



ELSEVIER

International Journal of Pharmaceutics 124 (1995) 87–96

**international  
journal of  
pharmaceutics**

# Simple coacervation of hydroxypropyl methylcellulose phthalate (HPMCP)

## I. Temperature and pH dependency of coacervate formation

G. Weiß<sup>a,\*</sup>, A. Knoch<sup>c</sup>, A. Laicher<sup>a</sup>, F. Stanislaus<sup>a</sup>, R. Daniels<sup>b</sup>

<sup>a</sup> Department of Pharmaceutical Technology, Klinge Pharma GmbH, Berg-am-Laim-Straße 129, 81673 Munich, Germany

<sup>b</sup> Institute of Pharmaceutical Technology, University of Regensburg, 93040 Regensburg, Germany

<sup>c</sup> Gödecke AG, 79090 Freiburg, Germany

Received 12 December 1994; accepted 28 February 1995

---

### Abstract

The simple coacervation of hydroxypropyl methylcellulose phthalate (HPMCP) on the addition of 20% (w/w) sodium sulphate solution was investigated as a function of the temperature and pH value of the aqueous polymer solution. Phase diagrams, quantitative investigations of the isolated polymer-rich phases and charge density measurements served to characterize phase separation. The existence of coacervate and precipitate phases of HPMCP was attributed to the chemical structure of the polymer. Analogous to other polymers such as gelatin or cellulose acetate phthalate, HPMCP formed polymer-rich coacervate and precipitate phases from aqueous solutions following the addition of electrolyte solutions. Increased temperature and total electrolyte content had a synergistic effect on phase separation. With increasing temperature the polymer content in the polymer-rich phase rose up to 23.6% (w/w) at 60° C corresponding to a polymer yield of 63.7%. This was accompanied by the gelation of the coacervate phase which was attributed to the temperature-dependent hydration of the methyl and hydroxypropyl substituents of the polymer. Moreover, a minimum pH value of the HPMCP solution was required for coacervate formation, otherwise the polymer was salted out as a precipitate. Charge density measurements showed that this was accompanied by the almost entire dissociation of the HPMCP carboxyl groups. They were hence responsible for the pH-dependent polymer hydration and essential to coacervate formation. The adjustment of an appropriate pH value is therefore a prerequisite for the formation of coacervate phases in the process of microencapsulation with HPMCP by simple coacervation. Owing to the temperature dependency of coacervate formation, the temperature course required for the microencapsulation process was found to run opposite to that described for cellulose acetate phthalate.

**Keywords:** Microencapsulation; Coacervation; Hydroxypropyl methylcellulose phthalate; Temperature; pH; Enteric; Phase diagram

---

\* Corresponding author.

## 1. Introduction

Several methods are known for the microencapsulation of drugs, e.g., fluid bed coating, spray-drying, solvent evaporation, polymerization and coacervation which are used for different technical applications (Bakan and Sloan, 1972; Sparks, 1981). **Coacervation is the method of choice for the production of pharmaceutical preparations with high active ingredient content and small particle size of the core material used.**

Whereas numerous papers have been published on the complex and simple coacervation of gelatin (Madan, 1979; Nixon et al., 1968; Nixon and Harris, 1986), systematic investigations of simple coacervation methods for enteric polymers are almost exclusively available for cellulose acetate phthalate (Merkle, 1972; Merkle and Speiser, 1973). A disadvantage of cellulose acetate phthalate for coacervation-based microencapsulation is the fact that only about 45% of the polymer can be salted out into the coacervate phase (Merkle and Speiser, 1973). Only a relatively small percentage is hence available for the coating of suspended core material which has a negative effect on the efficiency of the method as a whole.

Owing to the fact that hydroxypropyl methylcellulose phthalate (HPMCP) is less susceptible to hydrolysis than cellulose acetate phthalate, HPMCP is preferred in pharmaceutical technology (Bauer et al., 1988). Simple coacervation systems with this polymer have been described exclusively in the patent literature (Fekete and Tibor, 1983; Calanchi, 1984). These methods differ only slightly from the usually applied coacervation encapsulation procedures with other polymers such as gelatin and cellulose acetate phthalate, and cannot be performed with HPMCP. It is possible neither to form a coacervate phase with coating characteristics by adding acids at low temperatures (Fekete and Tibor, 1983) nor to prehardening or gel the coacervate phase formed by decreasing the temperature (Calanchi, 1984).

The aim of our investigations was therefore to study the suitability of HPMCP for microencapsulation by simple coacervation and to establish the prerequisites for a reproducible manufacturing procedure (Weiß, 1991). Based on the specific

colloid-chemical properties of HPMCP, the parameters affecting the coacervation of the polymer are described in this paper. Since the anionic character of the polyelectrolyte and the temperature-dependent dissolution behavior of the cellulose ether substituents are of particular significance here, the coacervate formation induced by the addition of a neutral electrolyte solution was investigated with respect to both temperature dependency and influence of the pH value.

## 2. Materials and methods

### 2.1. Materials

Hydroxypropyl methylcellulose phthalate (HP 55<sup>®</sup> lot no. 906077, Shinetsu Chemicals, Tokyo, Japan) had a specified content of 19.2% (w/w) methyl, 5.9% (w/w) hydroxypropyl and 32.4% (w/w) phthalyl moieties; 0.001 *N*-poly(diallyldimethyl)ammonium chloride (poly-DADMAC) was purchased from Müttek (Darmstadt, Germany); sodium sulphate (Merck, Darmstadt, Germany) was used as coacervating agent in a 20% (w/w) aqueous solution. All other chemicals were of analytical grade and were used as received.

### 2.2. Preparation of hydroxypropyl methylcellulose phthalate solutions

Unless mentioned otherwise, all trials were performed with polymer solutions of the following composition: HPMCP, 50 parts; sodium monohydrogen phosphate dihydrate, 20 parts; and demineralized water, 930 parts. All polymer solutions with other HPMCP content were prepared at a uniform ratio of HPMCP to sodium monohydrogen phosphate dihydrate (2.5:1). Sodium monohydrogen phosphate dihydrate was dissolved in water and HPMCP was subsequently suspended. Stirring for approx. 10 h at room temperature resulted in clear to slightly opalescent solutions with a pH value of 5.45 ( $\pm 0.05$ ). These solutions were used without further treatment. All trials were performed with polymer solutions stored at room temperature for a maximum of 2 weeks.

### 2.3. Temperature-dependent phase diagrams

Phase diagrams were established as described in the literature (Merkle, 1972). The polymer solutions (0.5–10% w/w) were weighed into a double-jacketed reactor (IKA Laborreaktor LR-A 250 with stirrer RE 162A S3, Janke and Kunkel, Staufen, Germany), adjusted to temperatures of 20, 35, 50 and 60°C by stirring (four-armed stirrer, two levels) and subsequently salted out by adding sodium sulphate solution (20% w/w) at a constant temperature. After each addition, a small sample was withdrawn and its appearance was observed microscopically (Olympus CK Inversmikroskop, Olympus Optical, Hamburg, Germany). The systems were then classified as either colloidal solutions, or coacervates and precipitates in equilibrium with the diluted polymer solutions. The resulting concentrations of polymer, water and total electrolyte (= total sodium monohydrogen phosphate and sodium sulphate) were presented as phase diagrams.

### 2.4. Coacervation temperature dependent upon total electrolyte content

The method used corresponds to the method for the determination of the cloud point which is frequently used for the characterization of surfactant solutions (Florence and Attwood, 1982). The HPMCP solutions (5% w/w) were adjusted to total electrolyte concentrations of 4.9–8.5% (w/w) by adding sodium sulphate solutions at room temperature. Subsequently, the saline polymer solutions were slowly heated or cooled under continuous stirring (see conditions above) until the appearance of coacervate droplets was observed microscopically.

### 2.5. pH-dependent phase diagrams

The HPMCP solutions (5% w/w) were adjusted to pH values of 4.75–7.0 by adding 1 N sodium hydroxide solution or diluted acetic acid (1% w/w) at room temperature under continuous stirring (see conditions above). Subsequently, the solutions were salted out at 35°C by adding

20% (w/w) sodium sulphate solution. Upon addition of the electrolyte solution, the pH value of the HPMCP solutions shifted as a result of the exchange of sodium ions with hydrogen ions. This effect was observed at all pH values (pH decrease of 0.2–0.5 units) and was therefore not taken into consideration. The assessment of the microscopic appearance of the polymer solutions was performed at 35°C as described under section 2.3.

### 2.6. Polyelectrolyte titration

The titration was performed as described in a previous paper (Weiß et al., 1993). 0.05 ml of an HPMCP solution (5% w/w) were diluted with 10 ml of water and the pH was adjusted by adding diluted acetic acid (0.05% w/w) or 0.01 N sodium hydroxide solution, respectively. The degree of dissociation of the phthalyl moieties at each pH value was calculated on the assumption that dissociation is completed at pH 7.0.

### 2.7. Wet weight of the polymer-rich phases

200.0 g HPMCP solution (5% w/w) were salted out at 20, 35, 50 and 60°C by adding 118.7 g sodium sulphate solution (20% w/w) under continuous stirring (conditions see above). Subsequently, the solutions were equilibrated for 15 min at the respective temperature. The samples were then centrifuged for 5 min at  $31\,000 \times g$  by keeping the temperature constant (Beckman J2-21 centrifuge with fixed angle rotor JA-20, Beckman Instruments, München, Germany). The supernatant equilibrium phases were carefully removed by suction and the remaining polymer-rich phases were weighed. The wet mass of the polymer-rich phases was calculated as percentage of the total sample weight.

### 2.8. Composition of the polymer-rich phases

Determination of the water, total electrolyte and polymer content of the isolated polymer-rich HPMCP phases was performed thermogravimetrically under oxidative conditions (thermoanalysis

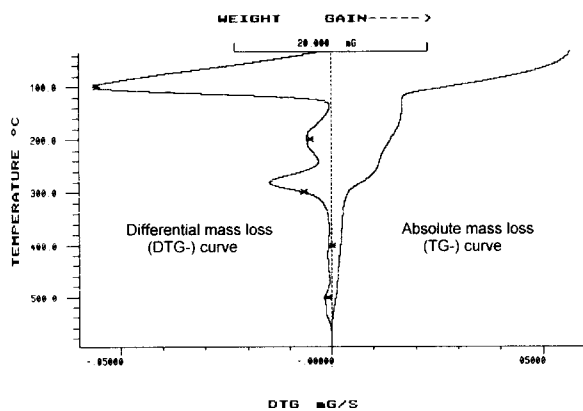


Fig. 1. Absolute mass loss (TG) curve and differentiated mass loss (DTG) curve of a polymer-rich HPMCP phase during the thermogravimetric content determination.

system TA 3000, thermoanalysis processor TC 10 A, measuring cell TG 50, microbalance M3-03, Mettler, Greifensee, Switzerland). The starting and final temperatures were 35 and 600°C respectively, and the heating rate was adjusted to 10°C/min. The measuring cell was purged with air at a flow rate of 100 ml/min. 20–40 mg samples were weighed into Alox pans. These conditions allowed for differentiated determination of the individual components of the polymer-rich phases during temperature increase (water evaporation, 35–140°C; polymer decomposition, 160–550°C; total electrolyte, residue on ignition). Fig. 1 shows the absolute mass loss (TG) curve and the differentiated mass loss (DTG) curve of a sample during thermogravimetric content determination. It should be noted that the decrease in mass occurring as a result of the conversion of sodium hydrogen phosphate into sodium pyrophosphate at approx. 200°C following the dehydration (D'Ans and Lax, 1949) was ignored since the amount was only minimal (no more than 0.05% of the total mass). The method was validated by measuring samples of known composition. The linearity of the method was determined for 1–15% (w/w) electrolyte, 2–30% (w/w) polymer and 70–96% (w/w) water. The regression coefficients for  $n = 6$  were  $r_{\text{HPMCP}} = 0.9998$ ,  $r_{\text{electrolyte}} = 0.997$  and  $r_{\text{water}} = 0.9997$ .

## 2.9. Polymer yield in the polymer-rich phases

The absolute HPMCP mass in the polymer-rich phases was determined by multiplication of the wet mass with the polymer content in the polymer-rich phases. The percentage HPMCP yield was then calculated on the basis of the polymer mass used per assay.

## 3. Results and discussion

Owing to their wetting properties and fluidity, coacervates are suitable for coating of suspended core materials due to their ability to cover the particles with a complete and homogeneous polymer coat. Moreover, all methods allowing for precipitation and gelation of an already existing coacervate coat (fixation) are advantageous for further processing of the microcapsules formed. In this paper, process parameters for the adjustment of HPMCP coacervate and precipitate phases are described by means of phase diagrams and the adequacy of these parameters for the control of the microencapsulation process is discussed.

### 3.1. Formation of coacervates and precipitates of HPMCP

When aqueous sodium sulphate solutions (20% w/w) were successively added to stirred HPMCP solutions at room temperature, the solutions became increasingly cloudy at total electrolyte concentrations of 8–9% (depending upon the polymer concentration). A coacervate phase with a typical emulsion-like appearance became visible under the microscope. Further addition of electrolyte led to the continuous dehydration of the polymer until the coacervate was transformed into a precipitate. Fig. 2 shows the microscopic images of typical coacervate and precipitate systems. The coacervate showed a clear, liquid and globular shape while the precipitate was of gel-like consistency showing streak-like 'dented' structures. When describing the phase separation behavior of HPMCP, a distinction is made between these two forms of salted-out HPMCP phases.

### 3.2. Temperature dependency of coacervate formation

The temperature dependency of HPMCP coacervate formation is illustrated by the three-component diagrams in Fig. 3. A comparison of the diagrams obtained at 20, 35, 50 and 60°C indicates that with increasing temperature both the coacervate and the precipitate phases have shifted towards lower electrolyte content at all polymer concentrations. This applies in particular to the 20–50°C temperature range, whereas a further temperature increase to 60°C has less effect on the location of the coacervate and precipitate areas. This means that less electrolyte is

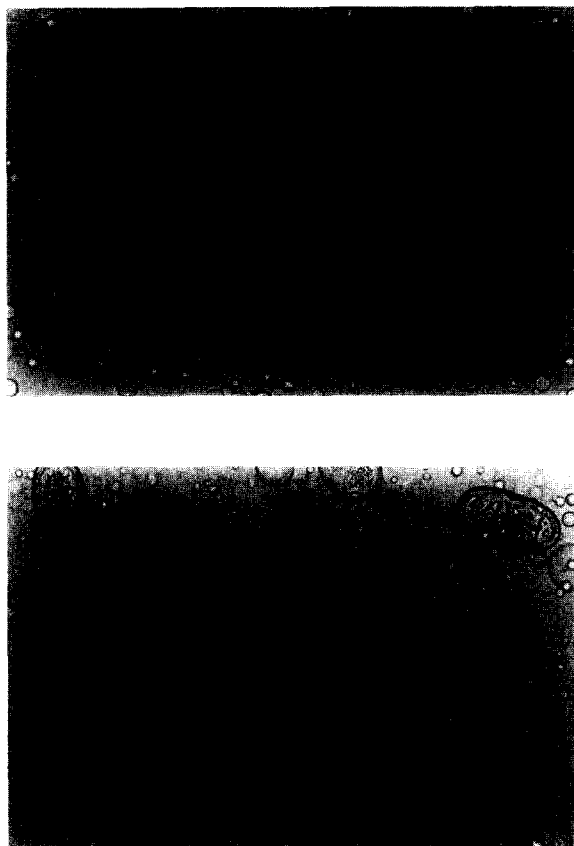


Fig. 2. Microscopic appearance of the HPMCP coacervate and precipitate phase. (A) Coacervate (5% HPMCP solution with 8.0% total electrolyte at 20°C); (B) precipitate (5% HPMCP solution with 10.0% total electrolyte at 20°C).

necessary for coacervate formation at higher temperature and that coacervates occurring at a certain temperature can be precipitated or solidified by increasing the temperature. There appears to be a synergistic effect between temperature increase and the addition of electrolyte.

In order to confirm this synergism, the coacervate formation temperature of 5% HPMCP solutions was determined as a function of the total electrolyte concentration. Fig. 4 demonstrates the relationship. With increasing total electrolyte concentration, the temperature required for coacervate formation showed an almost linear decrease from 60°C (4.9% w/w electrolyte) to 13°C (8.5% w/w electrolyte).

In order to investigate further the temperature dependency of the polymer phase separation, the coacervate and precipitate phases were isolated at various temperatures and investigated with respect to their wet weight, composition and polymer yield (Table 1). In the range from 20 to 35°C, the wet weight of the polymer-rich phases showed a marked increase. A further rise in temperature to 50°C resulted in merely a slight increase while, surprisingly, a slight drop in the wet weight occurred at 60°C. Furthermore, it became obvious from the compositions of the isolated polymer phases that increased temperature also continued to result in markedly higher HPMCP contents. Finally, a polymer content of 23.6% (w/w) was obtained at 60°C. In contrast, the percentage of total electrolyte remained almost constant over the entire temperature range. Fig. 5 summarizes the HPMCP phase separation with increasing temperature including the calculated HPMCP concentrations remaining in the equilibrium phases. The cloud point at approx. 13°C represents the temperature at which the described system starts to show phase separation. Below that temperature, a clear colloidal solution (one-phase system) exists.

Aside from the polymer content, the HPMCP yield also increased continuously with increasing temperature (Table 1). Finally, at a temperature of 60°C, 63.7% of the polymer used was available in the polymer-rich phase. In the temperature range between 20 and 50°C, in particular, HPMCP accumulated in the polymer-rich phase

while only a slight increase in the polymer yield was observed between 50 and 60°C. This may be accounted for by the drop in the wet weight occurring in this temperature range which was overcompensated by the steadily increasing HPMCP content of the polymer-rich phases. It can thus be assumed that a pronounced dehydra-

tion of the HPMCP molecules occurs within this temperature range. This seems to be attributable to the occurrence of a gelation point of the HPMCP coacervates which is also described in a comparable temperature range for the phthalate free polymers methyl and hydroxypropyl methylcellulose (Kato et al., 1986).

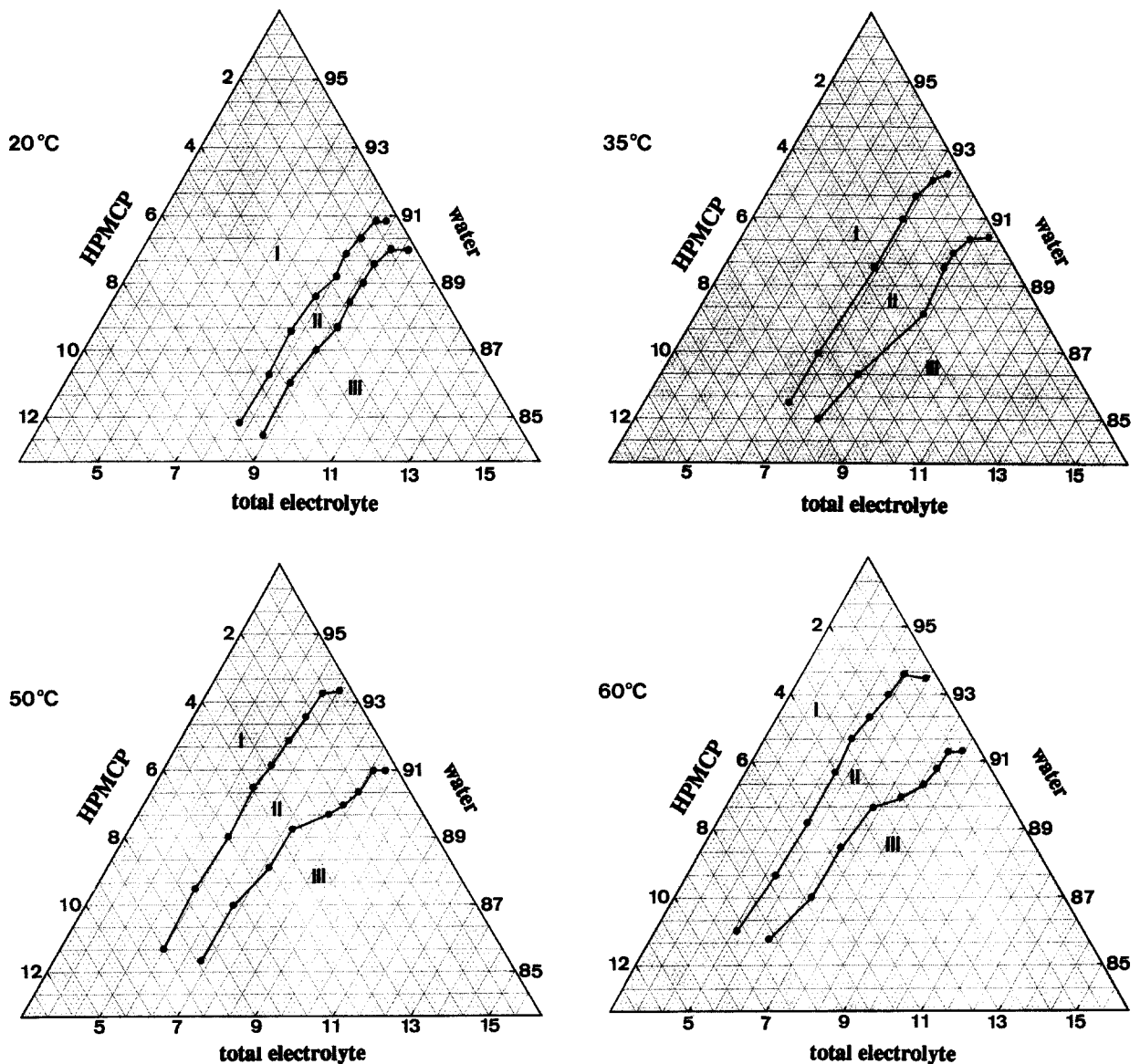


Fig. 3. Temperature dependency of HPMCP phase separation. (I) Colloidal solution; (II) coacervate in equilibrium with polymer solution; (III) precipitate in equilibrium with polymer solution.

Table 1

Wet weight and HPMCP yield of the polymer-rich phases as well as the quantitative compositions of the polymer-rich and equilibrium phases of HPMCP as a function of temperature

	Temperature of isolation			
	20° C	35° C	50° C	60° C
Wet weight <sup>a</sup> (% w/w) (S.D.)	1.17 (0.24)	7.21 (0.47)	8.87 (0.16)	8.46 (0.53)
Composition (% w/w)				
Polymer-rich phase <sup>a</sup> (S.D.)				
HPMCP	12.44 (0.42)	15.54 (0.32)	20.62 (0.78)	23.61 (0.19)
Total electrolyte	6.69 (0.05)	6.44 (0.04)	6.13 (0.06)	6.11 (0.05)
Water	80.87 (0.41)	78.02 (0.28)	73.25 (0.84)	70.28 (0.20)
Equilibrium phase <sup>b</sup>				
HPMCP	3.03	2.17	1.44	1.25
Total electrolyte	8.47	8.61	8.67	8.66
Water	88.50	89.22	89.89	90.09
Yield of HPMCP <sup>c</sup> (%)	4.7	35.7	58.3	63.7

<sup>a</sup>  $n = 4$ .

<sup>b</sup> Calculated from the results of the polymer-rich phase.

<sup>c</sup> Calculated from the results of the composition and the wet weights.

In accordance with results described in the literature on the temperature-dependent hydration behavior of methyl and hydroxypropyl methylcellulose solutions (Heyman, 1935; Levy and Schwarz, 1958; Keresztes and Kedvessy, 1965; Marriott and John, 1973; Sarkar, 1979; Mitchell et al., 1990), the temperature-dependent coacer-

vate formation of electrolyte-containing HPMCP solutions can be explained as follows: The increase in temperature leads to the reduction of hydrogen bonds which are primarily responsible for the hydration of the HPMCP ether moieties. The inorganic electrolyte solutions have a similar

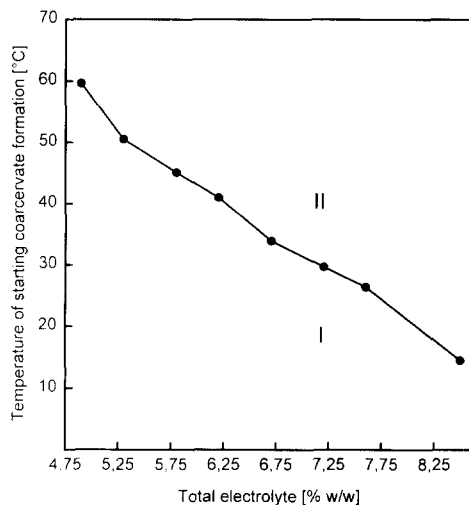


Fig. 4. Temperature of starting HPMCP coacervate formation as a function of total electrolyte concentration. (I) Colloidal solution; (II) coacervate in equilibrium with polymer solution.

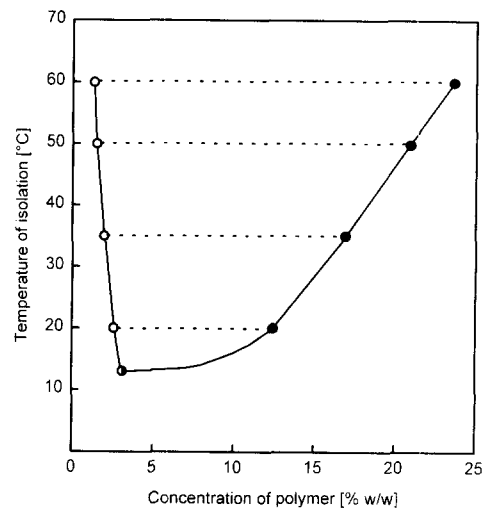


Fig. 5. Temperature-dependent phase diagram of the HPMCP system. (○) HPMCP concentration in the equilibrium phase; (●) HPMCP concentration in the polymer-rich phase; (●) cloud point.

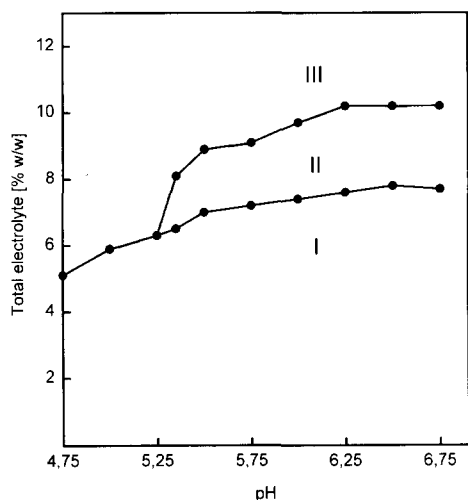


Fig. 6. pH-dependent phase diagram of the HPMCP system. (I) Colloidal solution; (II) coacervate in equilibrium with polymer solution; (III) precipitate in equilibrium with polymer solution.

effect by competing directly with the polymer for the hydrate water. The dehydration of the hydrophilic groups within the polymer (as a result of both the increase in temperature and the presence of electrolytes) leads to the increased association of hydrophobic regions of the polymer chains causing reversible phase separation in the form of coacervate droplets. The methoxyl groups appear to be of particular importance in this context (Sarkar, 1979).

### 3.3. pH dependency of coacervate formation

Since the dissociation of the anionic phthalyl moieties of HPMCP depends on the pH, the influence of this parameter on the phase separation behaviour was also investigated. Fig. 6 gives the results. With increasing pH, the electrolyte amount required to induce phase separation increased from 5.1% (w/w; pH 4.75) to 7.7% (w/w; pH 6.75). No coacervate could be formed below pH 5.25, since the polymer separated immediately in the precipitated form. Above pH 5.25, HPMCP was primarily salted out as a coacervate which was then transformed to a precipitate upon the addition of further electrolyte. While the

coacervate region extended initially with increasing pH, only marginal changes were observed throughout the further pH range investigated.

The charge density of HPMCP determined by polyelectrolyte titration and the percentage of dissociated carboxyl groups determined as a function of the pH value are shown in Fig. 7. The charge density increased from 1.66 mEq./g at pH 4.3 to 2.21 mEq./g at pH 7.0. Considering that coacervate phases occurred only in the pH range above 5.25, this means that approx. 95% of the phthalyl carboxyl groups had to be dissociated for coacervate formation. Polyelectrolyte titration and pH-dependent phase diagram were performed under not identical experimental conditions (polymer and electrolyte concentration, temperature) which may have influenced the degree of dissociation of the carboxyl groups. It can nonetheless be concluded that the almost complete dissociation of the polymer phthalyl carboxyl groups is an important prerequisite for the simple coacervate formation of HPMCP.

The relationship between the electrical charge of polymers and their ability to form simple coacervates is discussed controversially in the literature: With some polymers, a certain minimum

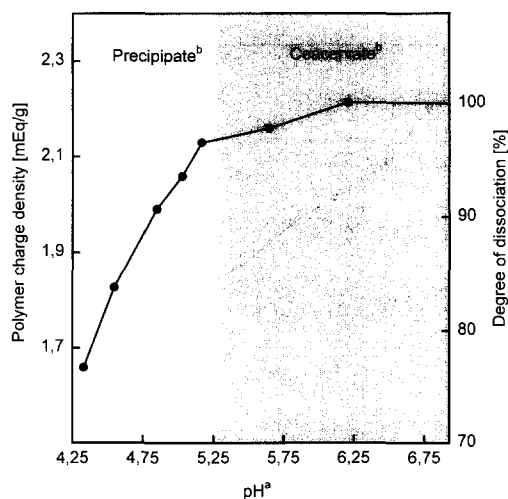


Fig. 7. Charge density and degree of dissociation of HPMCP as a function of pH. (a) HPMCP concentration of the solution, 0.025%; pH value after polyelectrolyte titration at 20°C; (b) according to Fig. 6.



charge seems to be necessary for coacervate formation (Khalil et al., 1968; Weiß et al., 1993) while, with other polymers, coacervation occurs independently of the electrical charge (Madan, 1979). There are even nonionic polymers which are assumed to form simple coacervates (Himmel, 1971; Salib et al., 1976). The results obtained with HPMCP indicate, however, that a certain charge or a minimum dissociation of the polymer phthalyl moieties is required for the formation of simple coacervate phases. It is assumed that the polymer would otherwise not be sufficiently hydrated to form sol-like coacervates containing a highly concentrated, liquid polymer phase.

#### 4. Conclusion

Coacervate formation of HPMCP is both temperature- and pH-dependent. This is attributable to the chemical structure of the polymer. While the phthalyl substituents are responsible for the pH-dependent hydration due to the fact that these moieties are capable of dissociation, the hydroxypropyl and methyl substituents of HPMCP are the reason for thermal phase separation and the tendency to gelation at higher temperatures.

Important process variables in the microencapsulation with HPMCP by simple coacervation are thus the pH value, the total electrolyte concentration and the temperature. The pH value of the HPMCP solution must be sufficiently high, since this is essential for the formation of coacervate phases on the whole. Regulation of the temperature can be used to further control the microencapsulation process: Increasing temperature allows for the separation of additional polymer-rich coacervate phase, thus increasing the polymer yield. Furthermore, the gelation of the coacervate at higher temperatures provides the possibility of performing certain recovery steps of the microencapsulation at increased temperatures. Overall, for the microencapsulation with HPMCP (Weiß et al., 1995) a temperature course is recommended that runs contrary to that described for cellulose acetate phthalate.

#### References

- Bakan, J.A. and Sloan, F.D., Microencapsulation of drugs. *Drug Cosmet. Ind.*, 110 (1972) 34–121.
- Bauer, K.H., Lehmann, K. and Osterwald, H.P., Rothgang, G., *Überzogene Arzneiformen*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1988, p. 221.
- Calanchi, M., Process for preparing microcapsules in a liquid vehicle. *European Patent Specification EP 0 038 585*, 1984.
- D'Ans, J. and Lax, E., *Taschenbuch für Chemiker und Physiker*, Springer, Göttingen, 1949, p. 246.
- Fekete, P. and Tibor, K., Microcapsules for oily materials. *Hung. Teljes HU 25 023*, 1983.
- Florence, A.T. and Attwood, D., *Physicochemical Principles of Pharmacy*, Chapman and Hall, New York, 1982, p. 212.
- Heyman, E., Studies on the sol-gel transformations: I. The inverse sol-gel transformation of methylcellulose in water. *Trans. Faraday Soc.*, 31 (1935) 846–864.
- Himmel, R.K., Method of making microscopic capsules. *US Patent 3 594 326*, 1971.
- Kato, T., Kozaki, N. and Takahashi, A., Lubrication enhancement by surface gelation of thin liquid films of methylcellulose and hydroxypropyl methylcellulose solutions. *Polym. J.*, 18 (1986) 189–191.
- Keresztes, A. and Kedvessy, G., Untersuchungen über die Hydratation der Methylcellulose. *Pharmazie*, 20 (1965) 371–375.
- Khalil, S.A.H., Nixon, J.R. and Carless, J.E., Role of pH in the coacervation of the systems: gelatin-water-ethanol and gelatin-water-sodium sulphate. *Pharm. Pharmacol.*, 20 (1968) 215–225.
- Levy, G. and Schwarz, T.W., The effect of certain additives on the gel point of methylcellulose. *J. Am. Pharm. Assoc. Sci. Ed.*, 47 (1958) 44–46.
- Madan, P.L., Methods of preparing microcapsules: coacervation, or phase separation. *Pharm. Technol. Int.*, 51–56 (1979/9).
- Marriott, P.H. and John, E.G., Influence of electrolytes on the hydration of methylcellulose in solution. *J. Pharm. Pharmacol.*, 25 (1973) 633–639.
- Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., The influence of additives on the cloud point, disintegration and dissolution of hydroxypropylmethylcellulose gels and matrix tablets. *Int. J. Pharm.*, 66 (1990) 233–242.
- Merkle, H.P., Zur Mikroverkapselung fester Arzneistoffe mittels Koacervation. Ph.D Thesis, ETH Zürich (1972).
- Merkle, H.P. and Speiser, P., Preparation and in vitro evaluation of cellulose acetate phthalate coacervate microcapsules. *J. Pharm. Sci.*, 62 (1973) 1444–1448.
- Nixon, J.R., Khalil, S.A.H. and Carless, J.E., Effect of electrolytes on coacervation of the systems gelatin-water-ethanol and gelatin-water-sodium sulphate. *J. Pharm. Pharmacol.*, 20 (1968) 348–354.
- Nixon, J.R. and Harris, M.S., Coacervate techniques for the preparation of microcapsules of possible pharmaceutical application. In Gorrod, J.W., Gibson, G.G. and Mitchard,

- M. (Eds), *Development of Drugs and Modern Medicines*, VCH-Verlagsgesellschaft, Weinheim/Ellis Horwood, Chichester, 1986, p. 425–434.
- Salib, N.N., El-Menshaw, M.E. and Ismail, A.A., Preparation and evaluation of the release characteristics of methylcellulose micropellets. *Pharm. Ind.*, 38 (1976) 577–580.
- Sarkar, N., Thermal gelation properties of methyl and hydroxypropyl methylcellulose. *J. Appl. Polym. Sci.*, 24 (1979) 1073–1087.
- Sparks, R.E., Microencapsulation. In Kirk, R.E. and Othmer, D.F. (Eds), (Ed.), *Encyclopedia of Chemical Technology*, Wiley, New York, Vol. 15, 3rd Edn, 1981, pp. 470–494.
- Weiß, G., Mikroverkapselung von Ibuprofen mit magensaftresistenten Polymeren durch einfache Koazervation. Ph.D Thesis, University of Regensburg (1991).
- Weiß, G., Knoch, A., Laicher, A., Stanislaus, F. and Daniels, R., Influence of polymer charge density on the simple coazervation of cellulose acetate phthalate. *Eur. J. Pharm. Biopharm.*, 39 (1993) 239–243.
- Weiß, G., Knoch, A., Laicher, A., Stanislaus, F. and Daniels, R., Simple coazervation of hydroxypropyl methylcellulose phthalate: II. Microencapsulation of ibuprofen. *Int. J. Pharm.*, 124 (1995) 97–105.