

# **SCALE-UP CONSIDERATIONS IN MICROENCAPSULATION OF IBUPROFEN BY SIMPLE COACERVATION OF CELLULOSE ACETATE PHTHALATE (CAP) AND CELLULOSE ACETATE TRIMELLITATE (CAT)**

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This paper describes the experience gathered by scaling-up the microencapsulation of ibuprofen through simple coacervation with cellulose acetate phthalate (CAP) and cellulose acetate trimellitate (CAT) from lab scale (350 mL) to pilot scale (18 L). Coacervation is one of several methods for enveloping core particles with polymer coats. It can be used advantageously when the core particles are smaller than 150  $\mu\text{m}$ , when other microencapsulation methods like fluid bed coating are limited with respect not only to appropriate air flow conditions but also to suitable processing times. Even though microencapsulation by coacervation has been used for more than 30 years for industrial purposes and has been widely described with respect to scientific aspects, only very little literature is available on the scale-up of this technology [1, 2].

Microencapsulation of ibuprofen with CAP and CAT was performed in order to mask the bitter and irritating taste of the drug. A simple coacervation technique was applied. The term „coacervation“ refers to the demixing and phase separation of polymer solutions whereby two phases are formed, one with high and the other with low polymer content. The polymer-rich phase is called „coacervate phase“ and the polymer-poor phase is the „equilibrium phase“. Phase separation is achieved by successively reducing the solubility of the polymer by appropriate procedural conditions. In case of enteric cellulose polymers, for example, phase separation is obtained by salting out with concentrated salt solutions. Since the coacervate phase is surface-active it can spontaneously envelope suspended drug crystals and thus yield microcapsules.

The simple coacervation microencapsulation with CAP has been described by Merkle and Speiser [3]. This technique was transferred to CAT and special processing conditions were adopted for the microencapsulation of ibuprofen [4 - 6]. Basically, the procedure is the same for both polymers, except for a few processing conditions such as the amount of anorganic salts required to dissolve and salt out the polymer which were adjusted specifically to the respective polymer used. Figure 1 summarizes the individual process steps for both polymers. First, CAP or CAT is dissolved in water by partial neutralization with sodium hydrogen phosphate. After heating the polymer solution to 60°C, ibuprofen is suspended. In the next manufacturing step, the polymer is successively salted out by slowly adding 20% sodium sulfate solution. In this process, the polymer separates in the form of coacervate droplets which envelope the suspended drug crystals. In the next step, the still liquid and thus unstable polymer shell is prefixed by cooling to 15°C. After washing with diluted sodium sulfate solution (5% and 9.5% Na<sub>2</sub>SO<sub>4</sub> for CAP and CAT respectively) to remove the surplus polymer from the equilibrium phase, the polymer shells are finally fixed by adding 5% acetic acid. Hereby CAP or CAT are reconverted to the water-insoluble nonionic form. The microcapsules are then washed three times with strongly diluted acetic acid to completely remove electrolytes still present in the swollen polymer shells. After filtration, drying and classification, the microcapsules are finally available as a powdery product.

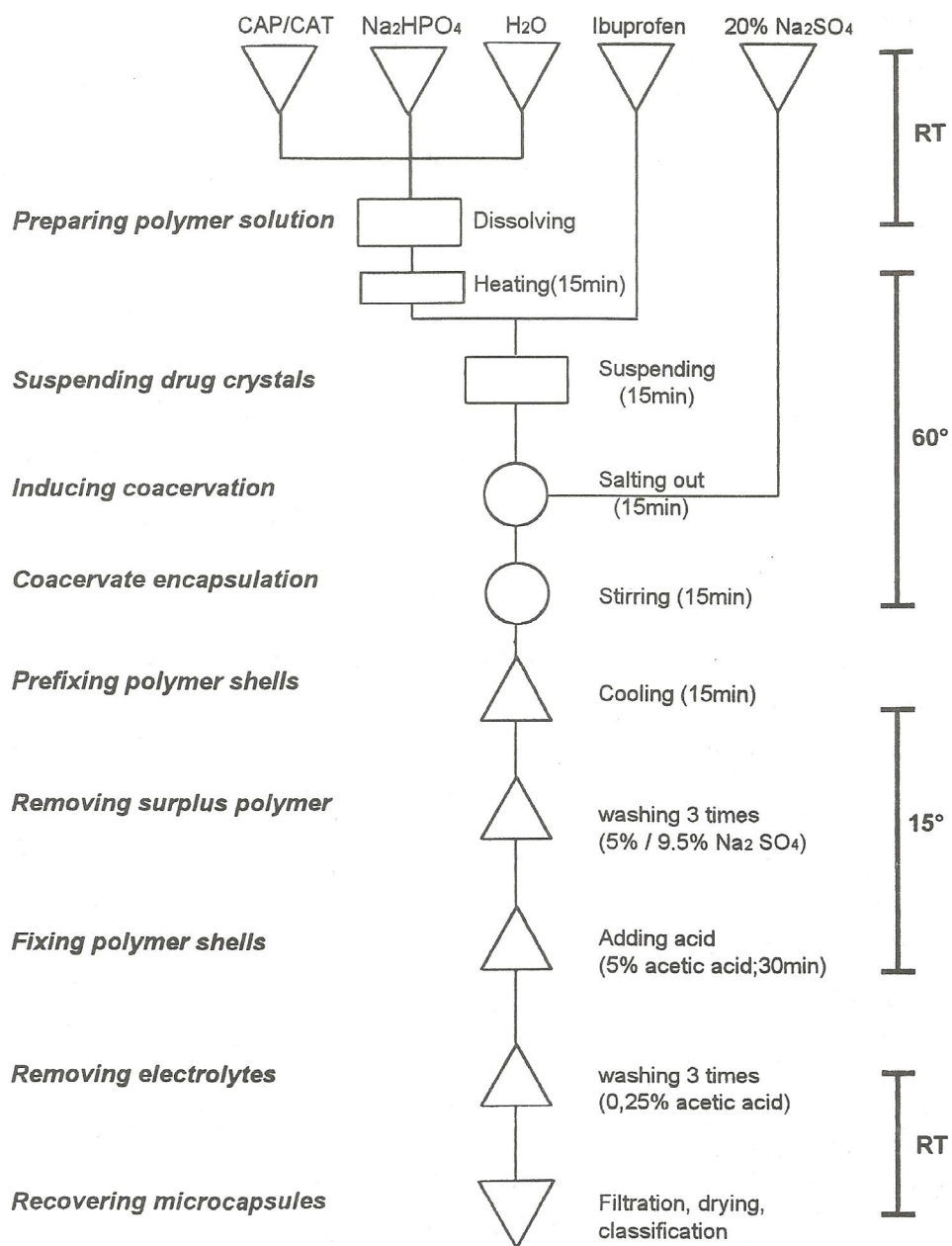


Fig. 1 Flow chart of ibuprofen microencapsulation by simple coacervation with CAP and CAT

For the scale-up of microencapsulation, the quality of the microcapsules may be influenced by three main factors [1]: the raw materials, the equipment used and the individual processing steps (fig. 2). In the investigations described here, the influence of polymers and active substance used were eliminated by using the same lots of CAP, CAT and ibuprofen in lab and pilot scale. Concerning the equipment same types of machines were used and only the batch-size was modified. In lab scale an IKA „Laborreaktor“ with a maximum filling volume of 350 mL (height 80 mm; diameter 90 mm) served as reactor. A modified Krieger Homofill was used for pilot scale experiments. This machine is of comparable geometric dimensions (height 400 mm; diameter 275 mm) and has a maximum filling volume of 18 L (fig. 3). The scale-up factor thus was about 50. Both reactors possess double jackets and were heated and cooled via a Haake waterbath F2-K. In case of the Homofill, the internal heating device was additionally used in order to speed up the heating process. For cooling tap water was used, in lab scale indirectly by cooling the water bath (equipped with a Haake temperature controller PG-10) and in pilot scale by directly feeding through the double jacket. For filtration and drying, comparable equipment was used, i.e. Büchner funnels of different size (diameter 100 and 400 mm), Petri dishes (diameter 150 mm) and stainless steel trays (dimensions 1000 x 1500 mm).

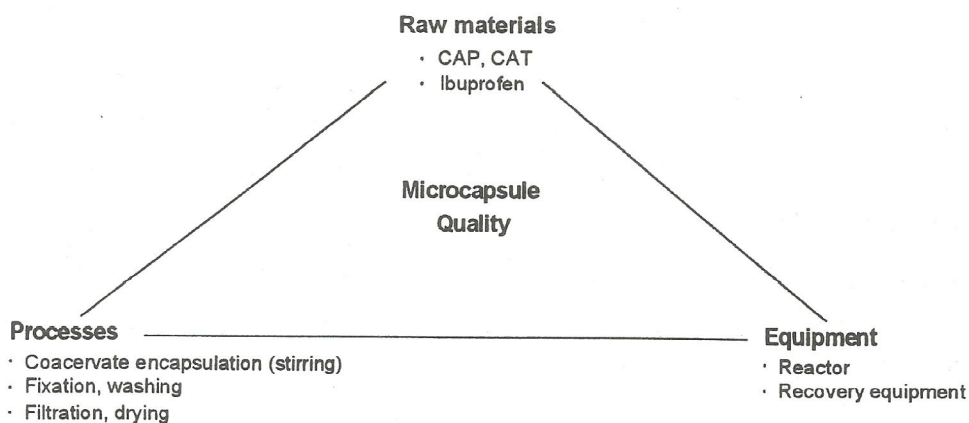


Fig. 2 Parameters determining microcapsule quality during scale-up

The choice of appropriate equipment for scale-up is especially important for the feasibility of individual processing steps which were optimized in lab scale. Crucial steps in scale-up of coacervation microencapsulation according to Crainich [1] are listed in figure 4. However, all processes involved in the simple coacervation with CAP and CAT which could be performed under identical or comparable conditions during scale-up of ibuprofen microencapsulation were considered as not being critical with respect to microcapsule quality. These parameters include temperature, heating and cooling rates, rate and order of excipient addition as well as filtration, drying and classification.



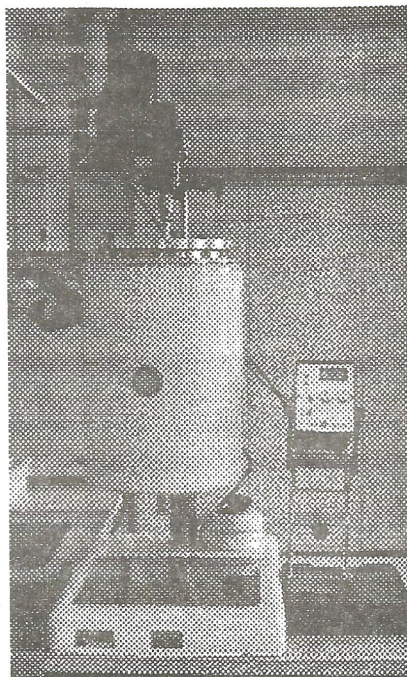
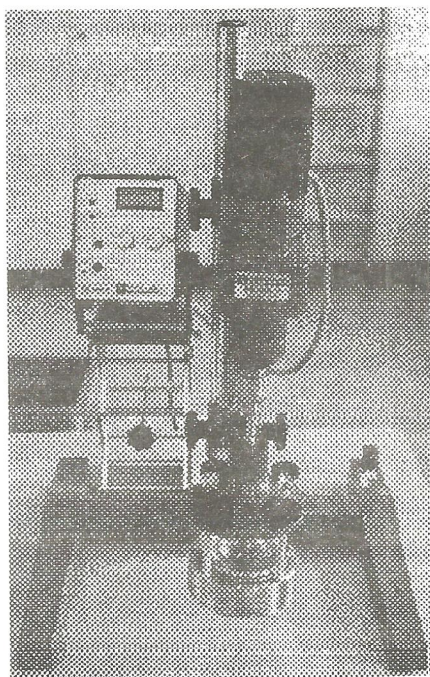


Fig. 3 Lab scale reactor (IKA Laborreaktor LR A 250) and pilot scale reactor (modified Krieger Homofill) used for microencapsulation; scale-up factor: 50

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- Stirring conditions
  - Processing times
  - Temperature
  - Heating and cooling rates
  - Rate of excipient addition
  - Washing steps  
(Time period and number of cycles)
  - Filtration conditions
  - Drying conditions
  - Classification
- 

Fig. 4 Crucial steps during scale-up of coacervation microencapsulation according to Crainich [1]

All processes which could not be kept constant during scale-up had to be modified for the pilot scale manufacture of ibuprofen microcapsules. This applied especially to the stirring conditions which were adjusted by visual and microscopic control. Hereby special attention was paid to the individual encapsulation of the drug crystals by the coacervate and to the absence of microcapsule aggregates during the cooling step. Owing to the considerably different dimensions of the two reactors which caused markedly different velocities in the vessels, the stirring conditions had to be modified substantially in pilot scale. For both scales, 4-blade stirrers on two levels were used. In case of pilot scale preparation, an anchor stirrer was additionally used to ensure sufficient mixing in the bottom part of the reactor. Moreover, three baffles were installed in the pilot scale reactor at a distance of 120° from each other and with an angle of 90° to the reactor wall in order to reduce the stirring speed necessary and to avoid the build-up of funnel-shaped product movement in the vessel. 350 and 100 rpm were chosen as stirring speeds in lab and pilot scale respectively. These conditions yielded microcapsules with microscopically similar characteristics during coacervate encapsulation and during recovery.

The next critical manufacturing steps which had to be adjusted for the pilot scale production of ibuprofen microcapsules were the washing processes with diluted sodium sulfate solution to remove surplus polymer and with 0.25% acetic acid to remove electrolytes from the still swollen coacervate shells. These processes differed markedly on both scales since the necessary time periods varied substantially. Figure 5 shows corresponding time periods necessary. While the processing times could be kept identical or similar on both scales for the manufacturing steps up to the prefixing of the polymer walls and for the final fixing and filtration of the microcapsules, markedly different time periods were necessary for the washing steps. This was caused by the lengthy sedimentation procedures which had to be performed before suction of the supernatant solutions. Owing to the larger dimensions of the pilot scale vessel, this manufacturing step was prolonged by a factor of approximately 5 - 6 (CAP) and 7 - 9 (CAT). Hereby the difference between the two enteric polymers arose from the different viscosities of the polymer solutions. Total manufacturing times for the ibuprofen microcapsules - except drying - were thus 200 min (CAP and CAT) in lab scale and 400 / 510 min (CAP / CAT) in pilot scale. While the differences between the two polymers were negligible in lab scale, they were evident in pilot scale.

There are basically two possibilities to circumvent these time losses. First, modified technological access can be made to shorten the sedimentation times, by using centrifugal forces for example [1]. However, this method has the disadvantage that appropriate mixing is required during the subsequent washing steps and that the two processes can not be performed in the same vessel so that the manufacturing becomes much more complicated. It might also be possible to perform a modified suction technique directly from the microcapsule suspension using a small mesh filter; however, the sieve may get plugged by the small-sized and still not finally fixed and thus sticky microcapsules. Another possibility would be to reduce the number of

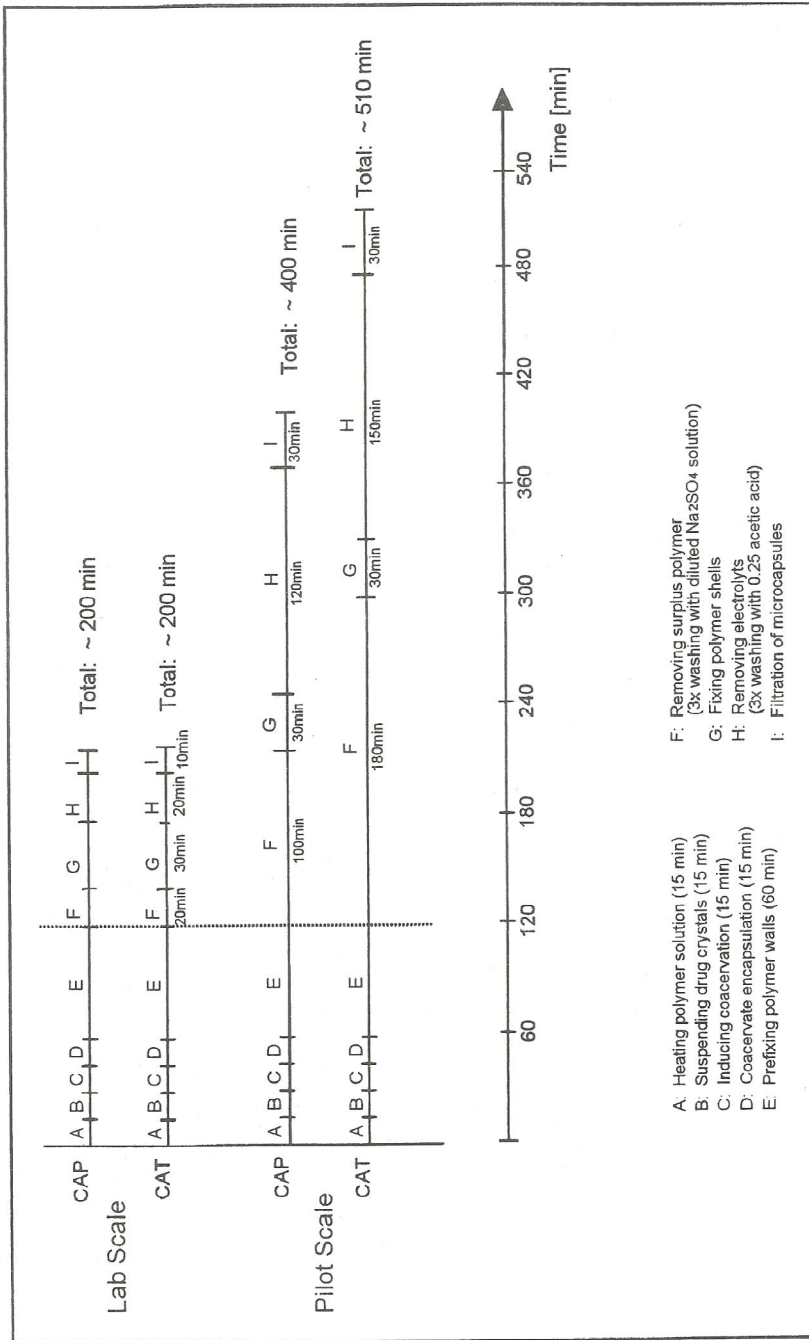


Fig. 5 Processing times for microencapsulation of ibuprofen with CAP and CAT in lab- and pilot scale



washing cycles provided that this procedure does not influence the microcapsule quality. To check the feasibility of this procedure, ibuprofen microcapsules prepared with CAP were washed once, twice or three times with 10 L of 0.25 the final rinse solution to remove electrolytes from the polymer shells. After filtration, drying and classification, microcapsules < 500  $\mu\text{m}$  were checked for their in-vitro dissolution characteristics. Figure 6 gives the results.

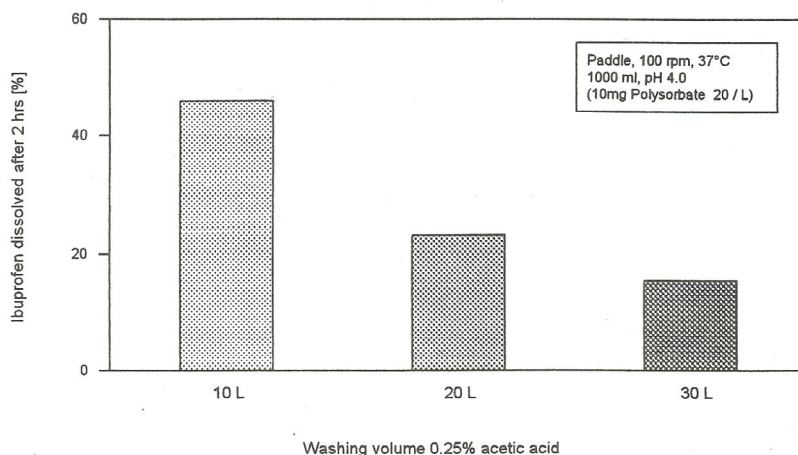


Fig. 6 Influence of washing intensity on the in-vitro dissolution of ibuprofen microcapsules prepared with CAP in pilot scale (paddle, 100 rpm, 37°C, 1000 mL, pH 4.0, 10 mg Polysorbate 20 / L)% acetic acid

Markedly higher amounts of ibuprofen were released after 2 hours dissolution testing at pH 4.0 when a reduced number of washing cycles was applied. This finding was confirmed by microscopic examination. In case of samples washed only once, the water added easily penetrated into the microcapsule shells and dissolved the polymer walls. Obviously the electrolytes used for salting out of the polymer could not be sufficiently removed by the single washing cycle. This seems understandable taking into account that the percentages of electrolytes present in the polymer-rich coacervate phase are 5.0% and 10.8% for CAP and CAT respectively [5, 6]. Consequently, the number of microcapsule washing cycles with 0.25% acetic acid cannot be reduced in pilot scale preparations.

The ibuprofen microcapsules prepared with CAP and CAT in lab- and pilot scale were finally characterized with respect to particle size, content, yield and in-vitro dissolu-



tion behaviour. Figures 1 and 8 show the corresponding results. Minor differences in the particle size distribution of the microcapsules were found for both polymers but in different directions. In case of CAP, the percentage of slightly bigger microcapsules (250 - 500  $\mu\text{m}$ ) and the yield of microcapsules < 500  $\mu\text{m}$  was reduced in pilot scale production. This might be caused by an aggregation of the microcapsules during the washing steps with diluted sodium sulfate solution, since the applied temperature (15°C) was higher than that proposed by Merkle (5°C) [3] and because the processing times for washing were markedly increased in pilot scale production. In the case of CAT a better mixing and suspending characteristic in the pilot scale reactor might, on the other hand, be responsible for the higher amounts of small-sized microcapsules and the greater yield of particles < 500  $\mu\text{m}$ . The prolonged sedimentation and washing times probably do not influence the extent of microcapsule aggregation as much as for CAP, since CAT possesses a higher gelation point than CAP [4]. Regarding the other investigated parameters, there was good agreement between the microcapsules prepared in lab and pilot scale for both polymers. The comparable data of the drug contents and of the in-vitro dissolution show the corresponding quality of the microcapsules produced.

	CAP microcapsules		CAT microcapsules	
	Lab scale	Pilot scale	Lab scale	Pilot scale
Particle size [%]				
< 500 $\mu\text{m}$	95	84	87	96
< 250 $\mu\text{m}$	86	81	46	94
< 140 $\mu\text{m}$	50	60	19	67
Content [%]				
Ibuprofen	89.9	90.4	85.9	82.6
Polymer	n.d.	9.1	n.d.	16.2
Water	n.d.	0.5	n.d.	1.2
Anorg. subst.	n.d.	< 0.03	n.d.	< 0.03
Yield [%]				
Solids total	72	78	78	81
MC < 500 $\mu\text{m}$	95	84	87	96
Ibuprofen / MC <sup>1)</sup>	81	76	73	83
Polymer / MC <sup>1)</sup>	30	26	40	55

Fig. 7 Characteristics of ibuprofen microcapsules prepared with CAP and CAT in lab and pilot scale (MC: microcapsules; n.d.: not determined; <sup>1)</sup> percentage ibuprofen or polymer available in microcapsules < 500  $\mu\text{m}$  related to the total weight of active ingredient or excipients per batch)

In summary it can be stated that microencapsulation of ibuprofen by simple coacervation with CAP and CAT was successfully scaled up from lab to pilot scale. The scale-up factor used was 50. The stirring conditions for pilot scale production were adapted under visual and microscopic control. Even though the conditions differ markedly with respect to stirring speed and stirring devices used, they yield microcapsules with comparable characteristics. Special attention has to be paid to all manufacturing steps which cannot be performed under similar processing times on both scales like washing and sedimentation of the microcapsules. Shortening or omitting these steps can substantially influence the microcapsule quality.

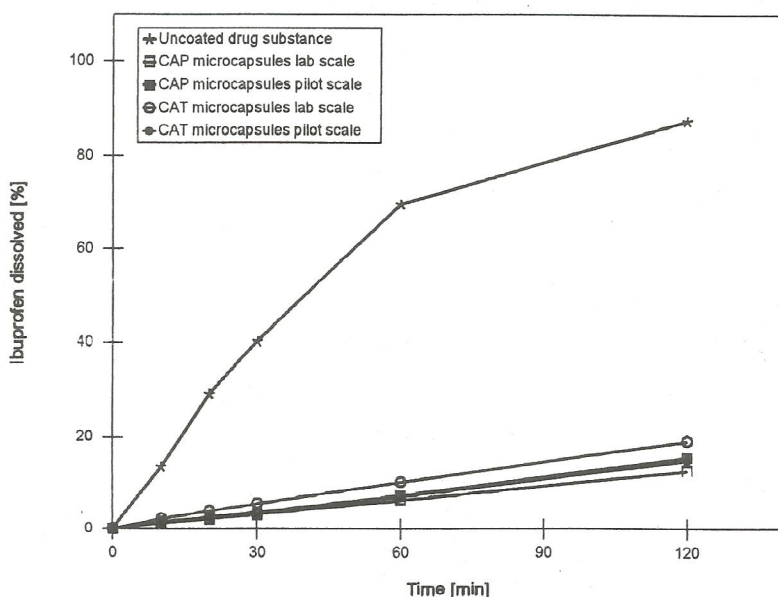


Fig. 8 In vitro dissolution of ibuprofen microcapsules prepared with CAP and CAT in lab and pilot scale (paddle, 100 rpm, 37°C, 1000mL, pH 4.0, 10 mg Polysorbate 20 / L)

## References

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