DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(20), 2751-2764 (1993)

MICROENCAPSULATION OF IBUPROFEN BY A COACERVATION PROCESS USING EUDRAGIT L100-55 AS AN ENTERIC POLYMER

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ABSTRACT

Ibuprofen microcapsules were prepared using Eudragit as enteric coating material and a simple coacervation method as coating process. Preliminary experiments based on results published with cellulose acetate phthalate led to the formation of a precipitate rather than a coacervate. Adjusting the polarity of the solvent in the Eudragit system by the addition of cosolvents enabled the transformation of the precipitate into a coacervate. This behaviour was qualitatively explained using the solubility parameter approach. The coacervate phase obtained from a system containing 2-propanol as cosolvent was assayed quantitatively in the absence and in the presence of ibuprofen. Due to the increased solubility of the drug in the cosolvent containing system, the composition of the coacervate phase was significantly altered when compared to a system without drug. The surface morphology of the microcapsules was assessed by scanning electron microscopy. The enteric properties of the microcapsules were tested according to the USP XXII test procedures. The permeability of the wall was evaluated by a dissolution test performed at pH 4. During stability testing over a period of 6 months the quality of the ibuprofen microcapsules remained almost unchanged.

INTRODUCTION

Ibuprofen, a non-steroidal anti-inflammatory drug, has an unpleasant taste. As this drug is mainly absorbed from the gastro-intestinal tract [1], an enteric coating provides sufficient taste masking without negatively affecting the availability of the drug. Furthermore, the formulation of a multiparticulate system is thought to be preferable to a single-unit dosage form because the small particles spread out more uniformly in the gastrointestinal tract. This results in a more reproducible drug absorption and reduces the risk of local irritations. A process had hence to be selected which is applicable to the coating of these small particles. Among the numerous methods described for microencapsulation [2,3] a coacervation process from aqueous medium appeared to be most suitable for the enteric coating of ibuprofen crystals [4] which are slightly soluble in water and soluble in most organic solvents [1]. Hereby the drug crystals are suspended in an aqueous polymer solution. By adding hydrophilic substances such as Na_2SO_4 a phase separation of the polymer is induced. The salted out phase (coacervate phase) is rich in polymer and can be deposited onto the dispersed drug particles to form the shell of the resulting microcapsules. Eudragit L 100-55 was chosen as enteric polymer because it is less susceptible to hydrolysis compared to the enteric cellulose esters [5,6]. However, only spray coating or organic phase separation processes have been reported so far with this coating material [7-11]. In addition, the application of organic phase separation would result in the formation of a matrix system (microspheres) rather than regular ibuprofen microcapsules because of the good solubility of this molecule in most organic solvents. Therefore, the objective of the present work was to characterise the simple coacervation of Eudragit L 100-55 from aqueous medium and to apply this process to the preparation of ibuprofen microcapsules.

MATERIALS AND METHODS

Materials

Ibuprofen (Lot: 223 964, Boots Co., GB-Nottingham) had a mean particle size of 72 μm; Eudragit L 100-55 (Lot: 13-80037, Röhm Pharma GmbH, D-Darmstadt) had an acid value of 325. They were used as received. All other chemicals were of analytical grade.

Preparation of aqueous Eudragit L 100-55 solutions

20 g Eudragit L 100-55 were suspended in 900 g water. 35 mL 1 N NaOH were added and the weight adjusted to 1000 g by adding water. The mixture was stirred for approx. 5 h until a clear solution was formed. The pH of the polymer solution was 5.85 ± 0.05.

Coacervation behaviour in the presence of cosolvents

50 g of the aqueous Eudragit solution were mixed with 37 g of a 2 % Na_2SO_4 solution. The mixture was heated to 30°C and small portions of cosolvent were added until the microscopic appearance revealed the existence of a coacervate. The formation of an emulsion-like system with homogeneous droplets of the salted-out polymer phase dispersed in a clear equilibrium solution was identified as coacervate.

Composition of the coacervate phase

200 g aqueous polymer solution were mixed with 61.2 g 2-propanol, 106.8 g of a 20% Na_2SO_4 solution were added and the system was then allowed to equilibrate for 15 min. The temperature of the system was maintained at 25°C. Subsequently, the samples were centrifuged at 31,300 g for 5 min. The supernatant equilibrium phase was carefully removed and the remaining coacervate was weighed. The percentage of the coacervate wet weight was calculated as 100·(mass of the coacervate / mass of the total system).

For studies including ibuprofen, this procedure had to be modified as follows: Ibuprofen was suspended in the cosolvent containing Eudragit solution. Due to the altered coacervation behaviour of the polymer a total of only 42.7 g 20 % Na_2SO_4 solution was used to induce the formation of the coacervate. After addition of 1/3 of the Na_2SO_4 solution, the undissolved fraction of the drug was removed by filtration (glass fibre microfilter 0.7 μm, Whatman, GB-Maidstone). The filtered solution was weighed and an adequate amount of the residual Na_2SO_4 solution was added.

The composition of the coacervate phase was determined by a thermogravimetric (TG) method. The thermoanalysis 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. The TG cell was purged with air and the flow rate was adjusted to 100mL/min. 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 - 140°C water and 2-propanol were evaporated, in the range from 160 - 550°C polymer and drug was decomposed and the residue at 600°C consisted of the electrolyte. The fraction of water was determined by subtracting from the total solvent content the amount of 2-propanol which was determined separately by a GC method [12]. The polymer content was calculated from the TG analysis by subtracting the ibuprofen content determined by HPLC from the total of polymer and drug.

Ibuprofen assay

Ibuprofen in the coacervate phase was determined by a HPLC method. The chromatographic system consisted of a LKB 2150 HPLC-pump, a Spectra-Physics SP 8875 injector, 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). The mobile phase consisted of methanol - 0.01M 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. 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%.

Preparation of microcapsules

The preparation of the ibuprofen microcapsules was performed using a laboratory processing unit IKA LR-A 250 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. The temperature was maintained constant at 25°C throughout the entire process.

200 g of an 2 % aqueous Eudragit solution were mixed with 61.2 g 2-propanol and 13.33 g ibuprofen were added. Subsequently, 42.7 g 20 % Na_2SO_4 solution were added slowly. After completion of the encapsulation step, the mixture was poured into 1.6 L diluted HCl (pH 3) within 10 min. After this solvent extraction step excess polymer was removed by washing the sedimented microcapsules 3 times with diluted HCl. Hardening of the capsule wall was achieved by adding 60 g 0.1 N HCl and stirring for 30 min. Electrolytes were extracted from the capsule shell by washing with 0.25% acetic acid. Finally, the capsules were filtered and then air-dried at room-temperature for 48 h. For further investigations only microcapsules were used which passed through a 500 μm sieve.

Scanning Electron Microscopy

The surface morphology of the microcapsules was examined by scanning electron microscopy. The microcapsules were fastened to aluminium mounts using a thin layer of conductant silver paint. The photomicrographs were taken on a Stereoscan 250 MK3 (Cambridge Instruments, GB-Cambridge) scanning electron microscope after sputtering the samples with a gold layer using a sputter coater S 150 (Edwards Kniese, D-Marburg).

Dissolution test

Dissolution was measured using a USP XXII dissolution apparatus II at a paddle speed of 100 rpm. pH 4.0 phosphate buffer containing 1 mL 1 % polysorbate 20 solution was utilised as dissolution medium (1000 mL) [12]. Sample size was approximately 20 mg microcapsules containing 15 mg ibuprofen. The drug released was determined by HPLC.

Enteric properties

The enteric properties were tested using a modified USP XXII paddle method for enteric coated articles. The specific conditions were: paddle speed 100 rpm; temperature 37°C; sample size approximately 250 mg microcapsules cotaining 200 mg ibuprofen. The initial dissolution medium was 1000 mL pH 1.2 simulated gastric fluid (2 g NaCl in 0.08 N HCl). After 120 min 14.2 g tris(hydroxymethyl)aminomethane were added and the pH adjusted to 7.2 by adding 2 N HCl or 2 N NaOH. Samples were withdrawn after 120, 130, 140, 150, 165, and 180 minutes and analysed for their ibuprofen content by HPLC.

Stability testing

The ibuprofen microcapsules were either stored in closed twist-off glasses at 20, 30, 40, and 50°C or placed in open petri-dishes where they were exposed to constant conditions of 20°C/55% rel. hum., 20°C/70% rel. hum., 30°C/55% rel. hum., and 30°C/70% rel. hum. in a humidity chamber. All samples were examined visually after 3 and 6 months. Dissolution tests were performed primarily with samples stored at 20°C, 50°C, 20°C/55% rel. hum. and 30°C/70% rel. hum.. Samples stored at the other conditions were not considered for dissolution testing when the samples exposed to the highest temperature and humidity did not show any significant changes.

RESULTS AND DISCUSSION

Preliminary experiments were made according to a procedure described in the literature on the simple coacervation of cellulose acetate phthalate (CAP) [13,14]: CAP was dissolved by adjusting the pH of the solution to 6.0. Subsequently, a 20 % Na_2SO_4 solution was added until phase separation occurred. Following this procedure with Eudragit L 100-55 instead of CAP, formation of a colloidal coagulate rather than a coacervate was observed. The difference in the behaviour of the two polymers was attributed to the lower polarity of Eudragit compared to that of CAP. This is obvious from the chemical structure of both polymers: Eudragit has an unpolar hydrocarbon backbone whereas the cellulose ester contains polar hydroxyl groups. As a result thereof, the formation of a liquid-like coacervate phase with the polymethacrylic acid derivative is not possible during the salting out process because of insufficient solvation of this polymer.

The polarity and the solution behaviour of a substance can be described using the solubility parameter approach [16,17]. The solubility parameters of polymethacrylic acid derivatives with H-bonding solvents were reported to be in the range of 9.5-11.4 $(cal/cm^3)^{1/2}$, those of cellulose derivatives in the range of 12.7-14.5 $(cal/cm^3)^{1/2}$ [18]. The values of both groups of polymers are clearly below the solubility parameter of water [23.4$(cal/cm^3)^{1/2}$]; however, the difference is smaller with the cellulose derivatives indicating a better solvation capability of water for these polymers than for the polymethacrylic acid derivatives. A sufficient solvation of the polymer is an essential prerequisite for the formation of a liquid coacervate phase. An attempt was therefore a made to adjust the polarity of the pure aqueous Eudragit solution by adding cosolvents, thus allowing the transformation of the colloidal precipitate into a coacervate. Methanol, ethanol, 1-propanol, 2-propanol and acetone were used as cosolvents. The amounts of each cosolvent necessary to obtain a coacervate from the coagulate is listed in Table 1. From the individual solubility parameters of the cosolvents and the amount added, the solubility parameter of the resulting system was calculated according to Equ. 1:

$$\delta_{tot} = \frac{m_w}{m_w + m_{cosolv}} \cdot \delta_{water} + \frac{m_{cosolv}}{m_w + m_{cosolv}} \cdot \delta_{cosolv} \qquad (1)$$

where δ_{tot} is the solubility parameter of the total system, δ_w is the solubility parameter of water, δ_{cosolv} is the solubility parameter of the cosolvent, m_w is the mass of the aqueous phase, m_w is the mass of the cosolvent.

TABLE 1

Solubility Parameters and Amounts of Cosolvents Required for the Formation of a Coacervate with Eudragit L 100-55 and Calculated Values of the Solubility Parameters of the Solvent Mixtures

Cosolvent	Solubility parameter of the cosolvent from [18] $(cal/cm^3)^{1/2}$	Amount of cosolvent required to form a coacervate (g)	Solubility parameter of the total solvent system $(cal/cm^3)^{1/2}$
Methanol	14.5	33	21.0
Ethanol	12.7	22	21.2
1-Propanol	11.9	13	21.9
2-Propanol	11.5	16	21.6
Acetone	9.9	16	21.3

From Table 1 it can be seen that the amount of cosolvent necessary to form a coacervate decreased with increasing number of C-atoms in the alkyl chain of the primary alcohols. The differences between 1-propanol, 2-propanol and acetone were marginal. The calculated solubility parameters for the solvent systems which enabled the formation of a coacervate were fairly similar for all cosolvents used and approximately 2 units below the solubility parameter of water. This was in the same order of magnitude as the difference of the solubility parameter of the polymethacrylic acid derivatives and the cellulose derivatives. Although the solubility parameter approach is primarily not intended for use with aqueous polymer solutions, it seems to be a valuable tool for qualitatively describing and understanding the changes in the behaviour of the Eudragit system after the addition of cosolvents.

As there were no obvious differences between the various cosolvents, further experiments were carried out using 2-propanol as a cosolvent. Ibuprofen was only slightly soluble in the pure aqueous Eudragit solution (0.1 %), whereas solubility was 1.3 % in the 2-propanol containing system. Since ibuprofen is a weak acid, the relatively high amount of dissolved drug caused the solution pH to decrease by 0.7 pH units. Another effect which was observed in the presence of ibuprofen was that the

amount of electrolyte necessary to induce the formation of a coacervate was reduced to 2.8 %, whereas in the absence of drug 5.8 % electrolyte were necessary.

To quantify the effect of dissolved ibuprofen on the coacervation behaviour, the composition of the coacervate and the equilibrium phase were determined. The results are summarised in Table 2. The concentration of all compounds in the coacervate phase - with the exception of water and total electrolyte- increased upon the addition of ibuprofen. The most outstanding effect was observed with the Eudragit yield, i.e. the fraction of total polymer salted out into the polymer-rich phase which exceeded 83 % in the presence of the drug. This polymer yield in the coacervate phase was untypically high when compared to results obtained from the simple coacervation with other polymers [12,13,15]. The assay of the coacervate revealed another interesting result: The solubility of ibuprofen in the coacervate phase was six times higher than in the equilibrium solution. Since drug molecules dissolved in the capsule shell have a potentially dramatic impact on the film permeability, this was regarded to be a critical process parameter.

Based on these results, an attempt was made to prepare ibuprofen microcapsules by simple coacervation of Eudragit from an aqueous system containing 2-propanol as a cosolvent. Scanning electron micrographs of the resulting microcapsules (Fig. 1) show aggregates of coated ibuprofen crystals with a characteristic surface texture that is probably due to ibuprofen which recrystallised during the solvent extraction step included in the manufacturing procedure [19]. Some damages in the coating observed on the surface of a few microcapsules could be attributed to the recovery procedure. They were generated when microcapsules which were sticking together were separated mechanically.

The quantitative composition of the microcapsules was determined to be: Ibuprofen 77.72 ± 0.24 %, Eudragit 21.32 ± 0.21 %, and water 0.96 ± 0.06 %. The barrier properties of the microcapsule wall were characterised by dissolution studies. As can be seen from Fig. 2, the microcapsules meet the requirements for enteric coated articles as listed in the USP XXII. However, this test procedure is no challenge for enteric coated ibuprofen because of the very low solubility of the drug at pH 1.2. Therefore, an additional dissolution test was performed in 0.05 M pH 4.0 phosphate buffer. Under these conditions the polymer was still insoluble [22], but the solubility of the drug was sufficiently high to allow for a distinction between high and low quality coatings. The release profiles obtained at pH 4 are shown in Fig. 3. After 2 hours,

TABLE 2

Quantitative Composition of Coacervate and Equilibrium Phase of Eudragit L 100-55 in the Absence and Presence of Ibuprofen

Wet Weight of the Coacervate Phase (mean value ± SD; n = 6)		
	without ibuprofen (% w/w)	with ibuprofen (% w/w)
	2.73 ± 0.10	4.98 ± 0.06
Composition of the Coacervate Phase (mean value ± SD; n = 4)		
	without ibuprofen (% w/w)	with ibuprofen (% w/w)
Eudragit L 100-55	15.10 ± 0.44	22.18 ± 0.74
Ibuprofen	-----	8.04 ± 0.34
Total Electrolyte	4.35 ± 0.05	1.72 ± 0.03
2-propanol	17.45 ± 0.32	23.28 ± 0.3
Water	63.10 ± 0.39	44.78 ± 0.71
Composition of the Equilibrium Solution (Calculated from Results of the Coacervate Phase)		
	without ibuprofen (% w/w)	with ibuprofen (% w/w)
Eudragit L 100-55	1.05	0.22
Ibuprofen	-----	1.3
Total Electrolyte	5.84	2.86
Water and 2-propanol	93.11	95.62
Eudragit L 100-55 Yield in the Coacervate Phase		
	without ibuprofen (% w/w)	with ibuprofen (% w/w)
	38.0	83.8

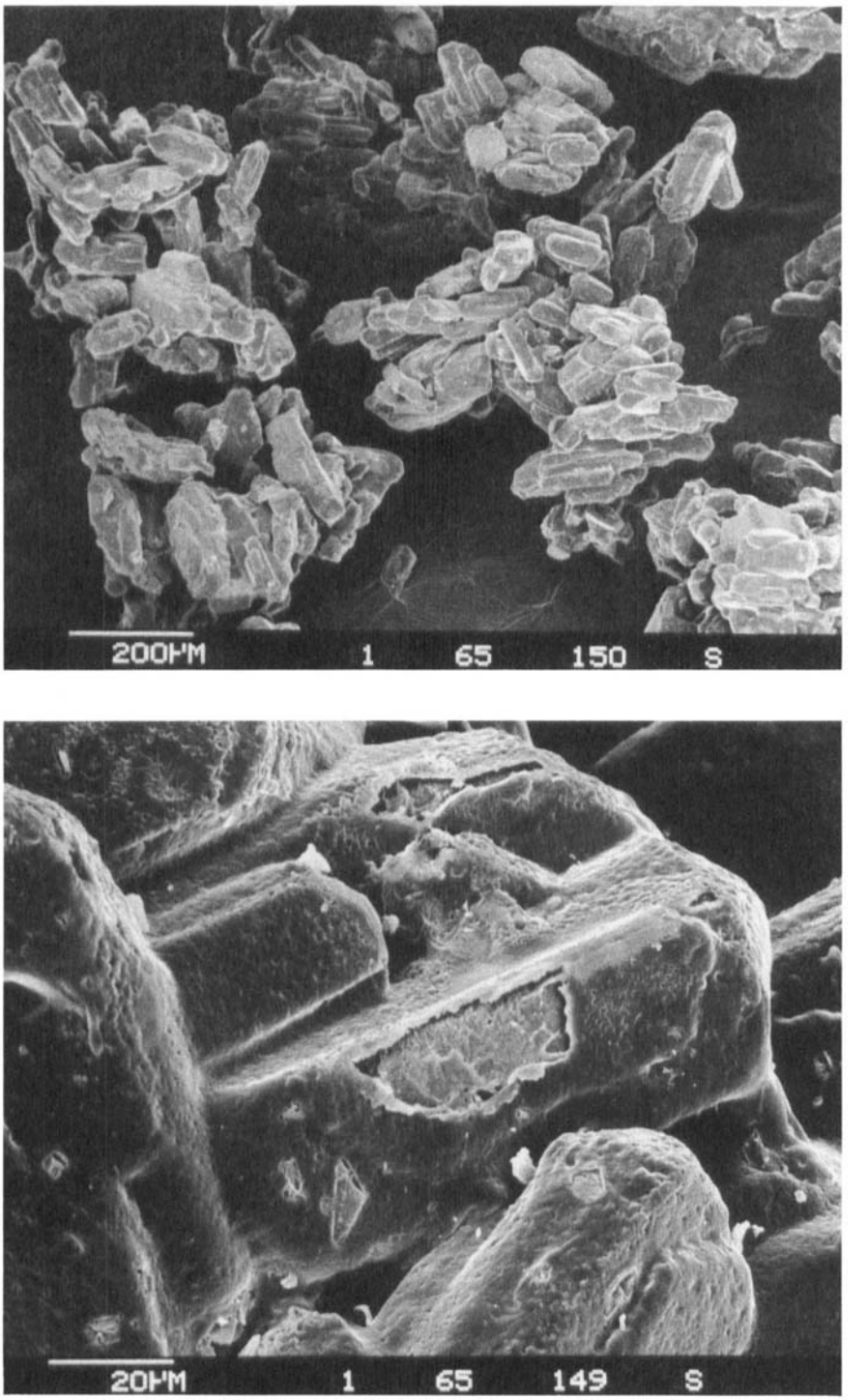

FIGURE 1

Scanning electron micrographs of the surface structure of ibuprofen microcapsules

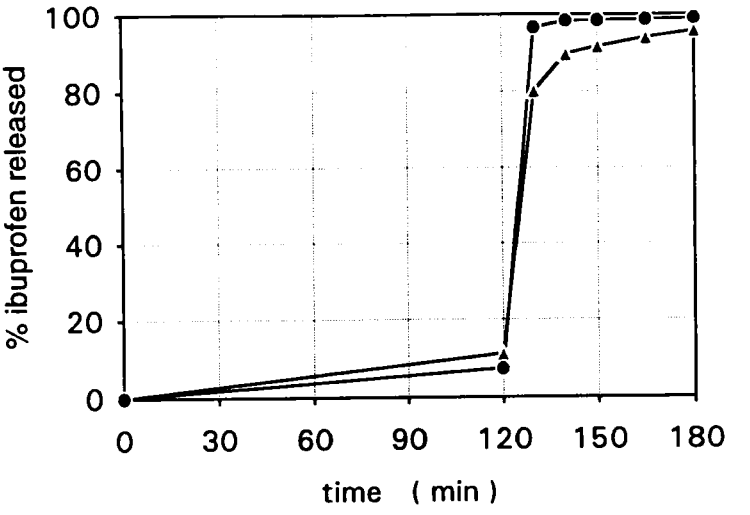

FIGURE 2

Effect of pH change (pH 1.2 to pH 7.2 after 120 min) on the ibuprofen release from uncoated crystals (▲) and Eudragit L 100-55 microcapsules (●)

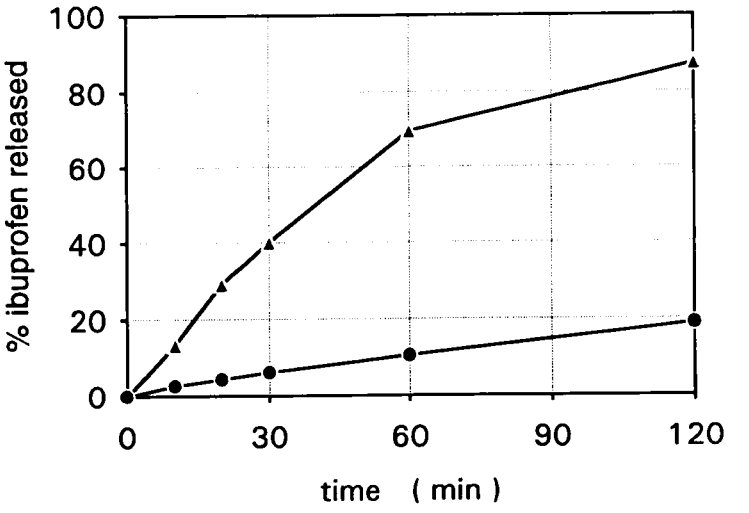

FIGURE 3

Release of ibuprofen from uncoated crystals (▲) and Eudragit L 100-55 microcapsules (●) in 0.05 M pH 4.0 phosphate buffer

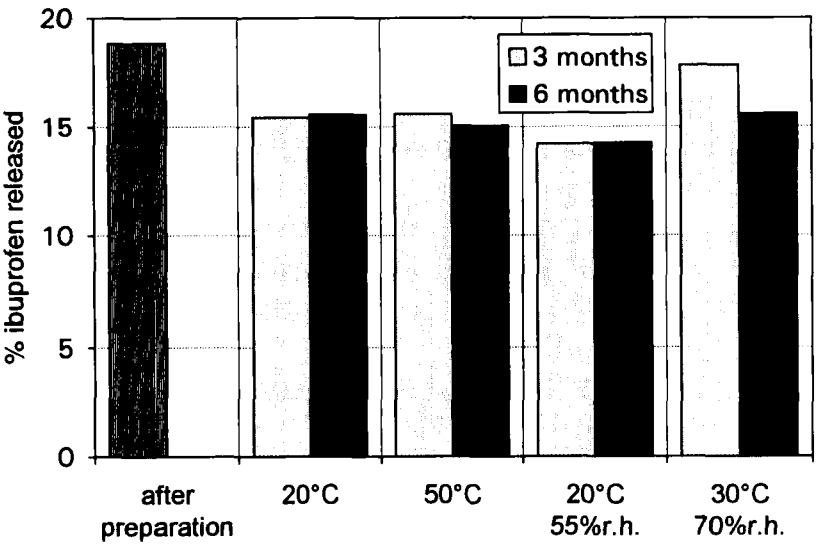

FIGURE 4

Effect of storage time and conditions on the amount of ibuprofen released from Eudragit L 100-55 microcapsules after 120 min in 0.05 M pH 4.0 phosphate buffer

18.9 % of the drug were released from the microcapsules whereas 87.4 % of uncoated ibuprofen crystals dissolved in the same period of time.

Compared to microcapsules prepared with other enteric polymers [12] the Eudragit microcapsules showed a slightly increased release rate. This behaviour was attributed to the increased solubility of ibuprofen in the Eudragit coacervate and to deffects in the capsule shell originating from the mechanical separation of aggregates both leading to a higher permeability of the polymer film. During storage the dissolution behaviour of the microcapsules did not change significantly, but a tendency towards slower release rates was observed (Fig. 4). After 6 months, samples stored at 50 °C showed some tendency to sticking, which was reversible after cooling to room temperature. The slightly decreased dissolution rate and the sticking phenomena could be explained by changes in the polymer film due to its low glass transition temperature [5], which could be additionally reduced by dissolved ibuprofen molecules [20]. At higher temperatures the Eudragit film presumably was in a glassy state where it showed an increased stickiness. In addition, storage at higher temperatures allowed the film to become more dense due to a curing effect as it was also reported for ethyl cellulose films [21].

CONCLUSIONS

From pure aqueous solutions of Eudragit it was not possible to obtain a coacervate by adding Na_2SO_4. It was shown that the addition of cosolvent such as 2-propanol to an aqueous solution of Eudragit allowed for the simple coacervation of this polymer. The system was characterised. The addition of cosolvent also had an impact on the solubility of the drug and could thus interfere with the film formation and permeability. Resulting ibuprofen microcapsules showed a sufficiently high quality and were stable during six months storage.

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