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Simple coacervation of hydroxypropyl methylcellulose phthalate (HPMCP)
II. Microencapsulation of ibuprofen

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Abstract

Microencapsulation with hydroxypropyl methylcellulose phthalate (HPMCP) through simple coacervation by the addition of 20% (w/w) sodium sulphate solution was investigated on the basis of the temperature-dependent coacervate formation of the polymer. The non-steroidal antirheumatic drug ibuprofen was used as model substance. This paper describes the microencapsulation process and the resulting microcapsules. Furthermore, the influence of docusate sodium present during encapsulation was investigated with respect to the phase separation behaviour of HPMCP and the wall characteristics of the microcapsules. Simple coacervation of HPMCP is a suitable method for the microencapsulation of ibuprofen. The coacervate enveloped the suspended drug which had no effect upon the phase separation of the polymer owing to the low solubility of ibuprofen in the HPMCP solution. The microencapsulation process was controlled by temperature increase: additional coacervate for the coating of the drug crystals was formed and the resulting coacervate shells were subsequently prehardened by jelling. This enabled the recovery and isolation of the microcapsules to be performed. The coating of the drug crystals occurred as twins and multiples when microencapsulation was performed without surfactant; SEM micrographs demonstrated the high shell quality of the microcapsules and polymer yield calculations showed the almost complete utilization of the coacervate for enveloping the drug crystals in surfactant-free systems. Small amounts of docusate sodium present during microencapsulation resulted in a more individual encapsulation of the ibuprofen crystals; however, coating by the coacervate was incomplete and the microcapsules showed clod-like polymer shell deficiencies. As a consequence, an increased release rate of ibuprofen at pH 4.0 was observed compared to microcapsules prepared without using surfactant. Since docusate sodium had no effect upon the phase separation behaviour of HPMCP under the conditions used for microencapsulation, the incomplete polymer coating was attributed to competition between surfactant and coacervate for the solid/liquid interface.

Keywords: Microencapsulation; Coacervation; Hydroxypropyl methylcellulose phthalate; Ibuprofen; Surfactant; Taste masking; Enteric

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1. Introduction

The coacervate formation of hydroxypropyl methylcellulose phthalate (HPMCP) is both pH- and temperature-dependent (Weiß et al., 1995). This is attributable to the chemical structure of the polymer. While the methyl and hydroxypropyl substituents are responsible for the temperature-dependent hydration and the tendency to gelation of the polymer at higher temperatures, the phthalyl substituents are the cause of pH-dependent hydration and coacervate formation. Therefore, a temperature gradient which runs contrary to that described for cellulose acetate phthalate (Merkle and Speiser, 1973) appears to be suitable for microencapsulation with HPMCP by simple coacervation. This study describes the feasibility of such a process and the quality of the resulting microcapsules.

Ibuprofen, a poorly water soluble drug belonging to the non-steroidal antirheumatic agents with arylpropionic acid structure (Reynolds, 1989), was used as model compound. Ibuprofen possesses a bitter taste and is irritating to the throat. Since ibuprofen is mainly absorbed in the small intestine (Geisslinger et al., 1989) its unpleasant taste can be masked by an enteric coating without loss of bioavailability. Furthermore, a multiparticulate system was thought to be preferable to a single-unit dosage form, since the small particles spread out more uniformly in the gastro-intestinal tract (Stanislaus and Huber, 1987).

2. Materials and methods

2.1. Materials

Ibuprofen distributed by Boots (Ibuprofen 50® lot no. 223964, Boots Co. PLC, Nottingham, UK) was chosen as active ingredient and was used without further treatment; hydroxypropyl methylcellulose phthalate (HP 55® lot no. 906077, Shinetsu Chemicals, Tokyo, Japan) had a specific content of 19.2% (w/w) methyl, 5.9% (w/w) hydroxypropyl and 32.4% (w/w) phthalyl moieties; docusate sodium (USP XXII) was purchased from Merck (Darmstadt, Germany) and was used in a 0.01 M aqueous solution; 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

All trials were performed with polymer solutions containing 50 parts HPMCP, 20 parts sodium monohydrogen phosphate dihydrate and 930 parts demineralized water. The solutions had a pH value of 5.45 (±0.05) and were prepared as described in the accompanying paper (Weiß et al., 1995). All trials were performed with polymer solutions stored at room temperature for a maximum of 2 weeks.

2.3. Wet weight, composition and polymer yield in the polymer-rich phases

The isolation of the polymer phases was performed as described previously (Weiß et al., 1995). The procedure had to be slightly modified in the case of ibuprofen- and surfactant-containing systems: Ibuprofen (33.3 g) was suspended in the 5% (w/w) HPMCP solution (200.0 g) at 35° C for approx. 15 min. After addition of one-third of the predetermined amount of the 20% (w/w) sodium sulphate solution (total 118.7 g), the undissolved part of the drug was removed by filtration (glass fiber microfilter 0.7 μm, Whatman, Maidstone, UK). The clear solution was then weighed and the calculated residual amount of the sodium sulphate solution was added. In the surfactant-containing system, the calculated amount of a 0.01 M solution of docusate sodium (total 0.9 g) was also added after filtration of the drug crystals in order to avoid adsorption-related loss of the surfactant.

The wet weights, compositions and polymer yields of the coacervates were determined as previously described (Weiß et al., 1995). In the case of drug-containing systems, the polymer content was calculated from the thermogravimetric analy-

sis by subtracting the ibuprofen content determined by HPLC from the total of polymer and drug.

2.4. Preparation of microcapsules

The microencapsulation of ibuprofen was performed in a double-jacketed reactor (IKA Laborreaktor LR-A 250 with stirrer RE 162A S3, Janke and Kunkel, Staufen, Germany) equipped with a four-armed stirrer on two levels. The stirring speed was set constant at 350 rpm.

The microencapsulation process is illustrated in Fig. 1: 200 g of the 5% (w/w) polymer solution were filled into the reactor and optionally 0.9 g docusate sodium solution (0.01 M) were added. 33.3 g ibuprofen were suspended at 20° C for approx. 15 min. Subsequently, 118.7 g of a 20% (w/w) sodium sulphate solution were added gradually within 15 min under continuous stirring. The system was then heated slowly to 50° C at a rate of 0.5° C/min (Haake F2-K water bath with PG10 temperature control unit, Haake Meßtechnik, Karlsruhe, Germany) to further induce phase separation and to preharden the HPMCP coacervate envelopes. While adding sodium sulphate solution and during heating, samples were withdrawn and examined microscopically (Olympus CK Inversmikroskop, Olympus Optical, Hamburg, Germany). The microcapsules were then decanted and washed three times with 200 g of an 8.5% (w/w) sodium sulphate solution at 50° C. Subsequently, the microcapsule walls were hardened by adding 150 g acetic acid (5% w/w) and stirring for 30 min. Further purification of the microcapsules was performed by washing three times with 200 g diluted acetic acid. The microcapsules were then filtered and air-dried on trays for 48 h. The dry microcapsules were carefully passed through a 500 μm sieve to

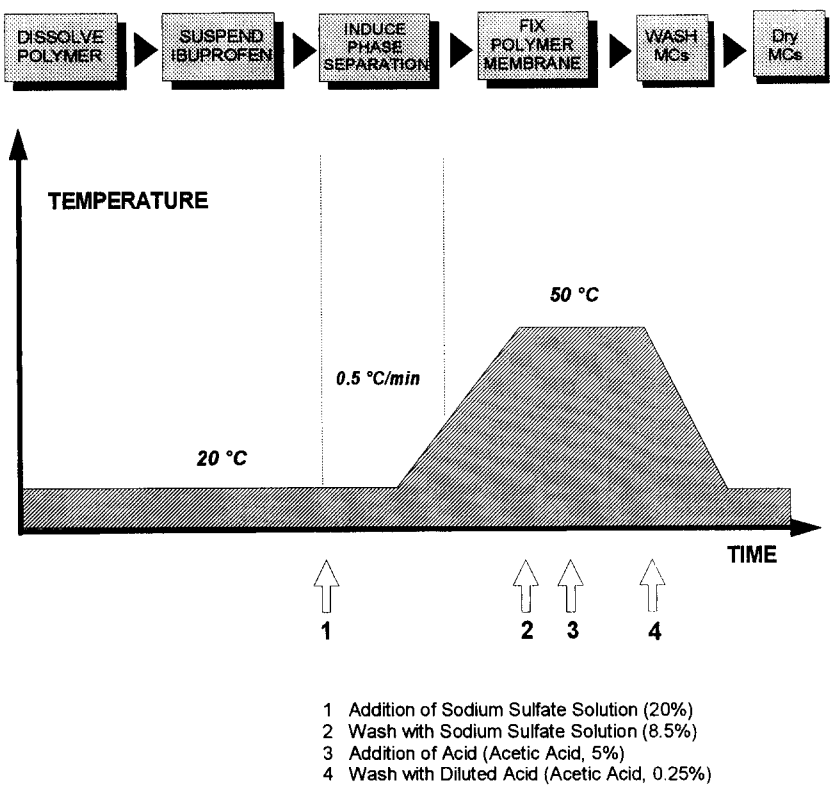

Fig. 1. Flow chart for the microencapsulation of ibuprofen by simple coacervation with HPMCP.

remove coarse particles and agglomerates. The yield of microcapsules with a particle size < 500 μm was 98%.

2.5. Ibuprofen assay

The ibuprofen content in the isolated polymer phases, microcapsules and samples withdrawn during the dissolution test was determined by an HPLC method (Weiß et al., 1993a).

2.6. HPMCP yield for microencapsulation

The calculation was based on the procedure described by Merkle and Speiser (1973). The absolute polymer mass precipitated on the ibuprofen crystals was determined from the polymer content and the total weight of the obtained microcapsules. The HPMCP yield was then calculated on the basis of the total amount of polymer used per microencapsulation.

2.7. Dissolution tests

The enteric properties of the microcapsules were tested by a modified USP XXII paddle method for enteric-coated articles. Approx. 250 mg microcapsules containing 200 mg ibuprofen were used at a paddle speed of 100 rpm (37° C). The initial dissolution medium was 1000 ml simulated gastric fluid pH 1.2 (2 g NaCl in 0.08 N HCl). After 120 min, 14.2 g Tris were added and the pH was adjusted to 7.2 by adding 2 N HCl or 2 N NaOH.

The integrity of the polymer wall was checked using an 0.05 M pH 4.0 phosphate buffer as dissolution medium (1000 ml) and the USP XXII dissolution apparatus II at a paddle speed of 100 rpm (37° C). The sample weight was approx. 20 mg microcapsules corresponding to 15 mg ibuprofen. All experiments were carried out 6-fold.

2.8. Powder characteristics

Determination of the particle size distribution was determined by sieve analysis (Alpine Luftstrahlsieb, Alpine, Augsburg, Germany). The mean particle size was calculated on the basis of the cumulative percentage mass of undersize material according to RRSB.

The untapped and tapped bulk densities were measured according to DIN 53912 and DIN ISO 787 part 11, respectively. Deviating from these methods, the samples were not dried for 2 h at 105° C because of the low melting point of ibuprofen. The angle of repose was determined according to DIN ISO 4324 and the water content of the microcapsules was analysed by Karl-Fischer titration (KF-Titrino 701 with Ti-Stand 703, Deutsche Metrohm, Filderstadt, Germany).

2.9. Scanning electron microscopy

The microcapsules were fixed on aluminium mounts using a thin layer of conductant silver

Table 1
Wet weight, quantitative composition and polymer yield of the polymer-rich phases of HPMCP isolated at 35° C in the absence and presence of ibuprofen as well as in the presence of an additional surfactant (docusate sodium)

	Without ibuprofen and without surfactant	With ibuprofen and without surfactant	With ibuprofen and with surfactant
Wet weight [a] (% w/w) (S.D.)	7.21 (0.47)	6.89 (0.67)	6.99 (0.59)
Composition [a] (% w/w) (S.D.)			
HPMCP	15.54 (0.32)	15.54 (0.13)	15.94 (0.43)
Ibuprofen	–	0.10 (0.01)	0.11 (0.00)
Total electrolyte	6.44 (0.04)	6.44 (0.08)	6.38 (0.13)
Water	78.02 (0.28)	77.92 (0.16)	77.57 (0.51)
Yield of HPMCP [b](%)	35.7	34.1	35.5

[a] $n = 4$.
[b] Calculated from the results of the compositions and the wet weights.

paint. The photomicrographs were taken by a Stereoscan 350 MK3 scanning electron microscope (Cambridge Instruments, Cambridge, UK) after sputtering the samples with a gold layer using a sputter coater S 150 (Edwards Kniese, Marburg, Germany).

3. Results and discussion

3.1. Effect of ibuprofen on coacervate formation

Primarily the influence of suspended ibuprofen on the coacervate formation of HPMCP was investigated. For this purpose, coacervation was induced at 35° C in drug-free and drug-containing systems. After isolation of the coacervates, they were characterized with respect to their wet weights, quantitative compositions and polymer yields (Table 1). None of the investigated parameters revealed a significant difference between the systems with and without active ingredient. This is probably the result of the very low solubility of ibuprofen in the HPMCP solution (< 0.1% w/w), which caused only a marginal pH drop (0.05 units) after suspending the drug. This behaviour is in contrast to the microencapsulation of ibuprofen by simple coacervation with cellulose acetate phthalate or Eudragit L100-55® where higher pH values of the polymer solutions or additionally present cosolvents led to an increased solubility of the drug and to a marked effect upon the phase separation of the polymers (Weiß et al., 1993a,b).

3.2. Microencapsulation

The coating behaviour of polymer solutions with various HPMCP concentrations was examined in preliminary trials. It became obvious that 5% (w/w) solutions were superior to 2% (w/w) solutions with respect to their ability for individual enveloping of suspended ibuprofen crystals (Weiß, 1991). All further microencapsulation experiments were hence performed with 5% (w/w) HPMCP solutions.

The course of ibuprofen microencapsulation by simple coacervation with HPMCP is illustrated in Fig. 1. After the addition of the 20% (w/w) sodium sulphate solution at 20° C, a coacervate became visible microscopically. However, the suspended drug crystals were coated only by a very thin and partly incomplete coacervate layer while

Fig. 2. Coating behaviour for the ibuprofen crystals by HPMCP coacervate at 20, 35 and 50° C.

a considerable amount of free coacervate occurred which was not used for coating. Subsequent gradual temperature increase to 35–40° C led to the formation of additional coacervate which was deposited around the ibuprofen crystals. Further increase in temperature up to 50° C resulted in the gelation of the polymer coats. This was seen microscopically by the spiral shape of the microcapsules and the crinkled structure of the polymer shells. Fig. 2 shows the different steps of coating during the temperature increase.

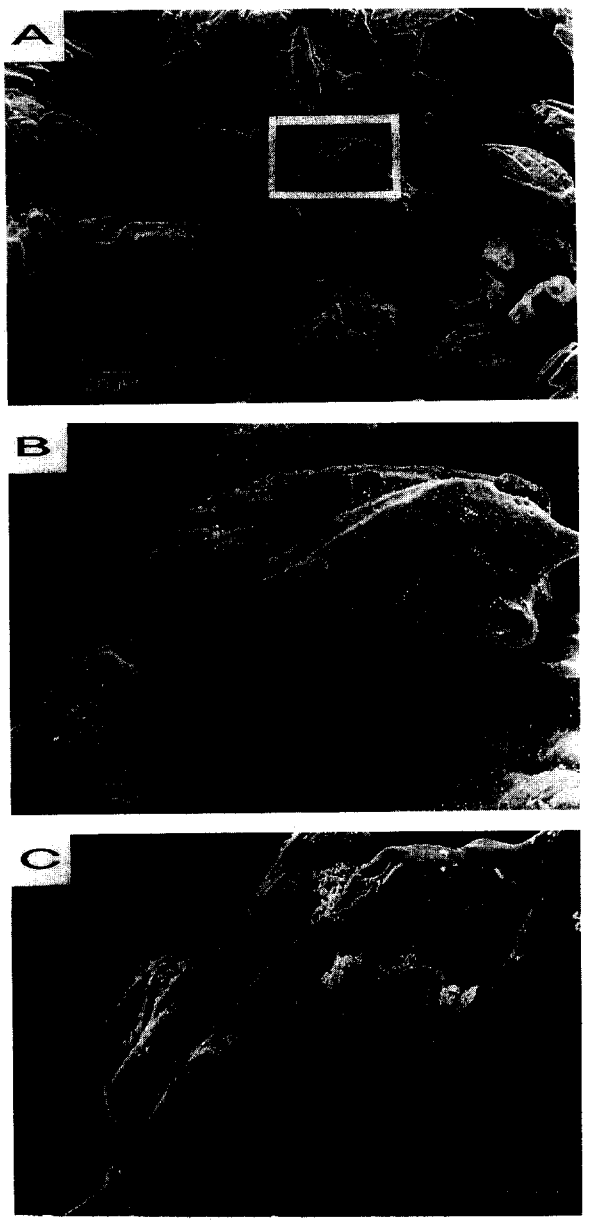

Fig. 3. SEM micrographs of ibuprofen microcapsules prepared in the absence (A,B) and presence of docusate sodium (C) during encapsulation.

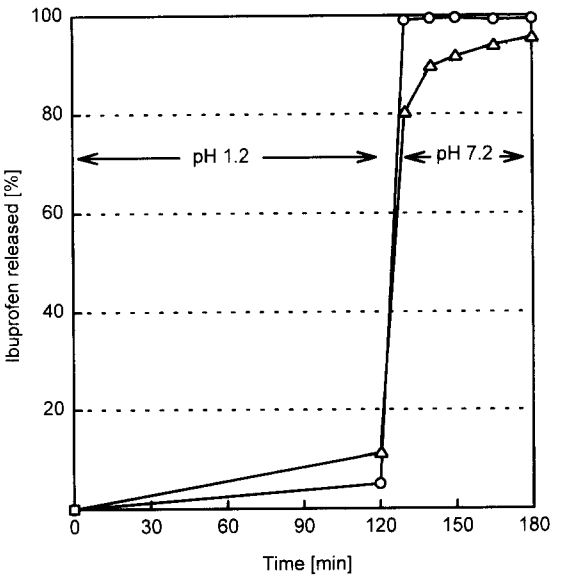

Fig. 4. Dissolution profile of ibuprofen during the enteric property test from microcapsules prepared in the absence of docusate sodium (○) in comparison to uncoated ibuprofen crystals (△).

The gelation of the HPMCP coacervate by increasing the temperature corresponds to the transition from the coacervate to the precipitate region in the temperature-dependent phase diagram of the polymer (Weiß et al., 1995; Fig. 3). Owing to the synergistic effect of total electrolyte and temperature, an analogous process should also be possible at 20° C by continuously increasing the amount of sodium sulphate added; however, the temperature rise method has the advantage that the process can be performed evenly over the whole vessel. This results in a more uniform gelation of the coacervate shells and moreover, reduces the amount of electrolyte necessary.

Microscopic in-process controls performed during the microencapsulation revealed a tendency towards the formation of twins and multi-

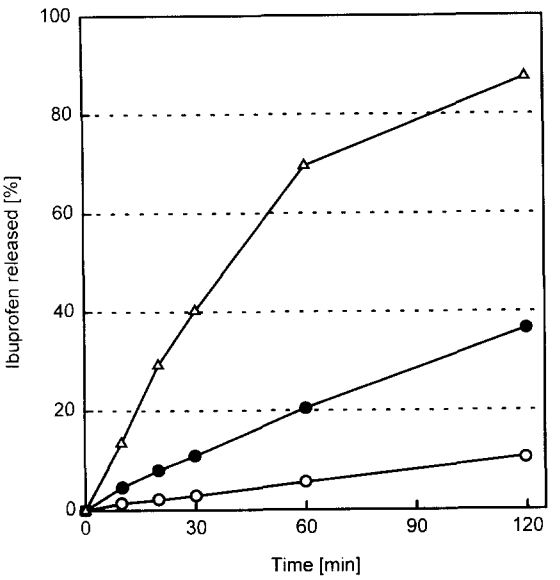

Fig. 5. Dissolution profile of ibuprofen at pH 4.0 from microcapsules prepared in the absence (○) and presence (●) of docusate sodium in comparison to uncoated ibuprofen crystals (△).

ples. This effect became more pronounced with increasing temperature and could partly be compensated by adding small amounts of docusate sodium solution. The use of surfactants for the improvement of the microencapsulation with HPMCP is also described in the literature (Fekete and Tibor, 1983; Calanchi, 1984). The effect of docusate sodium was hence investigated with respect to the phase separation behaviour of the polymer. Table 1 illustrates that neither the wet mass nor the composition or the polymer yield of the coacervates was affected by the presence of the surfactant.

3.3. Characterization of the microcapsules

Typical powder characteristics of the obtained microcapsules in comparison to the uncoated ibuprofen crystals are listed in Table 2. The mean particle size of the microcapsules is substantially larger than that of the uncoated drug. This is probably caused by collision-induced aggregations during manufacturing and by stickiness during the recovery and drying of the microcapsules; however, the imperfect suspending of the ibuprofen crystals might also have contributed to this result. The presence of docusate sodium during the microencapsulation revealed a more discrete enveloping of the drug. Table 2 also demonstrates that the microencapsulation of the active ingredient resulted in improved flow characteristics and smaller loose and tapped densities.

SEM micrographs of the samples are shown in Fig. 3. Distinct differences in the wall characteristics of microcapsules prepared with and without the presence of docusate sodium during encapsulation are visible. The active ingredient was encapsulated mostly as twins and multiples when no surfactant was used: The microcapsules possess thick and complete polymer coatings as well as poles typical of coacervation; except for a few and small crater-like dents no deficiencies in the capsule walls are visible. In contrast, when docusate

Table 2
Powder characteristics of ibuprofen HPMCP microcapsules prepared in the absence (microcapsules without surfactant) and presence of docusate sodium (microcapsules with surfactant), and of the uncoated ibuprofen crystals

	Microcapsules without sufactant	Microcapsules with surfactant	Ibuprofen crystals (uncoated)
Mean particle size d' (μm) [a]	210	137	72
Angle of repose (°)	32.9	n.d.	> 85
Untapped bulk density (g/ml)	0.43	n.d.	0.47
Tapped bulk density (g/ml)	0.51	n.d.	0.60

[a] d' calculated by RRSB.
n.d., not determined.

Table 3
Ibuprofen, water and HPMCP content of the microcapsules and HPMCP yield for microencapsulation in the absence (microcapsules without surfactant) and presence of docusate sodium (microcapsules with surfactant)

	Microcapsules without surfactant	Microcapsules with surfactant
Content (%)		
Ibuprofen [a] (S.D.)	83.78 (0.35)	85.58 (0.29)
Water [b] (S.D.)	0.64 (0.03)	0.59 (0.04)
HPMCP [c] (S.D.)	15.58 (0.29)	13.83 (0.24)
HPMCP yield for microencapsulation (%)	58.8	48.9

[a] $n = 4$.
[b] $n = 2$.
[c] Calculated as residue from the contents of ibuprofen and water.

sodium was present during the encapsulation process, the number of twins and multiples was distinctly reduced and the polymer coatings showed large clod-like deficiencies.

The compositions of the microcapsules prepared with and without docusate sodium as well as the corresponding HPMCP yields are given in Table 3. The HPMCP yield for microencapsulation in the docusate sodium-free system corresponds precisely to the percentage polymer salted out into the polymer-rich phase at 50° C (58.3%; Weiß et al., 1995; Table 3). This demonstrates the almost complete deposition of the coacervate around the suspended drug crystals during microencapsulation in the absence of docusate sodium and reveals the high efficiency of the procedure as compared to simple coacervation systems with cellulose acetate phthalate for which polymer yields of 45% are described in the literature (Merkle and Speiser, 1973).

However, the HPMCP content was significantly lower for the microcapsules prepared in the presence of docusate sodium. This resulted in approx. 10% less HPMCP yield compared to the surfactant-free microencapsulation system. Since a surfactant influence on the phase separation behaviour of HPMCP and especially on the polymer yield in the coacervate was not observed (compare to Table 1), the surfactant obviously does affect the ability of the coacervate to adhere to the ibuprofen crystals. This is in accordance with literature data describing other phase separation procedures where the encapsulation process was negatively affected by the addition of surfactants (Luzzi and Gerraughty, 1967; Siddiqui and Taylor, 1983; Rozenblat et al., 1989; Watts et al., 1991). These effects are attributed to electrostatic repulsions or competitive reactions to the surface to be coated. In the case of HPMCP, which is a phthalyl derivative of the surface-active hydroxypropyl methylcellulose (Sarkar, 1984; Fite', 1987), a competitive adsorption of the polymer and the surfactant at the ibuprofen surface can be discussed.

The microcapsules prepared from systems with and without docusate sodium were additionally characterized by dissolution tests. The microcapsules met the USP XXII requirements for enteric-coated articles (Fig. 4). At pH 1.2, less than 10% of the active ingredient was released within 2 h while ibuprofen was entirely dissolved within 10 min following a change in pH to 7.2. However, the dissolution profile of the microcapsules showed only slight differences from the pH-dependent dissolution behaviour of the uncoated drug. The release was hence additionally tested at pH 4.0 with reduced sample weights. While no polymer dissolution is detectable under these conditions (Adams, 1990; Spitael and Kinget, 1979), the solubility of the active ingredient in the dissolution medium is increased and a more differentiated statement on the microcapsule wall quality can be made. Fig. 5 gives the results. For both microcapsules, drug dissolution was delayed compared to uncoated ibuprofen; however, the incomplete polymer coat of the microcapsules

prepared with docusate sodium resulted in an approx. 3.5-fold higher dissolution rate compared to microcapsules prepared without surfactant.

4. Conclusion

The temperature dependency of the coacervate formation of hydroxypropyl methylcellulose phthalate (HPMCP) can be used for the microencapsulation by simple coacervation: The gelation of the polymer coats formed and the further processing of the microcapsules are performed at increased temperatures (50° C). The polymer yield of 58.8% demonstrates the high efficiency of this microencapsulation method (compared to simple coacervation with cellulose acetate phthalate) and the almost complete utilization of the coacervate for the coating of the ibuprofen crystals. While the percentage of twins and multiples can be distinctly reduced by adding docusate sodium, the resulting microcapsules show large clod-like deficiencies of the polymer shell. For the preparation of ibuprofen microcapsules which require high quality polymer coats for masking the bitter taste of the drug, the anionic surfactant docusate sodium should thus not be used for improving the discrete encapsulation of the drug crystals by the coacervate.

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