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Influence of Polymer Charge Density on the Simple Coacervation of Cellulose Acetate Phthalate

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Summary

In order to mask the unpleasant taste of ibuprofen, drug crystals were encapsulated with the enteric polymer cellulose acetate phthalate (CAP), by a simple coacervation method through the addition of a 20% (m/m) Na_2SO_4 solution. The effect of the pH value on the phase properties of CAP was studied in the absence of the drug. The appearance of the system was monitored microscopically in order to identify the existence of either a coacervate or a precipitate. In addition, the variation of the charge density of the polymer CAP with pH was determined using a particle charge detector. At least 80% of the phthalyl residues had to be dissociated for the formation of a coacervate phase.

The pH decreased upon the addition of ibuprofen and a precipitate rather than a coacervate was formed. The quantitative determination of the composition of the polymer rich phase in the presence of ibuprofen showed a significant increase in the amount of polymer which was salted out. By adjusting the pH with acetic acid, it was demonstrated that these differences were mainly due to the pH-shift induced by dissolved drug molecules.

In order to utilise the higher polymer yield of the precipitated system, ibuprofen microcapsules were prepared under these conditions. Scanning electron micrographs revealed that the ibuprofen crystals were coated completely and were nonagglomerated. Pinholes in the shell of a few microcapsules were attributed to the mechanical stress to which the microcapsules were subjected during their recovery from the suspension.

1 Introduction

Ibuprofen, a non-steroidal anti-rheumatic drug, has a bitter taste and is irritating to the throat. Since ibuprofen is mainly absorbed in the small intestine, no negative impact on its bioavailability is to be expected when its unpleasant taste is masked by coating with an enteric polymer (1). Furthermore, the formulation of a multiparticulate system seems to be preferable because a more uniform absorption of the drug is to be expected when compared to a single-unit dosage form. An enteric coating instead of a hydrosoluble film has the advantage that the resulting microcapsules can also be used for dosage forms which are dispersed in an aqueous medium before administration, e.g. dispersable tablets, or granules. Several methods are known for the microencapsulation of drugs (2). Due to the relatively small size of the ibuprofen crystals to be encapsulated, a coacervation method seems to be preferable (3). The term „coacervation" describes a partial miscibility occurring in polymer systems (4). Simple coacervation is a process, wherein phase separation is brought about by the addition of hydrophilic substances like Na_2SO_4. Under optimum conditions, the major part of the polymer is found in the colloid-rich phase (coacervate phase), while the solution at equilibrium contains only small amounts of the polymer. The coacervate phase, which is salted out, can be deposited on dispersed particles and therefore be used for the microencapsulation of a core material. Unfortunately, only little information about the coacervation behaviour of enteric polymers is available. Merkle and Speiser published results on the microencapsulation of phenacetin using a simple coacervation technique with CAP as enteric polymer (5, 6). Based on their results, we started our studies on the microencapsulation of ibuprofen. In contrast to the nonionic phenacetin, ibuprofen, being a weak acid and although only sparingly soluble, can influence the pH of the coacervation system.

The solubility of a polyacid depends on the dissociation of its acidic groups, which is determined by the pK_A of these groups and the pH of the aqueous medium (7). Since the formation of the coacervate phase depends on the hydration of the polymer, some impact of the drug molecule on the phase behaviour of CAP was to be expected. In this paper, the pH dependence of the simple coacervation of CAP was investigated. The ability of CAP to form a coacervate was related to its charge density. The influence of dissolved ibuprofen on the quantitative composition of the coacervate phase was assessed. Finally, microcapsules of ibuprofen were prepared using this system.

2 Materials and Methods

2.1 Materials

Ibuprofen (Lot: 223 964, Boots Co., GB-Nottingham) had a mean particle size of 72 µm (99% < 140 µm); cellulose acetate phthalate (Lot: 90 401, Eastman Chemical, USA-Kingsport, Tennessee) had a specified content of acetyl residues of 23.41% and a phthalyl content of 34.51%; 0.001 N poly-di-allyl-di-methyl-ammonium chloride (poly-DADMAC) was purchased from Muetek

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(D-Herrsching). They were used as received. All other chemicals were of analytical grade.

2.1.1 pH-dependent phase diagram

2% solutions of CAP in 1% $Na_2HPO_4 \cdot 2\,H_2O$ were adjusted to the designated pH value by adding small amounts of 0.1 N NaOH or 1% acetic acid under continuous stirring. Subsequently, the solutions were heated to 60 °C and small portions of aqueous Na_2SO_4 (20%) solution were added. After each addition, a small sample was taken and its appearance was observed microscopically. The system was then classified as either a colloidal solution, a coacervate or a precipitate.

2.1.2 Polyelectrolyte titration

The determination of polymer charge is based on the polyelectrolyte titration method developed by Schempp et al. (8, 9). The basic principles of this method are described elsewhere (10).

0.1 ml of a CAP solution (2% m/m) were pipetted into the PTFE reaction vessel of the particle charge detector PCD 02 (Muetek) and diluted with 10 ml of water. Subsequently, the pH was adjusted by adding 0.05% acetic acid or 0.01 N NaOH, respectively. The polymer charge density was determined by titrating with 0.001 N poly-DADMAC until the PCD potential dropped to zero. The required amount of titrant was proportional to the number of charges on the CAP. After titration and a 10 min equilibration period, the pH value of the mixture was measured using a digital pH-meter (type 644; Knick, D-Berlin) and a glass electrode (type 405 NSK 7; Ingold Meßtechnik, D-Steinbach).

2.1.3 Composition of the coacervate phase

200 g of a 2% solution of CAP in 1% $Na_2HPO_4 \cdot 2\,H_2O$ were heated to 60 °C, 59.4 g of a 20% Na_2SO_4 solution were added and the system was allowed to equilibrate for 15 min. Subsequently, the samples were centrifuged at 31.300 g for 5 min at 60 °C. The supernatant equilibrated phase was carefully removed and the remaining coacervate was weighed. The percentage of the coacervate (wet weight) was calculated as 100 ∗ (mass of coacervate/total mass of the system).

The following additional steps were necessary for studies with the drug. Ibuprofen was suspended in the CAP solution. After addition of one third of the predetermined amount of a 20% Na_2SO_4 solution, the undissolved part of the drug was removed by filtration (glass fibre microfilter 0.7 µm, Whatman, GB-Maidstone). The filtered solution was weighed and the residual amount of the Na_2SO_4 solution was added.

The composition of the coacervate phase was determined by a thermogravimetric (TG) method. The thermoanalytical system (TA 3000, Mettler, CH-Greifensee) consisted of a thermoanalysis processor TC 10 A, a TG measuring cell TG 50 and a microbalance M3-03. The starting temperature was 35 °C, the final temperature 600 °C and the heating rate was set at 10 °C min^{-1}. The TG cell was purged with air and the flow rate was adjusted to 100 ml min^{-1}. 20–40 mg samples were weighed into Alox pans.

The weight loss during the TG analysis could be interpreted as follows. In the range from 35 to 140 °C water evaporated, in the range from 160 to 550 °C polymer and drug decomposed and the residue at 600 °C consisted of the electrolyte. The polymer content was calculated from the TG analysis by subtracting the ibuprofen content determined by HPLC from the total of polymer and drug.

The method was validated by measuring samples of a known composition. The linearity of the method was determined for 1–15% electrolyte, 2–30% polymer, and 70–96% water. The regression coefficients for n = 6 were $r_{electrolyte} = 0.997$, $r_{polymer} = 0.9998$, and $r_{water} = 0.9997$.

2.1.4 Ibuprofen assay

Ibuprofen in the coacervate phase was determined by a HPLC method. The chromatographic system consisted of a LKB 2150 HPLC-pump (Pharmacia LKB, D-Freiburg), a Spectra-Physics SP 8875 injector (Spectra Physics, D-Darmstadt) a LKB 2151 UV-detector set at 220 nm and a Spectra-Physics SP 4290 integrator. The column was a Nucleosil C18 100, 5 µm (250 x 4.6 mm) (Machery-Nagel, D-Düren). The mobile phase consisted of methanol / 0.01 M KH_2PO_4 (adjusted to pH 3.0 with phosphoric acid) (70 : 20 v/v) and the flow rate was set at 1.0 ml min^{-1}. The injected volume was 20 µl. The linearity of the method was verified for a concentration range of 218 to 1088 ng per 20 µl. The coefficient of variation for 6 samples was 0.71%. The recovery was 100.5%.

2.1.5 Preparation of microcapsules

The preparation of the ibuprofen microcapsules was performed using a laboratory processing unit IKA LR-A 250 (Janke & Kunkel, D-Stauffen) equipped with a stirrer motor IKA RE 162 A S3 and a double 4-blade turbine agitator. The stirring speed was set at 350 rpm.

4 g of CAP were dispersed in a solution of 2 g $Na_2HPO_4 \cdot H_2O$ in 194 g of pure water and stirred for 10 h at room temperature to ensure complete dissolution of the polymer. The polymer solution was then heated to 60 °C and 13.33 g of ibuprofen were added. Subsequently, 59.4 g of a 20% (m/m) Na_2SO_4 solution were added gradually under stirring. When the formation of the coacervate phase was complete, the system was slowly (within 1 h) cooled to 15 °C. In order to remove excess polymer from the aqueous solution, the soft microcapsules were decanted 3 times and washed with 200 g of a 5% (m/m) Na_2SO_4 solution. Subsequently the walls of the microcapsules were hardened by adding 100 g of acetic acid (5%) and stirring for 30 min. Further purification of the microcapsules was performed by washing 3 times with 200 g acetic acid (0.25%). The supernatant was decanted, the microcapsules were filtered and then air-dried for 24 h. The dry microcapsules were passed through a 500 µm sieve to remove coarse particles and agglomerates.

2.1.6 Scanning electron microscopy

The microcapsules were fixed on aluminium mounts with the help of a thin layer of conductive silver paint. The microphotographs were taken on a Stereoscan 250 MK3 (Cambridge Instruments, GB-Cambridge) scanning electron microscope after coating the samples with a gold layer, using a sputter coater S 150 (Edwards Kniese, D-Marburg).

3 Results and Discussion

3.1 pH dependency of coacervate formation

When a polymer is salted out from a homogenous colloidal solution, phase separation may occur in various forms. Bungenberg de Jong classified phase separation processes as crystallisation, coacervation, precipitation and the formation of a gel (4). Definitions of these different colloidal states are given by the IUPAC (11). According to the IUPAC nomenclature, precipitation occurs in colloidally unstable systems and is observed in the form of a coagulum or flocs, whereby both terms can be used interchangeably. Coacervation, on the other hand, is the separation of colloidal systems into two liquid phases.

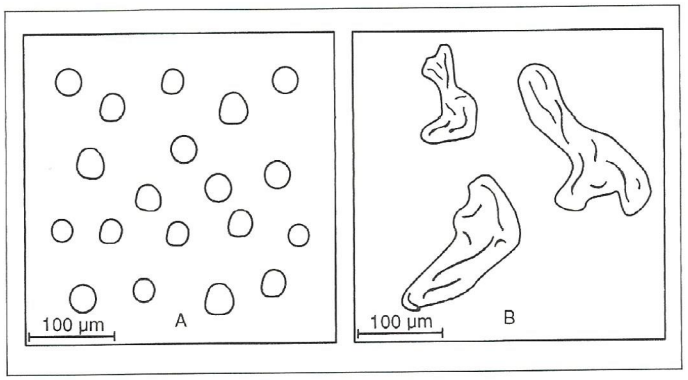

Fig. 1 Schematic representation of the microscopical appearance of a typical coacervate (A) and precipitate (B)

The phase properties of a CAP solution were examined by adding small increments of a Na_2SO_4 solution. The samples were assessed microscopically to identify the existence of either a coacervate or a precipitate. The distinction between them was made according to Fig. 1. The formation of an emulsion-like system with homogeneous droplets of the colloid-rich phase was identified as coacervate. All other kinds of phase separation including "structured", irregular agglomerates, were classified as precipitate. No attempts were made to identify other regions of the phase diagram.

Fig. 2 shows the influence of the pH on the phase properties of CAP. As the pH increased, the amount of salt necessary to induce a phase separation increased from about 3.5% (at pH 5) to approximately 4.5% (at pH 7). It was not possible to form a coacervate at pH values below 5.5, presumably because the hydration of the polymer was insufficient to produce a concentrated, liquid-like phase. Above pH 5.5, CAP was salted out as a coacervate which was transformed to a precipitate upon the addition of further electrolyte. With increasing pH, the coacervate region extended over a wider electrolyte concentration. Only marginal changes in the phase behaviour were observed above pH 6.25.

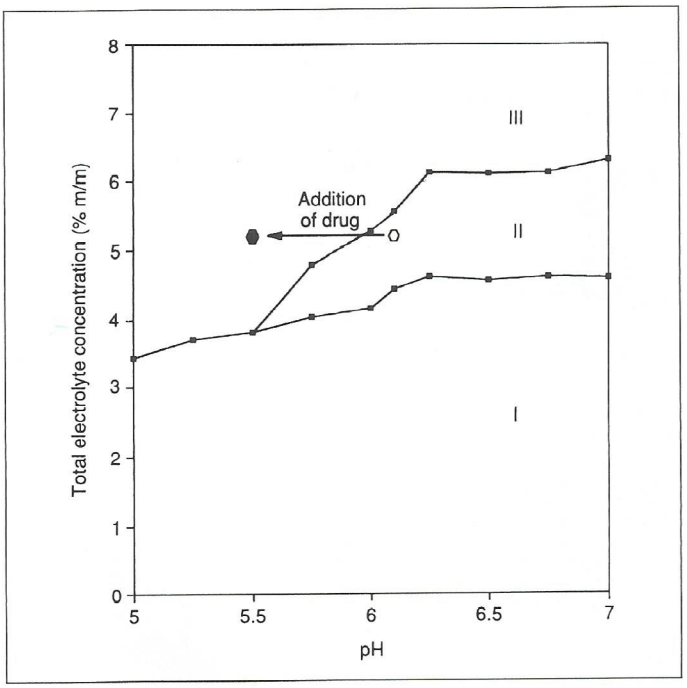

Fig. 2 Phase diagram of a 2% CAP solution as a function of the pH at 60 °C and influence of ibuprofen on the microscopic appearance of the polymer-rich phase after salting out
I: homogeneous colloidal solution
II: coacervate in equilibrium with polymer solution
III: precipitate in equilibrium with polymer solution
o : without drug
● : with drug

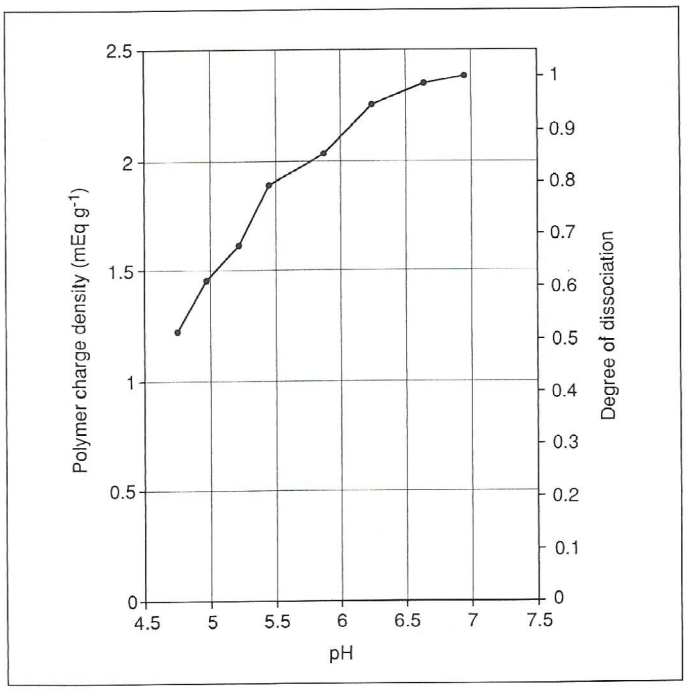

Fig. 3 Influence of the pH on the charge density and the degree of dissociation of CAP

The relationship between electrical charge of a polymer and the ability to form simple coacervates is discussed controversially in the literature (2, 12, 13, 15, 16). However, the result of this phase study illustrates the great impact of the pH on the coacervation behaviour of CAP. In accordance with the observations from Khalil (13), the above results indicated clearly that a minimum pH value, corresponding to a minimum degree of dissociation, was necessary to allow the formation of a coacervate phase of CAP.

The degree of dissociation of CAP at various pH values was determined by polyelectrolyte titration. The result is shown in Fig. 3. The polymer charge density raised from 1.18 mEq g^{-1} polymer, at pH 4.75, to a maximum of 2.32 mEq g^{-1} polymer at pH 7. Assuming that all phthalic acid carboxylic groups were dissociated at pH 7, the degree of dissociation, α can be calculated as follows:

$$\alpha = \frac{\text{charge density}}{\text{charge density at pH 7}} \quad (1)$$

According to Eq. 1, the degree of dissociation at the minimum coacervation pH value, $\alpha_{pH\,5.5}$, was calculated to be 0.8.

The relationship between pH and pK_{app}, the apparent pK_A of a polyacid, can be described by Eq. 2.

$$pH = pK_{app} + \log\left(\frac{\alpha}{1-\alpha}\right) \quad (2)$$

From Fig. 3 the apparent pK_A can be extrapolated for $\alpha = 0.5$ to be 4.7, which is close to the result published by Ibrahim et al. (17).

It can thus be concluded that the pH of the CAP system should be approximately 1 unit higher than the apparent pK_A in order to avoid the precipitation of the polymer.

Taking into account these results and in order to avoid (1) the hydrolysis of the ester groups of CAP and (2) excess dissolution

Table 1 Influence of dissolved ibuprofen on the pH value of a 2% CAP solution

System	Temperature	pH (±0.05)
2% CAP without drug	20 °C	6.05
2% CAP with drug	20 °C	5.85
2% CAP without drug	60 °C	5.95
2% CAP with drug	60 °C	5.50

of the weak acid ibuprofen, the composition for the CAP solution to be used for the microencapsulation process was chosen as follows: 10 g CAP, 20 g $Na_2HPO_4 \cdot H_2O$, and 970 g water. The pH of the resulting polymer solution was 6.05.

3.2 Influence of the drug on the coacervation of CAP

The solubility of ibuprofen in this CAP solution was determined to be less than 0.1% (14). The influence of the dissolved drug on the pH of the CAP solution is given in Table 1.

Although the drug is only sparingly soluble in this medium, the pH decreased significantly. This effect became more pronounced at higher temperature due to the solubility of ibuprofen increasing with temperature. As the dissociation of the carboxylic groups on the CAP was not strongly dependent upon temperature, the pH of a CAP solution without drug was only slightly affected by heating.

The influence of this pH-shift caused by the drug on the phase behaviour of CAP is shown in Fig. 2. After the addition of ibuprofen, the system appeared as a precipitate rather than a regular coacervate.

To quantify this effect, the composition of a system with and without drug was determined. The results are summarized in Table 2. Comparing both systems, the most prominent effect was observed on the CAP yield, i.e. the fraction of total polymer salted out into the polymer-rich phase. Upon the addition of ibuprofen, this value showed a threefold increase and exceeded 47%. This effect is a result of an increase of both the CAP content and the volume (wet weight) of the coacervate phase.

If one assumes that the impact of ibuprofen on the phase separation of CAP is due to the change in pH, without any specific polymer/drug interactions, the same effect should be obtained by adjusting the pH with any kind of acid. Therefore, the phase separation was studied after adjusting the pH of the system to 5.5 with acetic acid. The results from these experiments are shown in Table 3.

There is no significant difference in the wet weight, the CAP concentration and the polymer yield between the two systems

Table 3 Wet weight, CAP content and CAP yield of a coacervate phase of CAP without ibuprofen, with ibuprofen and without ibuprofen but pH adjustment with acetic acid (mean value ± SD; n = 4)

	without ibuprofen (% m/m)	with ibuprofen (% m/m)	with acetic acid (% m/m)
Wet weight	2.33 ± 0.33	6.86 ± 0.54	6.41 ± 0.26
CAP content	8.87 ± 0.18	10.64 ± 0.70	10.89 ± 0.88
CAP yield	13.38 ± 1.88	47.30 ± 5.28	45.21 ± 4.08

Table 2 Quantitative composition of coacervate and equilibrium phase of CAP in the absence and presence of ibuprofen

Wet weight of the polymer-rich phase (mean value ± SD; n = 4)	without ibuprofen (% m/m)	with ibuprofen (% m/m)
	2.33 ± 0.33	6.86 ± 0.54
Composition of the polymer-rich phase (mean value ± SD; n = 4)	without ibuprofen (% m/m)	with ibuprofen (% m/m)
CAP	8.87 ± 0.18	10.87 ± 0.70
Ibuprofen	—	0.23 ± 0.03
Total electrolyte	5.04 ± 0.04	5.06 ± 0.21
Water	86.09 ± 0.17	84.07 ± 0.65
Composition of the equilibrium solution (calculated from results of the polymer-rich phase)	without ibuprofen (% m/m)	with ibuprofen (% m/m)
CAP	1.37	0.87
Ibuprofen	—	0.1
Total electrolyte	5.20	5.21
Water	93.43	93.82
CAP yield in the polymer-rich phase	without ibuprofen (% m/m)	with ibuprofen (% m/m)
	13.4	47.3

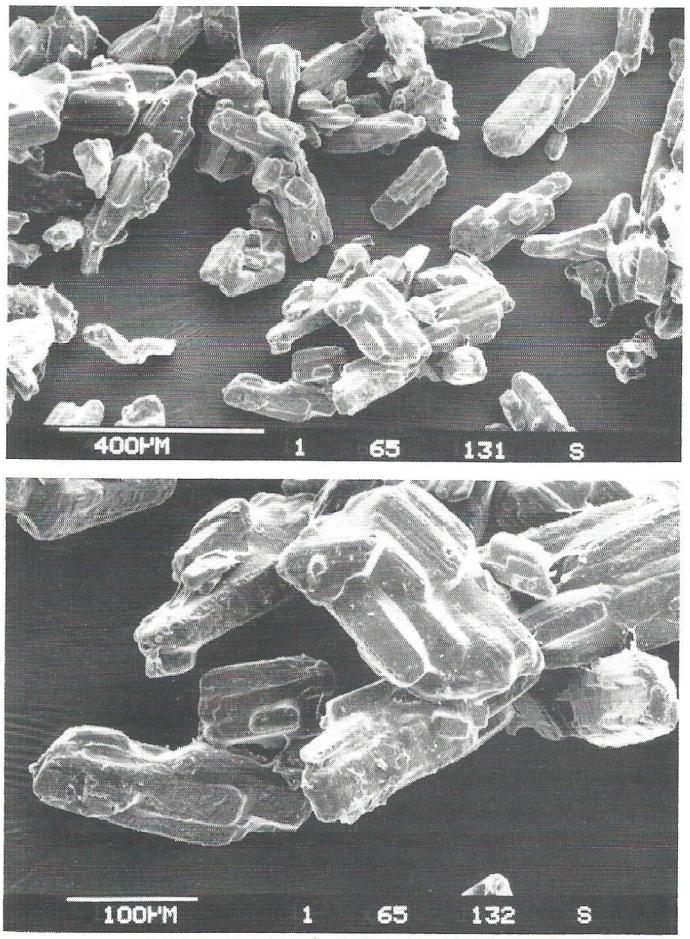

Fig. 4 Scanning electron micrographs of the surface structure of CAP microcapsules

which were identical with respect to pH. The increase in the polymer yield in the presence of ibuprofen could therefore be attributed to the change in the pH.

3.3 Microencapsulation of ibuprofen

The success of a microencapsulation process depends to a great extent upon the amount of polymer which can be deposited around the core material. With a coacervation method, the quality of the final product is influenced by the polymer yield. A smooth and almost complete coating will result only if the coalescence of the individual particles of the coating material is sufficiently high. In addition, it is also favourable from an economic point of view to run the encapsulation process with a optimum polymer yield.

An attempt was made to encapsulate ibuprofen crystals using a CAP system not forming a regular coacervate phase. Scanning electron micrographs of the resulting ibuprofen microcapsules are shown in Fig. 4.

Ibuprofen was coated completely under the experimental conditions chosen. Most of the crystals were coated individually and only few aggregates were formed. Ruptures of the coating at the edges of the crystals were not observed, indicating the suitability of this encapsulation process. However, some pinholes (2–4 μm in diameter) were detected at a higher magnification. According to their appearance and location on the flat side of the crystals these holes were attributed to the mechanical stress encountered during the recovery of the microcapsules from the suspensions.

4 Conclusions

The phase separation of CAP is largely dependent on the degree of dissociation of the polymer. The formation of a regular coacervate was only possible when more than 80% of the phthalyl moieties on the CAP were dissociated, providing a sufficiently high hydration of the polymer. The polymer yield in the salted out phase could be significantly increased by decreasing the pH. Although at lower pH values no regular coacervate phase was formed, ibuprofen could be encapsulated resulting in microcapsules of high quality.

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