the MCs were heated for

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curing. The other materials were purchased from Nacalai Tesque, Inc., Kyoto, Japan.

Determination of M.W. The M.W. of each HPC was determined by gel permeation chromatography equipped with a differential refractometer, using Toso G3000HXL, G2000HXL, GMHXL and GRCXLL columns. These columns were calibrated with polystyrene standards. Tetrahydrofuran solution containing each HPC was analyzed at 40 °C with a flow rate of 2.3 ml/min. The number-average molecular weight, M_n, and the weight-average one, M_w, were 60000 and 171000 for HPC-L, 48000 and 131000 for HPC-SL and 26000 and 65000 for HPC-SSL, respectively.

Determination of LCST LCST of HPC dissolved in a 0.9% saline solution was determined by measuring the transmittance change of the HPC solutions at 550 nm, using a Shimadzu UV-2100 UV-visible spectrophotometer equipped with a programmed temperature controller (SPR-8, Shimadzu, Kyoto, Japan). The polymer concentration of test solutions was fixed at 20% (w/v). Using an intermittent heating process, the transmittance at predetermined temperatures was monitored isothermally until its value became constant. The LCST of the HPC solutions was defined as the inflection point in the curve of solution transmittance *versus* temperature, according to the report of Harsh and Gehrke.[26]

Coating Apparatus A Grow Max (140) spouted bed coater assisted with a draft tube and bottom-spray (Fuji Paudal Co., Ltd., Osaka, Japan) was used. A pneumatic spray nozzle with a liquid outlet caliber of 1.0 mm and a bag-filter with an opening of about 5 μm were employed throughout all experiments.

Particle Size Distribution Sieve analysis was performed using a Ro-tap shaker as previously reported.[22]

Release Tests Release tests were performed by the JP XIII paddle method at 200 rpm in a 0.9% aqueous saline solution, as previously reported.[18] To make film-formation complete, curing of MCs was carried out by mixing MCs with 2% of anhydrous silica and then by heating in an air stream oven at 80 °C for 12 h. The MCs thus cured were used as samples. The concentration of released CCSS was monitored by taking an aliquot of 2 ml through a 0.22 μm filter at specific time points, replacing the solution with fresh dissolution fluid and determining CCSS from its absorbance at 363 nm spectrophotometrically.

Results

Particle Structure The ideal structure of negatively thermosensitive controlled-release MCs designed in our preliminary study is schematically illustrated in Fig. 1.[18] This MC was composed of a calcium carbonate core of 75—90 μm, a drug-layer of CCSS and binder, a subcoat of EC, a thermosensitive polymer-layer of HPC and an overcoat of EC in that order. HPC is an LCST polymer and its water-solubility drastically changes at the LCST[23—26]; it is soluble in water at temperatures below the LCST while it precipitates above the LCST. When temperature was below the LCST, therefore, HPC was possibly dissolved in the release medium during the drug release process. In such a situation, it was anticipated that HPC should be washed out from the MC surfaces. Consequently, it could not work as a thermosensitive diffusion barrier, as far as only a simple HPC membrane existed on the MC surfaces. Hence, an HPC layer sandwiched between temperature-insensitive, water-insoluble EC membranes was formed on the drug-layered particles, as shown in Fig. 1. Such a multi-layered membrane can be easily produced by the Wurster process.[22,27] By constructing this membrane structure, the HPC layer could still be fixed on the MC surfaces, even if the MCs were exposed to temperatures below the LCST. This sandwiched HPC membrane exhibited a negatively thermosensitive drug release due to the inverse temperature-dependence of its water-solubility. Namely, drug release at temperatures above the LCST was more suppressed by formation of water-insoluble or less water-permeable HPC layer in the MCs, while HPC layer dissolved in the MCs at temperatures below the LCST did not act as a diffusion barrier, leading to fast release. Based on this particle structure proposed in our preliminary report,[18] three kinds of MCs consisting of different grades or M.W. of HPC layer were prepared in the present study and their effect on the thermosensitivity of CCSS release from each MC was examined.

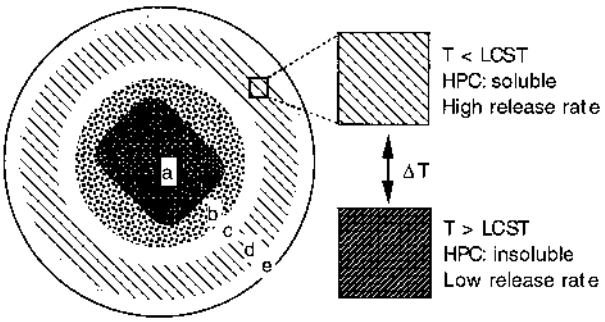

Fig. 1. Schematic Diagram of MCs with Negatively Thermosensitive Drug Release

a, calcium carbonate core; b, drug layer; c, subcoat of EC; d, thermosensitive layer of HPC; e, overcoat of EC.

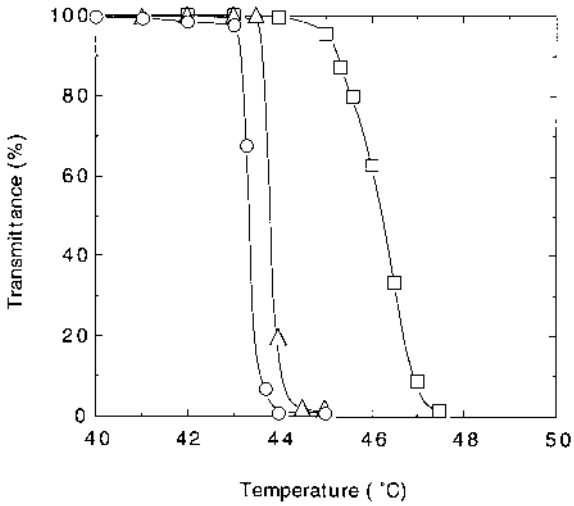

Fig. 2. Transmittance Change of HPC Dissolved in 0.9% Saline Solution at 550 nm with Response to Stepwise Temperature Change

Grade of HPC: circles, L; triangles, SL; squares, SSL. The concentration of HPC: 20% (w/v).

LCST of HPC Figure 2 shows the transmittance curves for three types of HPC dissolved at 20% (w/v) in the 0.9% saline solution with response to a stepwise shift of the surrounding temperature. On heating, the HPC solutions turned intense white at temperatures where transmittance showed low values of around a few percent. Transmittance of either HPC-SL or HPC-L was sharply decreased with rising temperature, while that of HPC-SSL tended to be somewhat broadly changed. The LCST was shifted to higher temperature as the M.W. of HPC became small: the spectrophotometrically determined LCST was 43.7 °C for L, 44.2 °C for SL and 47.1 °C for SSL, respectively. The LCST obtained for 10% (w/v) aqueous solutions of HPC-L or -SL used in the present study (data not shown) were comparable with the published data,[23] but that of HPC-SSL was approximately 3 °C higher than the corresponding value reported in the literature.[23] The commercial HPC obtained from different

Table 1. Formulation and Operating Conditions in the Preparation of MCs

Formulation:			
Core			
Subcoated particles (g)[a]	40	40	40
Thermosensitive layer			
HPC-L (g)	25		
HPC-SL (g)		25	
HPC-SSL (g)			25
Water (g)	ad.	ad.	ad.
Total (g)	750	625	500
Overcoat			
Aquacoat® (g)[b]	12.8	12.8	12.8
Dibutyl sebacate (g)	1.92	1.92	1.92
Water (g)	ad.	ad.	ad.
Total (g)	128	128	128
Operating conditions:			
Inlet air temperature (°C)	55—60	55—60	55—60
Outlet air temperature (°C)	32—37	30—37	29—36
Inlet air rate (m^3/min)	0.34—0.39	0.36—0.38	0.34—0.36
Liquid flow rate (ml/min)	2.7—3.0	2.7—3.0	2.7—3.0
Spray air pressure (kg/cm^2)	3.0—3.2	3.2—3.4	3.2—3.3
Spray air flow rate (l/min)	64—67	65—67	67—69
Product:			
Yield (%)	94	92	93
Mass median diameter (μm)	141	140	138

a) 90—106 μm. *b*) On a dry basis.

manufacturers might differ in the degree of substitution as well as the molecular weight distributions, and these might be responsible for the variation in the LCST.

Preparation of MCs The details of MC formulation, the operating conditions of the Grow Max (140) spouted bed coater in the preparation of MCs, and the properties of the products are shown in Table 1. The subcoated particles were prepared by layering CCSS (25 g) with 10 g of HPC-SSL onto calcium carbonate particles (200 g) and, thereafter, by subcoating the drug-layered particles with Aquacoat (31 g) containing dibutyl sebacate (4.7 g) as a plasticizer. The subcoated particles thus obtained were sieved into 90—106 μm and 40 g of the fractionated particles were used for subsequent coating to make MCs. The yields of the MCs were from 92 to 94%. The mass median diameters of the MCs were 141 μm with HPC-L, 140 μm with HPC-SL and 138 μm with HPC-SSL, respectively.

Thermosensitivity of Drug Release from MCs A typical example of CCSS release at various temperatures is shown in Fig. 3 for the MCs with an HPC-L layer. Release from the corresponding MCs without the overcoat of EC, and the subcoated particles, are also shown. Negatively thermosensitive CCSS release was observed neither from the MCs without the overcoat of EC nor the subcoated particles, within the temperature range employed here. The CCSS release was simply enhanced with elevation of dissolution temperature (Figs. 3a, b), though the release at 50 °C tended to be somewhat suppressed. Thus, the outer layer of HPC on the MCs hardly played a role as a thermosensitive diffusion barrier. In contrast, MCs with the overcoat of EC exhibited negative thermosensitivity, as expected (Fig. 3c). In the range from 20 to 37 °C, CCSS release from MCs with the EC overcoat was enhanced with rising temperature, just as for MCs without the EC overcoat, but release became slow as temperature approached the LCST of HPC. Similar trends were also observed in MCs with HPC-SL or HPC-SSL layers (data not shown).

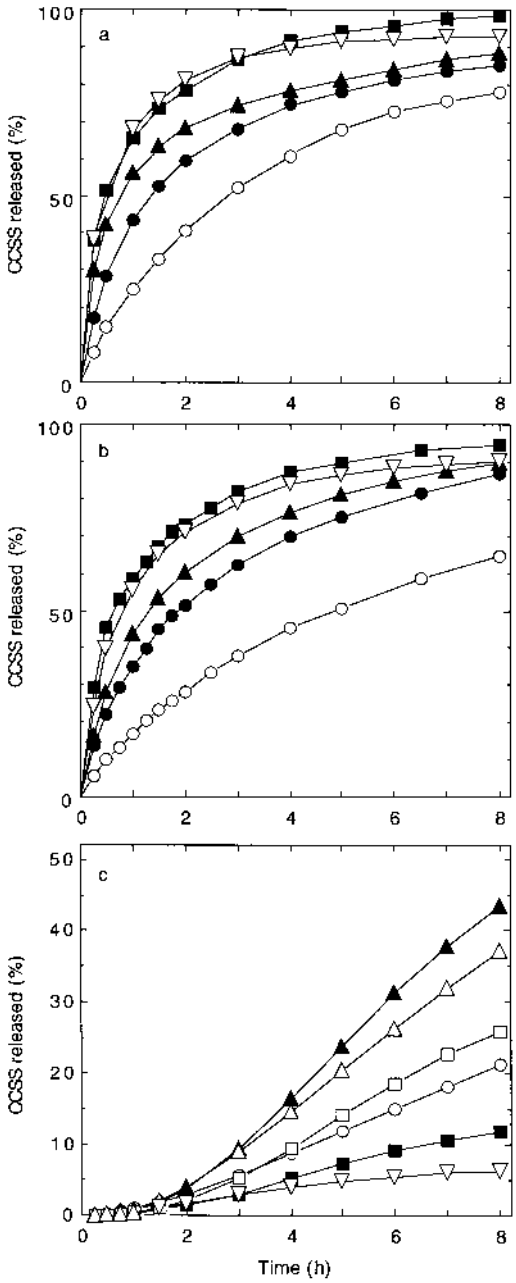

Fig. 3. CCSS Release from MCs Containing Thermosensitive Layer of HPC-L with or without Overcoat of EC as a Function of Dissolution Temperature

a, Subcoated particle; b, MCs without overcoat of EC; c, MCs with overcoat of EC. Dissolution temperature (°C): open circles, 20; closed circles, 30; open triangles, 31; closed triangles, 37; open squares, 41; closed squares, 45; open inverse-triangles, 50.

Most of the release profiles shown in Fig. 3 were characterized by the first-order release, with or without a lag time. Therefore, the slope of the linear regression line, estimated by the least-squares method from the semi-log plots of the percent remaining *versus* time, was regarded as the apparent release rate constant. Figure 4 shows Arrhenius plots of the apparent release rate constant thus estimated for MCs with or without the EC overcoat. For each MC without the EC overcoat, release rate constant at temperatures ranging from 20 to 45 °C gave a straight line, in which the release rate simply increased with temperature. The rate constant was somewhat

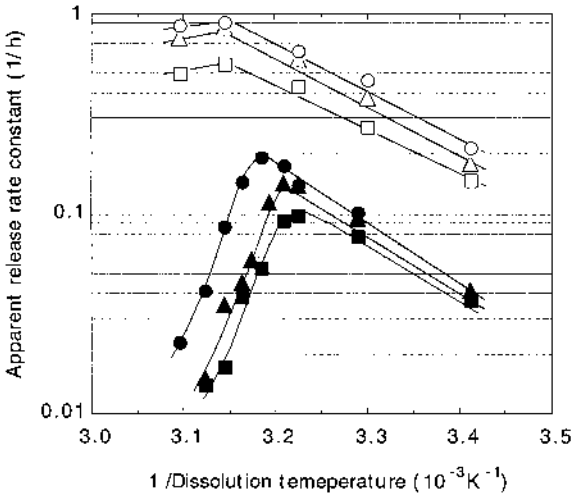

Fig. 4. Logarithmic Plots of Apparent Dissolution Rate Constants of CCSS from MCs with or without Overcoat of EC as a Function of Reciprocal Dissolution Temperature

Type of MCs: open symbols, MCs without overcoat of EC; closed, MCs with overcoat of EC. Grade of HPC: circles, SSL; triangles, SL; squares, L.

lower at 50 °C than at 45 °C in each case, but the decrease was very small. In contrast, release rate of the MCs with the EC overcoat began to reduce remarkably as temperature became close to the LCST. It was also found that the higher the LCST of the HPC was, the higher the temperatures where the rate constants began to rapidly decrease. The minimum rate constant at temperatures above the LCSTs observed in Fig. 4 were approximately 10 times smaller than the maximum observed at temperatures near the LCSTs.

Discussion

Major approaches to produce thermosensitive controlled-release particulate devices are directed to surface-graft polymerization of thermosensitive acrylic polymers on ready-made particulate materials[14,16] or emulsion copolymerization of acrylic monomers with a crosslinker in liquid phases.[15] The most commonly studied class of thermosensitive acrylic polymers is poly(*N*-alkyl substituted acrylamide)s, in particular, poly(*N*-isopropyl acrylamide (NIPAAm)) which has an LCST at around 32 °C.[28] These polymers are useful for freely designing a variety of devices because their properties can be modified easily by altering their monomer compositions.[2—5] To date, several concepts using these synthetic polymers have been proposed in order to provide microparticles with thermosensitive release ability.[14—17,21] However, critical problems are, for example, the toxicity and biocompatibility of the synthetic materials. Thus, use of a material that has been generally recognized as safe should afford a practical advantage, provided that thermosensitive controlled-release particulate systems can be prepared by means of a simple preparation method. Certain polymeric materials widely used as pharmaceutical ingredients have been shown to have inverse temperature-dependent water-solubility.[13] These include HPC, hydroxypropyl methyl cellulose, methyl cellulose, polyethylene glycol, polyvinyl alcohol and so on. Among these, HPC was selected as a thermosensitive polymer in this study because its LCST is around 40 °C, which is close to body temperature, and may lead to a variety of biomedical applications. MCs incorporating this polymer were

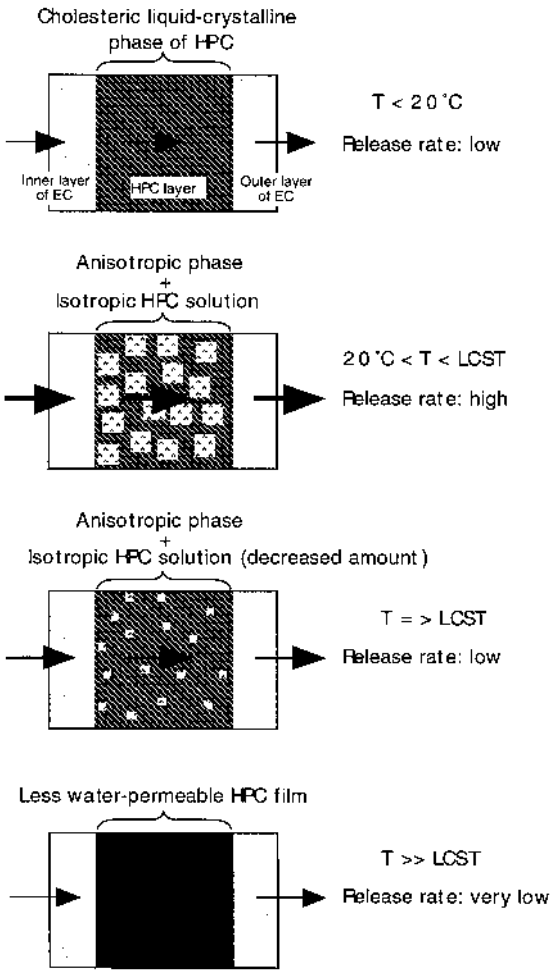

Fig. 5. Schematic Diagram of Estimated Release Mechanisms on MCs with HPC Layer Sandwiched between EC Membranes

prepared by the Wurster process characterized as a mechanical microencapsulation method using a simple wet-spraying process.[27]

The major concern with preparation of MCs containing a HPC layer was the high agglomeration tendency of coated particles due to the strong binding strength of HPC commonly used as a binder for granulation.[29] Although the use of certain additives such as sodium chloride or polyethylene glycol is effective for suppressing agglomeration,[29] they may undesirably affect the LCST of HPC. In order to suppress agglomeration when using plain HPC without any additives, the concentration of HPC in the spray solution and the liquid flow rate were set as low as possible. Consequently, no significant agglomeration was observed. The product yield was more than 90%, indicating that both the HPC layer and the EC overcoat formed well on the subcoated particles.

MCs having the HPC layer sandwiched between EC membranes demonstrated a peculiar thermosensitive drug release profile. As shown in Fig. 3c, CCSS release increased with rising temperature, but began to decrease at temperatures over 37 °C for HPC-L, 39 °C for HPC-SL and 41 °C for HPC-SSL, respectively. Unlike the thermosensitive MCs having a coat of poly(NIPAAm) latex with core-shell structure, prepared in our previous study,[21] the peculiar release profile observed in the present study seemed to reflect a unique temperature-dependent phase separation of HPC

aqueous solution.

The peculiar pattern observed in the Arrhenius plots in Fig. 4 may be interpreted by taking account of the phase separation behavior of HPC. Werbowyj and Gray[23] found that HPC forms an ordered liquid-crystalline phase with cholesteric structure in concentrated aqueous solution. The critical concentration necessary for formation of this phase was found to be 41 and 42 wt% for HPC with a nominal M_w of 60000 and 100000, respectively. More precise work on the relationship between the temperature and polymer concentration in the phase separation behavior was accomplished by Fortin and Cherlet.[25] They investigated the phase diagram of HPC in water with carefully fractionated samples having a M_w between 28000 and 140000. The phase diagram proposed in their report delimits three regions: a region with a pure isotropic phase, a two-phase region and a region with an anisotropic single-phase. At polymer weight fractions lower than approximately 50%, isotropic solutions exist as a single, stable phase below the LCST, 42 °C, and it separates into an infinitely diluted solution and an anisotropic phase (cholesteric liquid crystal) with about 80% HPC concentration above 42 °C. At the HPC weight fractions of 50% to 55%, two phases of 50% and 55% HPC concentration, which are isotropic and anisotropic, respectively, coexist at temperatures below about 20 °C. The HPC concentration of the latter increases to about 80% upon heating to 42 °C, and two phases, an infinitely diluted solution and an anisotropic phase with about 80% HPC concentration, are present above 42 °C. At 55% to 80% weight fraction, an anisotropic phase is formed at temperatures below the transition temperature, and the phase separates at the transition temperature into the following phases: the anisotropic phase with about 80% HPC concentration and the phase with 50% HPC concentration below 42 °C, or the infinitely diluted solution above 42 °C whose fraction is drastically reduced at 42 °C. At HPC weight fractions above 80%, an anisotropic single-phase always exists.

It was difficult to quantitatively determine the amount of water existing in the HPC layer during the water-uptake process since the dimensions of the HPC layer and the EC coat were obscure. However, on the microscopic observation it was found that the MCs did not expand by more than approximately 10% in diameter in the dissolution fluid in the temperature range employed. For example, assuming that the MCs were spherical and isotropically expanded up to 10% in diameter, and that the expansion originated from only water-uptake of the HPC layer without any volume changes in the inner subcoated part of the particle and the outer EC membrane, and that the density of EC is identical with that of HPC (1.2224 g/cm^2), the concentration of HPC in the HPC layer was estimated to be 60%.

According to the preceding phase diagram,[25] the trends in the change of the Arrhenius plots shown in Fig. 4 can be explained. Namely, below 20 °C the cholesteric liquid-crystalline phase, a possibly strong diffusion barrier for solutes, was probably formed in the HPC layer of the MCs, leading to slow CCSS release and the low apparent release rate constant. At about 20 °C, the isotropic HPC solution in equilibrium with the anisotropic phase probably begins to form. Upon further heating, CCSS release would be enhanced by the increase in the fraction of the isotropic phase in addition to thermally enhanced diffusion of CCSS. Once the temperature reaches the LCST, meanwhile, the HPC concentration of the isotropic phase was infinitely decreased and the fraction of the isotropic phase in turn suffered a drastic decrease. As a result, the anisotropic phase of 80% HPC concentration was again more predominant over the isotropic phase in the system. At temperatures far higher than the LCST, the HPC layer does not appear to dissolve any further, because, for example, the release rate constant at 50 °C was lower than that at 20 °C where a strong permeation barrier by the liquid-crystalline phase of HPC would be formed. A schematic diagram of the estimated release mechanisms is shown in Fig. 5.

These considerations showed that the drug release rate constant began to decrease above the LCST of HPC solution. Fortin and Cherlet[25] described the cloud points (LCST) as being independent of the M_w of HPC. In contrast, the LCST depended on the HPC grade in this study (Fig. 2). The variation probably originated from the use of unfractionated commercial HPC in this study, unlike the carefully fractionated HPC used by Fortin and Cherlet.[25] Corresponding to their LCSTs, HPC used in this study displayed a transition temperature where the drug release rate constant began to decrease.

Mustafa *et al*. investigated a dye (disodium fluorescein, M.W.=386) diffusion in isotropic and liquid crystalline aqueous HPC.[30] They suggested that neither diffusion nor apparent activation energy was altered markedly by the liquid crystalline transition, but yet the measurements were carried out over a restricted temperature range, *i.e*., 15 to 40 °C at polymer concentrations of 2 to 58 wt%, which do not fully cover the range in the present study. A more detailed study is necessary to clarify the possibility of formation of the cholesteric liquid-crystalline phase in MCs and its effect on CCSS diffusion.

MCs with the EC overcoat demonstrated a significant, sharp temperature-dependent change of release rate constant over a relatively narrow temperature range. For instance, the maximum release rate constant at 37 °C was approximately 10 times higher, compared to the minimum one at 50 °C. This was not inferior in magnitude to those of the negatively thermosensitive controlled-release microparticulate systems using synthetic polymers such as poly(*N*-alkyl substitute acrylamide)s hitherto developed.[15,16] Such a large difference of release rate constant within a relatively small temperature change could not be achieved in MCs without the overcoat of EC. Thus, the construction of the HPC layer sandwiched between EC coats made it possible to impart negatively thermosensitive drug release properties to the MCs because of the peculiar temperature-dependent phase separation behavior.

The key structural feature of these designed MCs is the sandwiched layers. The negatively temperature-dependent drug-release demonstrated in this study was the result of this membrane structure. Other types of stimuli-sensitive polymers such as an enteric polymer having pH-dependent solubility may be usable in these MCs, if these polymers can be sandwiched between inert polymer layers successfully. Integrating the membrane structure proposed here with these polymers, which can drastically alter their water-solubility in response to various stimuli, may possibly enable us to discover other types of stimuli-sensitive controlled-release MCs.

This approach does not require use of a newly synthesized material, or a complicated preparation method.

Conclusion

In this study, MCs with negatively thermosensitive controlled-release properties were prepared using three grades of commercial HPC, based on the design proposed in our previous study. The effect of the HPC grade on the thermosensitivity of drug release from the MCs was investigated. MCs were prepared by the Wurster process without significant agglomeration, irrespective of the grade of HPC employed. Construction of the HPC layer sandwiched between EC membranes on the MC made it possible to produce negatively thermosensitive drug release above the LCST. The temperature dependence of the apparent drug-release rate constant was controllable by using HPC having varied LCST. This probably resulted from molecular weight dependence for the temperature-dependent phase separation behavior of the HPC layer in the MCs.

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