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Master Thesis

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Continuous Microencapsulation of APIs in a Tubular Reactor

Kontinuierliche Mikroverkapselung von Wirkstoffen in einem Rohrreaktor

written by

Alexandra Thurnberger

in cooperation with

Research Center Pharmaceutical Engineering

and

Siemens

Advisor

Univ.-Prof. Dr. techn. Dipl.-Ing. Johannes G. Khinast

and

Dipl.-Ing. Maximilian Besenhard

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SIEMENS

research center pharmaceutical engineering

Abstract

Down to the present day, batch processes dominate the production of pharmaceuticals. The scale-up from small sized production equipment used in the early phase of development is highly complex from a regulatory and physical. Beside the scale-up problem, long throughput times, low production rates and output quantities driven by fixed batch sizes are the main drawbacks of batch production. As a result, the pharmaceutical industry encourages the development of innovative processing technologies, of which the most important is the continuous manufacturing.

Beside crystallization and granulation, coating processes are still considered as a bottleneck for an entirely continuous manufacturing process.

This Thesis presents a continuous coating process for active pharmaceutical ingredients operated in tubular reactor. Ibuprofen, a poorly water soluble non-steroidal and anti-inflammatory drug (NSAIDS), was used as model core material. Two processes were developed to coat the core material with two different enteric polymers by means of coacervation, i.e. hydroxypropylmethylcellulose phthalate (HPMCP) or Eudragit L 100-55.

The core material was suspended in an aqueous solution containing one of these enteric polymers, fed into the tubing and mixed with a sodium sulfate solution (antisolvent) to induce coacervation. A subsequent temperature treatment was used to optimize the microencapsulation of crystals by the polymer rich coacervate phase. Cross linking of the coating shell was achieved by mixing the processed material with an acidic solution (pH < 3). Flow rates, temperature profiles and polymer/antisolvent ratios had to be tuned rigorously to avoid excessive agglomeration. Optical- and scanning electron microscopy, as well as dissolution studies were used to investigate the coating quality. All continuously coated crystals revealed an excellent microencapsulation efficiency under the microscope, but only the crystals with the Eudragit L 100-55 coated material featured good enteric coating properties during the dissolution studies. This Master Thesis proves the potential of the tubular reactor design for continuous coating applications.

Kurzfassung

In der Arzneistoffproduktion kommen bis heute hauptsächlich Batch-Prozesse zum Einsatz, welche jedoch häufig komplexe Problemstellungen in Bezug auf Scale-up beinhalten. Sowohl lange Durchlaufzeiten, geringe Produktionsraten als auch inhomogenen Prozessbedingungen und dadurch variierender Produktqualitäten, stellen die Hauptschwierigkeiten der Batch-Prozesse dar.

Auf Kristallisations- und Granulationsprozessen, als auch Coating-Prozesse liegt ein Hauptaugenmerk in Entwicklung und Forschung.

Ziel dieser Masterarbeit war es, einen kontinuierlichen Coating-Prozess zu entwickeln. Das verwendete Verfahren beruhte auf der Mikroverkapselung durch einfache Koazervation, wobei die Durchführung in einem Rohrreaktor erfolgte. Als Modelkern wurde Ibuprofen, ein schlecht wasserlöslicher und nichtsteroidalen entzündungshemmender Arzneistoff (NSAR), verwendet. Als magensaftresistente Überzüge kamen zwei unterschiedliche Polymere, Hydroxypropylmethylcellulose phatalate (HPMCP) und Eudragit L 100-55, zum Einsatz.

Für beide entwickelten kontinuierlichen Coating-Prozesse wurde Ibuprofen in der Polymer-Lösung (HPMCP oder Eudragit) suspendiert und in den Rohrreaktor gepumpt. Um die Koazervation herbeizuführen erfolgte die Zugabe einer Natriumsulfat-Lösung (Antisolvent) in den Rohrreaktor. Zur Optimierung der Verkapselung war eine exakte Temperaturregelung notwendig. Die Härtung der Mikrokapseln wurde durch den Einsatz saurer Lösungen (pH < 3) erwirkt. Die Einstellungen von Pumpraten, Temperaturen und Chemikalienkonzentrationen wurden geeignet gewählt, um Agglomeraten zu reduzieren. Um die Qualität der produzierten Mikrokapseln zu bestimmen wurden Mikroskop- und Elektronenmikroskopbilder erstellt. Die Bestimmung der säureresistenten Eigenschaften der Mikrokapseln erfolgte im sauren Medium mit Hilfe eines Dissolutions-Tests. Die Mikroskop- als auch die Elektronenmikroskopbilder der Mikrokapseln zeigten sehr gut umhüllte Ibuprofenkristalle. In den Dissolutions-Tests konnte säureresistentes Verhalten nachgewiesen werden wobei insbesondere die Eudragit-Mikrokapseln sehr gute Eigenschaften aufwiesen. Im Rahmen dieser Masterarbeit war es möglich die Realisierbarkeit eines kontinuierlichen Coating-Prozesses in einem Rohrreaktor zu zeigen. Weitere Forschung vor allem in Bezug auf Prozessoptimierung könnte dazu beitragen die erzielten Ergebnisse noch zu verbessern.

Danksagung

Zuerst möchte ich mich bei der Research Center Pharmaceutical Engineering GmbH (RCPE) und der Siemens AG bedanken, welche diese Arbeit ermöglicht und finanziert haben. Besonderer Dank gilt Univ.-Prof. Dr. Johannes Khinast, der mich bei dieser Arbeit betreut und unterstützt hat.

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Abbreviations

API ..... Active pharmaceutical ingredient

ASA ..... Acetylsalicylic acid

HPMCP ..... Hydroxypropylmethylcellulose phthalate

DSC..... Differential scanning calorimetry

NIR ..... Near infrared

UV/Vis ..... Ultraviolet/visible

SEM ..... Scanning electron microscopy

NSAID ..... Non-steroidal anti-inflammatory drugs

NSAR..... Nichtsteroidalen Antirheumatika

1 Introduction

Tradition and regulatory issues are reasons leading to the fact that manufacturing of solid dosage forms and pharmaceutical products in general, is dominated by batch processes. In-line milling, spray drying or semi continuous processes like tablet compression typical continuous processes are modified in a way to operate them batch wise (Plumb, 2005). Advantages provided by batch processes are e.g. that single batches can be accepted or rejected in respect of quality assurance. Relating to the equipment present well-known equipment can be reused for these new manufacturing processes. Limited time for process development and batch processes with multi-purpose equipment were shown to be more profitable than a continuous processes even in the case of high capacities (Goršek & Glavič, 1997).
Nevertheless, the scale up from small sized production equipment used in the early phase of development is highly complex and often leading to heavy complications. Complications not only induced by regulatory because of extensive validation is require (Qiu et al., 2009), (Närhi & Nordström, 2005). The design of larger equipment only based on geometrical similarity is insufficient (Montante, Pinelli, & Magelli, 2003), (Leuenberger, 2001), (Klinzing & Bell, 2005). Industrial scaled apertures tend to generate inhomogeneous process conditions hindering process control and entail fluctuations in product quality. Complications are not only caused by scale up, also long throughput times and low production rates as well as the output quantities driven by batch size are disadvantages of batch production. As a result, the pharmaceutical industry encourages the development and implementation of innovative processing technologies, most important continuous manufacturing. Above all, this trend is supported by the regulatory bodies (FDA, 2004).

By coating pharmaceuticals improvements e.g. in the ease of handling, an increase in drug's safety by indicating drug identity or an increase in drug's shelf-life by protecting it from environmental influences could be reached ("Innovations in coating technology.," 2008), (Gouin, 2004). Running sustained release or enteric coating processes a need to design them in a way that perfect controllability is guaranteed reachable by a detailed process understanding.

A frequently described microencapsulation technique which is relevant for the food and pharmaceutical industry is coacervation (Nakagawa & Nagao, 2012), (Weiß, Knoch, Laicher, Stanislaus, & Daniels, 1995a) (Ganderton, Jones, McGinity, & Nairm, 1995). Fundamental studies on the development of new innovative continuous coating processes are absent. The objective of this Thesis was the poof of principle of a continuous coating process operated in

a tubular reactor utilizing simple coacervation. Ibuprofen was used as core and Hydroxypropylmethylcellulose phthalate (HPMCP) and Eudragit® L100-55 were used as coating material since they belong to the most widely used enteric coatings in the pharmaceutical industry.

First, the state of the art is presented followed by the description of the used materials and applied methods. The results and discussion section contains the preliminary studies, the developed continuous processes as well as the analysis of the produced microcapsules. Finally, the results of this Thesis are summarized.

2 State of the art

Coating of pharmaceuticals is the result of long research induced by the wish of changing product characteristics of pharmaceuticals. As a consequence of the need of different products characteristics, various types of coatings and coating processes have been established.

The following pages give an introduction into the field of coating and continuous processes. Microencapsulation and coacervation are discussed separately because of their importance for this work.

2.1 Types of Coatings

As mentioned in the introduction the coating of pharmaceuticals has several motives. The optical appearance of a solid dosage form, i.e. color and surface structure, might be tuned by marketing reasons. This aesthetic coatings, in despite of its name, are also used to protect tablets against moisture, oxidation or UV-light or to increase the storability. Other purposes of a coating layer could be the increase in drugs' shelf-life by protecting the active pharmaceutical ingredient (API) from environmental influences or the masking of a bitter or sour taste. (Waßmann, Kumpugdee-Vollrath, & Krause, 2011). A sketch of a coated particle is depicted in Fig. 2-1.

In addition, coatings can be used for the mechanical stabilization during a manufacturing or packaging process and therefore the protection of employees working with the API. (Kumpugdee-Vollrath, Gögenbakan, Krause, Müller, & Waßmann, 2011).

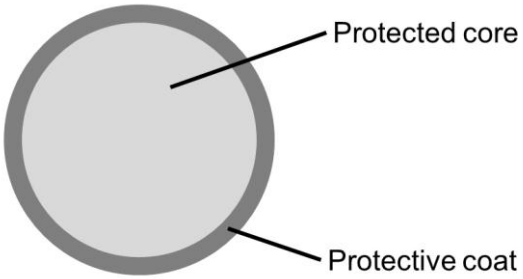

Fig. 2-1 Sketch of a coated particle in accord with Mörl (Mörl, 2011).

The pH-value in the stomach is typically between pH 1 and pH 4. Due to an enteric coating, the dosage forms must be able to withstand this acidic milieu and dissolve at the small intestine at a pH-value in the range of pH 5 to pH 7. The resorption of some APIs in the small intestine is better than in the stomach, or high dosages are necessary in the intestine (e.g. anthelminthics) (Kumpugdee-Vollrath et al., 2011). The protection of API against gastric acid as well as the protection of the gastric mucosa against API is the aim of an enteric coating.

Sustained release coatings enable the possibility of a delayed release of the API over time. They offer numerous benefits in application. In some cases a low concentration of API in the body is needed over certain hours by the reason of therapeutically advantages or advantages in compliance. An example for the therapeutic benefit is the inhibition of side effects caused by high concentrations of API. The compliance could be raised by the possibility to take a dosage form e.g. just once a day (Kumpugdee-Vollrath et al., 2011). Novel coating strategies open up opportunities to integrate API into coating layers or to produce multilayer coating. In the case of multilayer coating the fine tuning of dissolution properties is realizable (Mörl, 2011).

2.2 Coating processes

The most common coating devices are coating drums, coating pans or fluidized bed reactors (see Fig. 2-2).

A coating drum consists in a horizontal drum which contains the core material, which rotates around its longitudinal axis. Mixing is determined by the rotating rate of the drum, drum particles loading and particle sizes. The liquid coating mixture (consisting of a volatile solvent and a coating former) is sprayed onto the particles by mean of nozzles. The volatile liquid is

vaporized by heating the drum shell or by using a hot air stream. Alternatively a coating pan can be used. The coating pan is composed of a plate-like drum installed at a specific angle and a nozzle, which generally is placed over the particles. Mixing of the particles is only induced by the rotation of the coating pan. The open construction of the pan enables an easy approach in order to spray the liquid coating mixture and at the same time to guarantees a sufficient air flow for drying. The application of fluidized bed reactors is the third commonly used method to coat particles. An airstream enters the reactor at the bottom and keeps the particles suspended in the reactor. The liquid coating material is sprayed onto the particles by a nozzle located on the bottom, the top or tangential. Due to the air stream that keeps the particles, suspended the volatile solvent can be evaporated (Mörl, 2011).

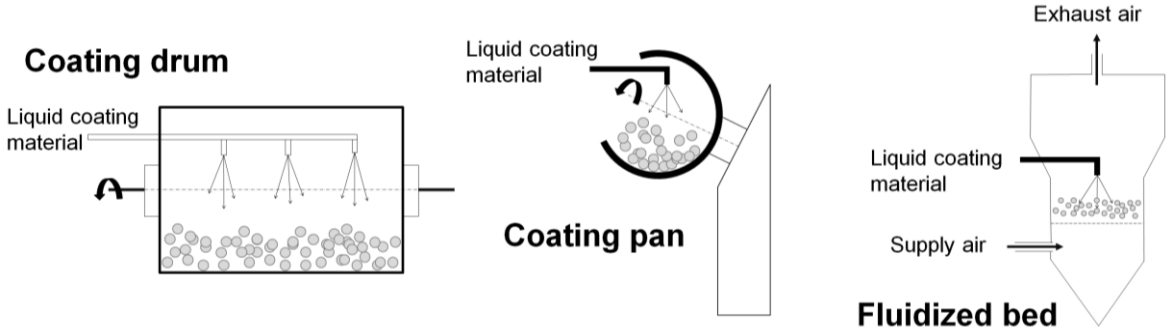

Fig. 2-2 Sketches of common used coating processed according to Mörl (Mörl, 2011, pp. 7-15)

For further information on industrial relevant coating processes the reader is referred to the work of Mörl (Mörl, 2011) and Kumpugdee-Vollrath (Kumpugdee-Vollrath et al., 2011). Microencapsulation processes are described separately within this Thesis (see section 2.3).

In the case of continuous processing crystallization (Eder et al., 2010) and granulation (Vervaet & Remon, 2005) coating processes are still considered as a bottleneck for an entirely continuous manufacturing process. Even though innovations in coating technology evidence that pharmaceutical companies focus on continuous coating ("Innovations in coating technology.," 2008), available literature does not reflect this trend. A few investigations are reported regarding continuously operated pan coaters (Ferrero, 1993), (O'Hara & Marjeram, 2006), (Cunningham, Hansell, Nuneviller, & Rajabi-Siahboomi, 2010), (Suzzi et al., 2012) fluidized bed (Liborius, 1993), (Jacob, Rümpler, & Waskow, 2006a), (Teunou & Poncelet,

2002) and spouted bed reactors (Jacob, Rümpler, & Waskow, 2006b) which are aimed mostly at tablet coating.

2.3 Microencapsulation

Microencapsulation means the surrounding of solid or liquid particles (between 1 μm and 1000 μm) by a coat (typically gelatine, natural or synthetic polymers) to spherical or elliptic shapes. This coat can be permeable, semi permeable or closed and it accounts for 2 % to 30 % of the weight of the whole microcapsule ("Mikrokapseln," n.d.).

Generally microcapsules used for pharmaceutical applications are spherical particles which consist in an active component forming the core and covered by an excipient polymeric matrix. Due to this really broad definition, also coated powders or other types of particulate material containing a substance are included. In this case it does not matter if the containing substance is solid, liquid or gaseous (Arshady, 1989). Differences between microspheres and microcapsules are presented in Fig. 2-3.

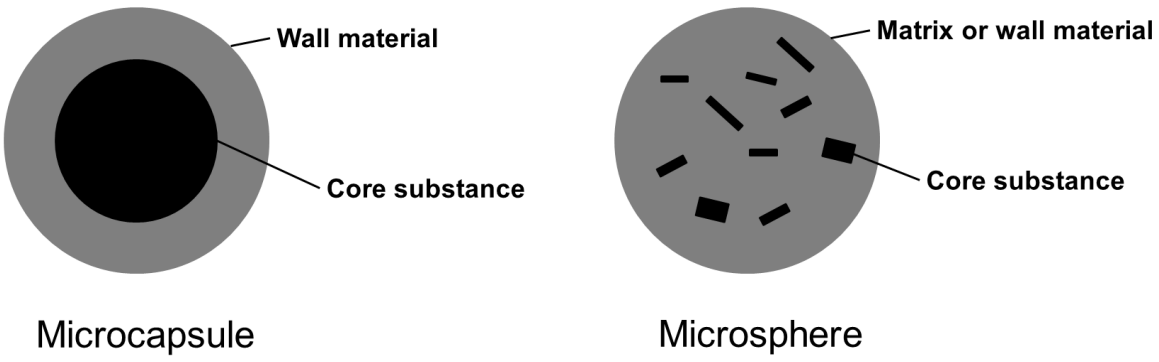

Fig. 2-3 Sketch of a microcapsule and a microsphere in accord with Dubernet and Benoit (Dubernet & Benoit, 1986)**.**

The definition of microcapsules and microspheres as defined in "Terminology for biorelated polymers and applications (IUPAC Recommendations 2012)" (Vert et al., 2012) can be found in Tab. 2-1.

Tab. 2-1 Difference between microcapsules and microspheres as described in "Terminology for biorelated polymers and applications (IUPAC Recommendations 2012)" (Vert et al., 2012)

Microcapsule	Microsphere
"Hollow *microparticle* composed of a solid shell surrounding a core-forming space available to permanently or temporarily entrapped substances. *Note*: The substances can be drugs, pesticides, dyes, etc."(Vert et al., 2012)	"Microparticle of spherical shape without membrane or any distinct outer layer. (See *microcapsule*.) *Note*: The absence of outer layer forming a distinct phase is important to distinguish micro - spheres from microcapsules because it leads to first-order diffusion phenomena, whereas diffusion is zero order in the case of microcapsules."(Vert et al., 2012)

The story of microencapsulation started with the preparation of microcapsules for the production of microencapsulated dyes used in carbonless copying paper by Green and Schleicher in 1950 (Green, 1957) (Green & Schleicher, 1957). Today microcapsules used in pharmaceutical applications are most commonly manufactured to protect the API from environmental influences, to prevent an interaction between an API and other substances, or to produce controlled release of the API Incompatibilities can be avoided by separation of the substances realized by a coating layer (Swarbick, 2007, pp. 1729-1747)

An additional example for the wide range of opportunities of microcapsules is the encapsulation of fluids for the creation of free-flowing powders. A high demand in such free-flowing powders can be found in food industry especially in dry flavour production. The liquid form of the most used flavour compounds at room temperature is not acceptable for industrial scale production. By encapsulating these liquids, it is possible to obtain free-flowing powders, thus the grade of manufacturability can be raised to a high level (Barbosa-Cánovas, Ortega-Rivas, Juliano, & Yan, 2005).

Taking all these factors into account microcapsules have a really broad field of applications. However, the production of microcapsules is a challenge for several disciplines of engineering.

Mechanical-physical as well as chemical processes are used for the production of microcapsules. Some common encapsulation methods are described below (Sliwka, 1975).

Mechanical-physical processes

- **Spray drying:** A dispersion containing the core material and a polymer dissolved in a volatile liquid is sprayed into an inert hot stream of gas. After the evaporation of the volatile liquid, the core material remains encapsulated by the polymer.

- **Fluidized bed:** Microencapsulation by fluidized beds and the coating of pharmaceuticals by fluidized beds are similar and it has been already described in section 2.2.

- **Centrifugal processes:** Particles forming the core are passed over a thin film of liquid coating material at a high speed. By passing the film, small parts of coating material are carried away by the cores. After hardening, the coating material is congealed and the formation of microcapsules is accomplished.

Chemical processes

- **Coating by polycondensation of monomers:** A common used chemical encapsulation process is based on the principle of interfacial polycondensation. A monomer is dissolved in water and a second immiscible solution is added. Immediately a polyamide film is build which is insoluble in both phases. The reactivity of the monomers is the critical criteria for the selection of cores and liquids.

- **Coacervation:** Due to its importance for this work, coacervation is described in more detail in section 2.4.

Produced microcapsules can be than used for the manufacturing of other dosage forms, such as for example capsules, suspensions or tablets.

2.4 Coacervation

Bungenberg de Jong and Kruyt described as early as 1929 the process of coacervation. The process needed a new term, because "segregation" was already used for a different process. So they created the term "coacervation" for the process and "coacervate" for the segregated liquid aggregate. In addition the Authors described several systems for which they had observed coacervation (Bungenberg de Jong & Kruyt, 1929).

An example of coacervation is described in the work of Arshady (Arshady, 1990), where an aqueous solution of gelatine is heated up to about 60°C. Then ethanol is added dropwise and a formation of two phases takes place, since gelatine is insoluble in ethanol. One phase contains much more gelatine than the other one. Further Arshady explains the onset of coacervation, i.e. the formation of a polymer rich phase, by a reduction in the solvation of gelatine due to the addition of ethanol.

Solvation describes the interaction between a solvent (liquid) and a dissolved substance, for example the surrounding of water molecules around sodium ions when dissolving sodium chloride in water (Bruice, 2011, pp. 142-143). The reduction of solvation causes an increase of the power of attraction between the polymer molecules (Arshady, 1990) which provokes the phase separation. Therefore, the onset of coacervation describes the generation of a polymer rich phase (Arshady, 1990). The phase separation, i.e. the formation of the polymer rich phase and a dilute supernatant in equilibrium, is caused by an increase in entropy (Bohidar, 2008). Fig. 2-4 shows a simplified representation of polymer molecules in a solution, a coacervate and a precipitate.

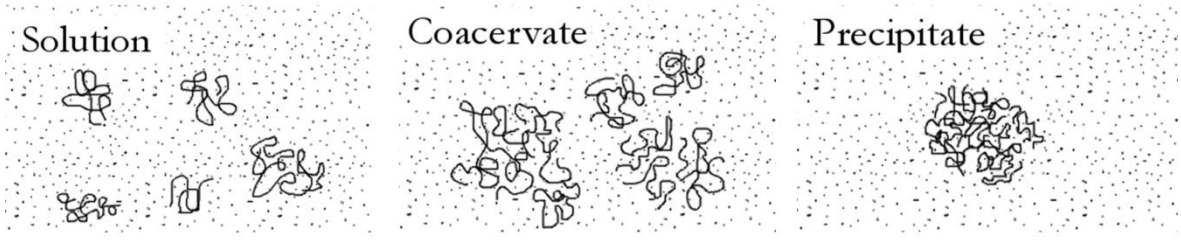

Fig. 2-4 Schematic presentation of the position of coacervate compared with polymer solution and precipitate in accord with Arshady (Arshady, 1990)**. Scattered polymer is contained in a solution while a coacervate contains much more cluttered polymer. If a clump of polymer is build it is called precipitate.**

Nevertheless, two different mechanisms of phase separation, named simple and complex coacervation, have been already characterized and are typically used for manufacturing processes. In the case of simple coacervation, the phase separation can be induced for example by sodium or ammonia salts, by a temperature change or a change in pH-value (Bauer, Frömmig, & Führer, 2006). This method requires fairly large quantities of polymer (Bauer et al., 2006). In aqueous solutions the process of coacervation is caused by the decrease of the hydrate shell of the dissolved macromolecules which is leading to a decrease in solubility. If there are non-aqueous components in solution, the process of coacervation is also caused by a decrease of solubility of the macromolecules (Merkle, 1972, pp. 14-15). Complex coacervation uses two oppositely charged polymers in solution which forms a precipitate because of they form a complex which leads to the neutralization of the charges of both polymers and therefore to the formation of the coacervate phase (for example gelatine and Arabic gum) (Mollet & Grubenmann, 2000). By building complexes, the solubility of the coacervate decreases (Merkle, 1972, p. 14).

When producing microcapsules by coacervation some requirements have to be fulfilled (Arshady, 1990). These are:

- Compatibility between core material and coating polymer
- Insolubility of the core material in the coacervation medium

Taking these criteria into account, there are two opportunities to coat the core material by means of coacervation. The first one is to coat the core by newly build coacervate drops. The second one is to form larger coacervate droplet at first and then add the cores subsequently. In general it is possible that both mechanisms work at the same time. Influences for the production of individual or coagulated microcapsules to their final morphology are for example the core-coat ratio, the size of the core particles, the stirring speed or the temperature (Arshady, 1990).

Generally, microencapsulation by means of coacervation is executed in four steps, as shown in Fig. 2-5. The first step (Phase I) is to suspend the core material into the polymer solution. Afterwards, a change of conditions (as described for simple coacervation and for complex coacervation) induces the coacervation process, as shown in step two (Phase II). In addition, Phase II shows the onset of phase separation, which is the start of the coacervation process. The third step (Phase III) is the sedimentation of the coacervate, i.e. the polymer rich phase,

onto the core material's surface. The last step (Phase IV) consists in the formation of a surrounding layer onto the surface of the cores.

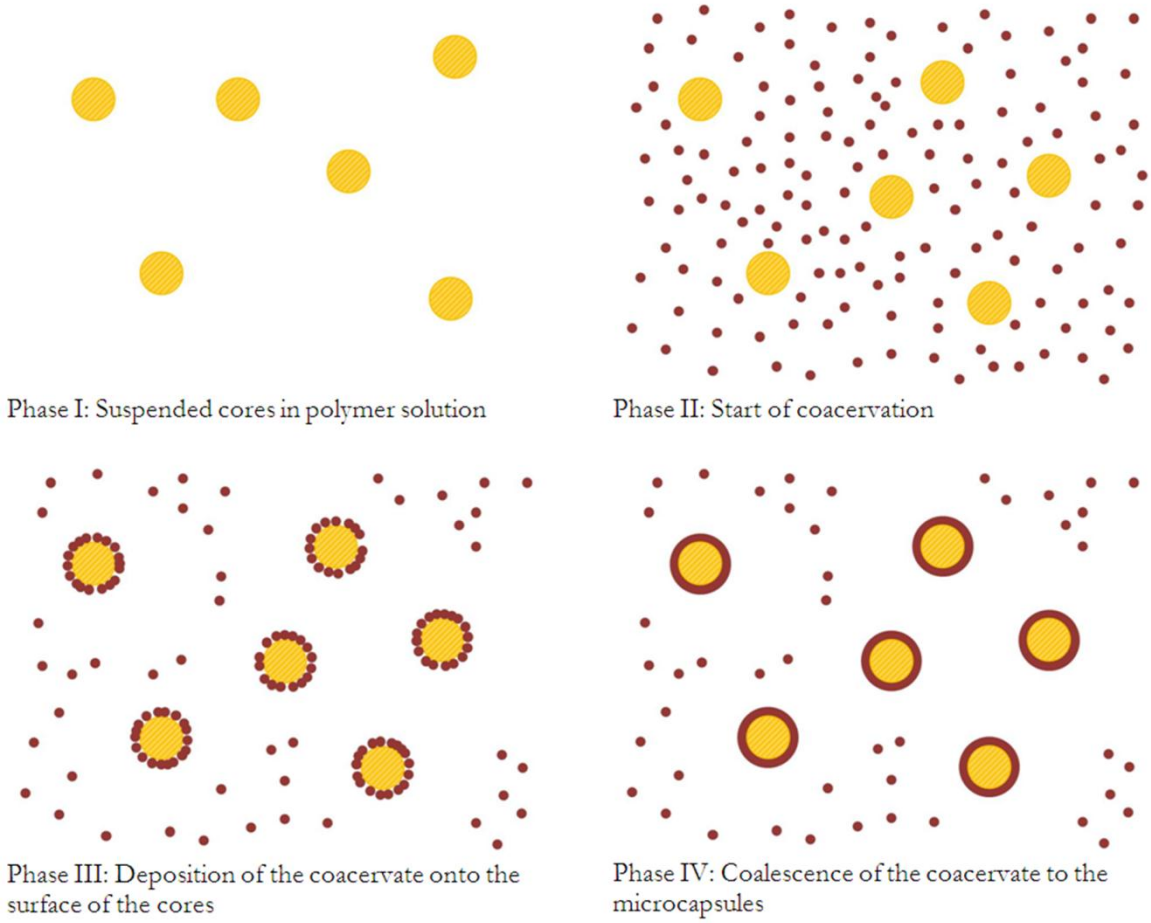

Fig. 2-5 Schematic draft process of microencapsulation by means of coacervation in accord with Mollet and Grubenmann (Mollet & Grubenmann, 2000)**. In the first step the core material is suspended in the polymer solution (Phase I). Step two is a change of conditions (e.g. temperature change or pH change) leading to the start of the coacervation process which is the separation of the phases (Phase II). Followed by the moving of the built coacervate onto the surface of the core material (Phase III) the end is the formation of a surrounding layer (Phase IV).**

2.5 Tubular reactor

The application of tubular reactors is gaining interest in current research not only for the generation of nano and micro particles (Kawase & Miura, 2007), (Yadav, Barandiaran, & de la Cal, 2012), (Eder et al., 2012) and effective chemical synthesis (Kopetzki, Lévesque, & Seeberger, 2013), (Lévesque & Seeberger, 2011), (Wahab, Ellames, Passey, & Watts, 2010).

Roberge et al. identified three reactions classes which would in principal benefit from a continuously operated (micro) reactor (Roberge, 2004), (Roberge, Ducry, Bieler, Cretton, & Zimmermann, 2005)

- Class A: very fast reactions < 1 s, mainly controlled by the mixing process;
- Class B: rapid reactions 10 s – 20 min predominantly controlled by the kinetic;
- Class C: slow reactions > 20 min where a large heat accumulation is observed.

According to the Authors, around half of the processes in the fine chemical and pharmaceutical industry, fall into one of these classes.

An introduction into the theory of tubular reactors in general is given by literature for example by Denbigh and Turne (Denbigh & Turne, 1984, pp. 2-6) which is summarized in following paragraphs. As already described in the introduction continuous processes have many benefits e.g. high level auf automation and product quality or a reduction of process steps and manpower.

Tubular reactors are often used for gas and liquid reactions e.g. for the cracking of hydrocarbons to ethylene or the sulphonation of olefins. In this case the reactor is containing just the reacting fluid what is typical for a homogeneous reaction. But also heterogeneous reactions are operated in the tubular reactor for example catalytic reactions. In this instance, the reactor is packed with the solid catalyst. Examples for such heterogeneous reactions are the ammonia or methanol synthesis.

Tubular reactors can be operated with or without heat transfer through the wall. It is also to bear in mind that the temperature can be changed by exothermic or endothermic reactions along flow direction. Often heating or cooling is necessary. Also the heating of reactants before the entrance into the tubular reactor could be essential to decrease reaction time.

The term "tubular reactor" is derived from its form which is mostly a tube or a pipe. The main characteristic of a tubular reactor is its ability to be operated in a continuous mode. Therefore a steady movement of reagents in a spatial direction is necessary. In general there are plugs which are moving along the flow direction and are not mixed with each other. Hence, this kind of reactor is also called plug-flow reactor.

In most cases the reactor is realized as a large-diameter cylinder or as tubes in parallel fixed between to headers. These tubes are a few centimeters in diameter but many meters long.

All the operation modes of the tubular reactor described so far are realized by the axially flow of the reactants along the tube, but there are also other ways to run it. It is possible that the reactants pass a packed catalyst radial through a perforated cylinder containing a perforated central tube. In this central tube the resulting product can be collected. The requirement of a plug-flow is just given by the missing mixing between the points in flow direction.

All tubular reactors is common the change of composition of the reacting fluid in direction of flow. Different compositions in radial direction because of temperature gradients and receptively or velocity gradients are possible.

3 Materials and methods

Following sections present the used chemicals and apparatus as well as the applied methods. Percentages are given as mass percent within this Thesis.

3.1 Chemicals and apparatus

Hydroxypropylmethylcellulose phthalate (Shin-Etsu Chemical Co. Ltd. Tokyo, HPMCP (Hypromellose Phthalate NF), HP-55, Nominal Phthalyl Content: 31 %, Viscosity Type: 40 cSt., Lot Number 2102188).

Eudragit L 100-55 (Methacrylic Acid – Ethyl Acrylate Copolymer (1:1) Type A Ph. Eur., Methacrylic Acid Copolymer Type C NF, Emulgator Sodium Laurilsulfate (ca. 0.7 %) Polysorbate 80 (ca. 2.3 %)).

Ethanol denaturized ≥ 99.8 % with about 1 % MEK (Carl Roth GmbH + Co KG Karlsruhe).

o-Phosphoric acid Rotipuran® M=98.00 g/mol (Carl Roth GmbH + Co KG Karlsruhe).

di-Sodiumhydrogenphosphate dihydrate ≥ 99.5 % (Carl Roth GmbH + Co KG Karlsruhe).

Sodium sulfate ≥ 99 % (Carl Roth GmbH + Co KG Karlsruhe).

Hydrochloric acid 1 N (Carl Roth GmbH + Co KG Karlsruhe).

Acetic acid Rotipuran® 100 % M=60.05 g/mol (Carl Roth GmbH + Co KG Karlsruhe).

Sodium hydroxide solution 1 N (Carl Roth GmbH + Co KG Karlsruhe).

Isopropyl alcohol technical (VWR Prolabo VWR International Wien).

Gelatine (Carl Roth GmbH + Co KG Karlsruhe, Gelatine, Platin, reinst, 240 Bloom and Gelating, Gold, reinst, 180 Bloom).

Potassium dihydrogen phosphate ≥ 99 % (Carl Roth GmbH + Co KG Karlsruhe).

Tween 20-LQ-(RB) (Croda Europe Ltd).

Analytical balance (Denver Instruments Si-234A, d=0.0001 g).

Balance (Satorius CPA34001S, d=0.1 g).

pH-Meter (Mettler Toledo Five Easy).

DSC (Netzsch DSC 204 F1).

UV/Vis spectrometer (UV/Vis Perkin Elmer Lambda 950 950H6121002).

Centrifuge (Hettich Universal 320 R).

Dissolution test (Erweka dissolution test Erweka DT 820).

Syringe (Braun Melsungen AG Injekt Luer Solo 10 mL).

Syringe cannula (Braun 100 Sterican Ø 0.90 x 70 mm Carl Roth GmbH + Co KG Karlsruhe).

Syringe filter:

Rotilabo®syringe filter nylon nonsterile pore size 0.20 µm nominal diameter 13 mm Carl Roth GmbH + Co KG Karlsruhe.

Chromafil® PTFE Xtra PTFE-45/25 Carl Roth GmbH + Co KG Karlsruhe.

Peristaltic pumps:

Ismatek Type ISM 831 C (provides multiple slots) denoted as P I within this Thesis.

Ismatek Model ISM 829 B (provides multiple slots) denoted as P II within this Thesis.

Heidolph Pumpdrive Type PD5106 (provides one slot) denoted as P III within this Thesis.

All pumps used Pharmed® tubes (d_i=2.8 mm and d_o=5 mm) for pumping.

Thermostatic bathes:

Lauda Type E 111 Ecoline Staredition denoted as B I within this Thesis.

Lauda A 24 denoted as B II within this Thesis.

Magnetic stirrers:

VWR Advanced VMS-C4 denoted as S I within this Thesis.

Ikamag RCT (facilitates stirring and tempering) denoted as S II within this Thesis.

Microscopes:

Reicher Biovar Type 3000108 used for the continuous coating process.

Leica DM 4000 microscope equipped with a DFC 290 camera.

SEM Zeiss Ultra 55 Carl Zeiss, Germany.

Sieving tower (Retsch AS 200 AS control, Amplitude 0.7 mm/g, interval time 10 sec, sieving time 5 min).

Tubes and fittings:

Polysiloxane tubes (inner diameter (d_i) = 2.0 mm, outer diameter (d_o) = 4.0 mm).

Straight fittings (PTFE, d_i=3 mm).

Y-fittings (PTFE, d_i=3 mm).

Straight fittings (PTFE, d_i=3 mm) including a wires horizontal and vertical are denoted as "Crossers" within this Thesis (see Fig. 3-2).

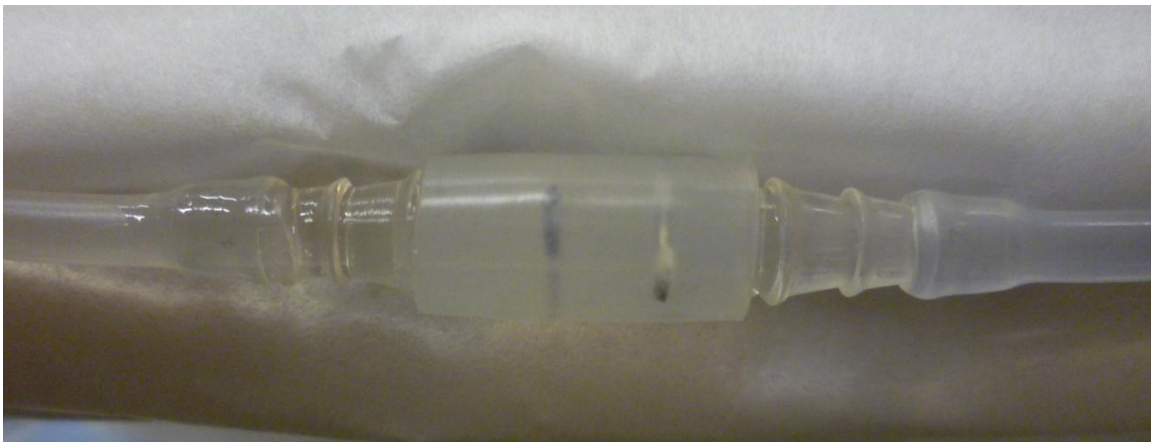

Fig. 3-1 Photograph of a "Crosser". Around the "Crosser" a silicon tube is placed to seal the fitting. Left and right tubes are connected.

3.2 Characterization of the active pharmaceutical ingredient and the coating materials

The following sections present detailed information of the used active pharmaceutical ingredient and coating materials.

3.2.1 Ibuprofen

The most investigated substance of the class of aryl propionic acid derivatives is ibuprofen which is a nonsteriodal anti-inflammatory drug. Ibuprofen is inhibiting the cyclooxygenase (important for the regulation of inflammatory processes) in a not selective way but nevertheless a benefit of especially this drug is the lower risks of gastrointestinal side-effects (the lowest in this class). Because of that, ibuprofen is used in the anti-rheumatism therapy in low dosages. Another positive effect is its short half-life and the fact that its metabolites are not active. For oral application with a fast onset of effect the use of the salt D,L-Lysine instead of the free acid could be beneficial because of the higher water solubility what is leading to a faster dissolving in the gastrointestinal tract (Mutschler, Geisslinger, Kroemer, Ruth, & Schäfter-Korting, 2008, p. 243).

The inhibition of cyclooxygenase initiated by the S-enantiomer is much higher than by the R-enantiomer. Based on this fact, in some countries drugs containing just the S-enantiomer are available. There is no clear evidence, that the half amount of just one enantiomer is more tolerated than the normal racemate. In addition, some of the aryl propionic acid derivatives

are transformed from the R-enantiomer to the more active S-enantiomer in varies species (Mutschler et al., 2008, p. 243).

The maximum daily dose of ibuprofen as over counter drug is located at 1200 mg. However, in the anti-rheumatism therapy the maximum daily dose is raised to 2400 mg. The structural formula of ibuprofen is shown in Fig. 3-2 (Mutschler et al., 2008, p. 243).

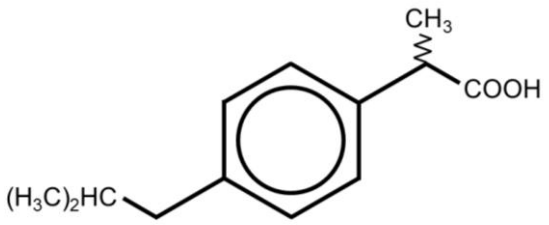

Fig. 3-2 Structural formula of ibuprofen in accord with Mutschler (Mutschler et al., 2008, p. 243)**.**

The most important facts of ibuprofen or its correct IUPAC-name (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid are summarized in Tab. 3-1.

Tab. 3-1 Important data of ibuprofen ("Ibuprofen," n.d.)

CAS number	15687-27-1
Chemical formula	$C_{13}H_{18}O_2$
Molecular weight	206.27
Melting point	74 to 76 °C
pK_a	4.4
Appearance	white or nearly white powder or crystals
Solubility	nearly insoluble in water, good soluble in most of organic solvents

Characteristics of used ibuprofen

The used ibuprofen (ibuprofen 25) was purchased from BASF Germany. The volumetric particle size distribution of the raw material (see Fig. 3-3) shows an x_{50} of 34.13 ± 0.30 μm.

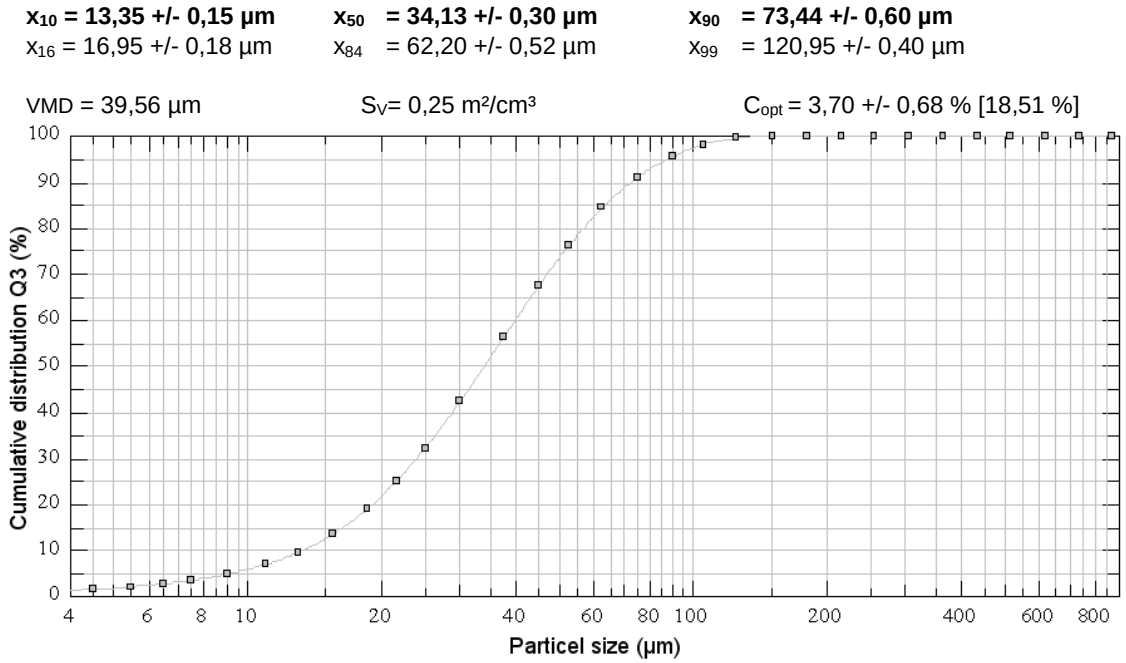

Fig. 3-3 Particle size distribution of used raw material. Correlation of particle size and cumulative distribution (%).

In order to confirm that the used raw material is a racemic mixture of ibuprofen a differential scanning calorimetry (DSC) with a heating rate of 10 K/min was performed. The DSC plot is presented in Fig. 3-4.

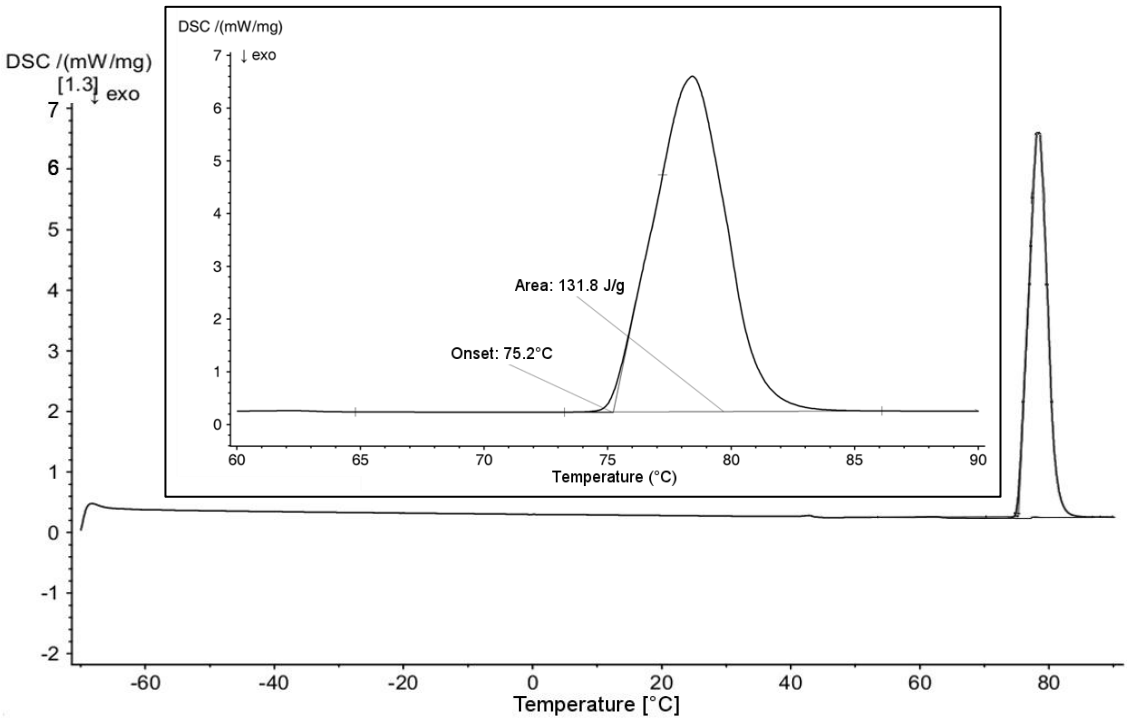

Fig. 3-4 Differential scanning calorimetry (DSC) plot of the used uncoated ibuprofen. The onset is located at 75.2°C (peak area = 131.8 J/g). The important temperature range between 60°C and 90°C is enlarged.

From the performed DSC it can be concluded that the used ibuprofen is present as a racemic mixture. The measured melting point of 75.2°C is in accordance with Shimokawa et al. (74.0 ± 0.4°C for a racemate and 50.3 ± 0.4°C for one enantiomer (Shimokawa, Saegusa, Wada, & Ishii, 2013)).

3.2.2 Hydroxypropylmethylcellulose phthalate

Hydroxypropylmethylcellulose phthalate (HPMCP) is a monophthalic acid ester of hypromellose which contains methoxy, 2-hydroxypropoxy and phthaloyl groups. The content of phthaloyl groups varies between 21 % and 35 %. Typical appearances for HPMCP are white or almost white powders respectively granular powder or free-flowing flakes. It is practically insoluble in water and pure ethanol. Despite, in mixtures of equal volumes of methanol and acetone or methanol and methylene chloride it is well soluble ("Monographs," 2008).

By changing the contents of substituents, different types of film-forming substances are created which are soluble at different pH-values. For example HPMCP 50 is soluble in at a pH-value greater 5, HPMCP 55 at a pH greater 5.5. HPMCP is used as an enteric coating and is manufactured in different processes ("Hypromellosephthalat," n.d.). In Fig. 3-5 the structural formula of HPMCP is depicted.

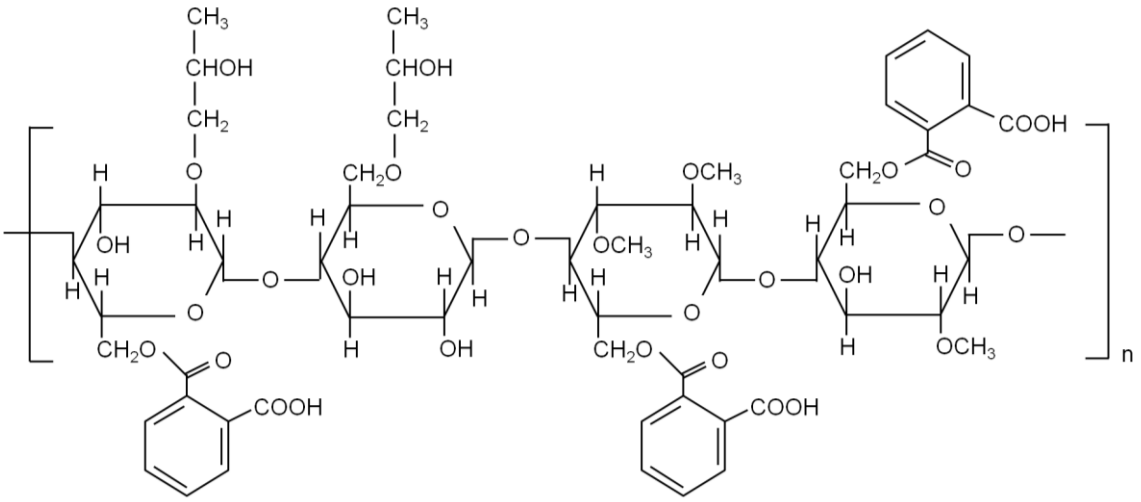

Fig. 3-5 Structural formula of HPMCP in accord with Weiß (Weiß, 1991).

Characteristics of the used Hydroxypropylmethylcellulose phthalate

The used Hydroxypropylmethylcellulose phthalate was ordered from Harke Pharma GmbH Mülheim an der Ruhr and produced by ShinEtsu Chemical Co. Ltd - Japan. Analysis data of the substance are listed in Tab. 3-2.

Tab. 3-2 Analysis data of HPMCP (ShinEtsu, 2013)**.**

Analysis data		
Product Name	HPMCP	
Grade	HP-55	
Nominal Phthalyl Content	31 %	
Viscosity Type	40 cSt	
Lot Number	2102188	
Quantity	1 kg	
Manufacture Date	31.10.2012	
Recommended Re-Evaluation Date	30.10.2015	
Analysis Date	02.11.2012	
Issue No.	D5120130200244002-1-01	
Viscosity	41.9	mPa*s
	41.1	cSt
Chloride	≤ 0.07	%
Heavy metals	≤ 0.001	%
Limit of free phthalic acid	0.16	%
Water	0.8	%
Residue on ignition	0.02	%
Phthalyl content	33	%
Methoxy content	19.5	%
Hydoxypropoxy content	6.2	%

3.2.3 Eudragit

In general Eudragit is the trade name for acrylic resins (Evonik Röhm GmbH). As described in literature ("Eudragit (R)," n.d.) Eudragit is used as film forming substances, as binders for granulation or similar applications. There for there are different types of Eudragit: E, L and S, FS 30 D, RL and RS and NE 30 D and L 30 D ("Eudragit (R)," n.d.).

E-types:

These Eudragit types are mostly used for film formation for example in the end of the production of oral dosage forms. The polymer is soluble in polar organic solvents and insoluble in water or saliva. In acidic milieu it swells and dissolves. Therefore, they can be used for coatings which should be soluble in gastric juice ("Eudragit (R)," n.d.).

L- and S-types

L- and S-types of Eudragit are soluble in the intestinal juice. The L-type swells at pH-value higher than 5 and dissolves at a pH-value higher than 5.5. The S-type swells at a pH-value higher than 6.5 and dissolves at a pH-value higher than 7. Both of them are soluble in polar organic solvents and insoluble in water. They are mostly used for enteric coatings ("Eudragit (R)," n.d.).

RL- and RS-types

In this case the abbreviation R means retard. So the films are general insoluble and independent of the pH-value. The RL form has a high and the RS form a low permeability. They are used for example for retard release application ("Eudragit (R)," n.d.).

NE 30 D and L 30 D types

- NE 30 D and L 30 D types are used for enteric coatings which should be soluble in the small intestine ("Eudragit (R)," n.d.).

The structural formula of Eudragit L 100-55 is shown in Fig. 3-6.

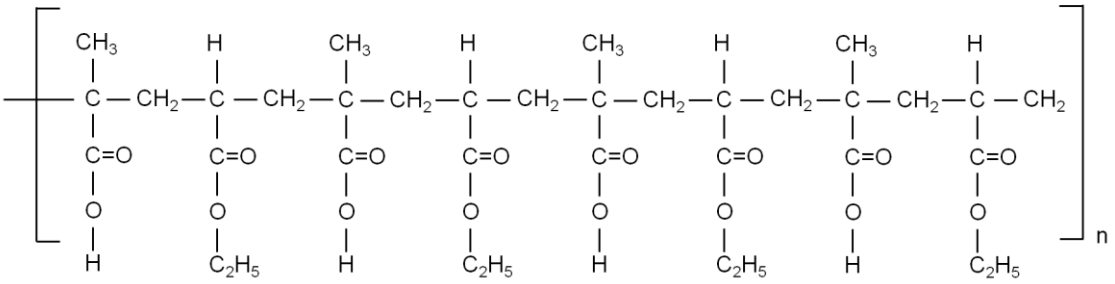

Fig. 3-6 Structural formula of Eudragit L 100-55 in accord with Weiß (Weiß, 1991)**.**

Characteristics of the used Eudragit

Eudragit® L 100-55 was ordered and produced by Evonik Industries AG Darmstadt. Technical data of the substance are listed in Tab. 3-3.

Tab. 3-3 Technical data of Eudragit® L 100-55 (Evonik, 2011).

Technical data		
Product Name	Eudragit® L 100-55	
Ph. Eur.	Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Type A	
Sodium Laurilsulfate	0.7 %	
Polysorbate 80	2.3 %	
Ratio of the free carboxyl groups to the ester groups	Approx. 1:1	
Lot Number	B100204189	
Quantity	400 g	
Stability at least until end of	02/2013	
Analysis Date		
Issue No.		
Viscosity	100 – 200	mPa*s
	15 – 45	mm^2*s^{-1}
Heavy metals	≤ 0.002	%
Arsenic	≤ 0.0002	%
Water	≤ 5	%
Residue on ignition	0.4	%

3.3 UV/Vis measurements

UV/Vis (Ultraviolet/Visible) spectroscopy (Kessler, 2006) is routinely used in analytical chemistry, e.g. for the quantitative determination of liquid compositions. Typically an UV/Vis spectrometer is operated in a wavelength range of 200 nm till 780 nm. Because of the possibility to use the same detectors until 1000 nm often also NIR-range (near infrared) is included. One of the biggest advantages of UV/Vis spectrometry is the high sensitivity at the least possible costs. In general, spectroscopy uses the wavelength and concentration (Beert-Lampert law) depending absorption characteristics of different molecules for qualitative and quantitative analysis. In the case of UV/Vis, light is mainly absorbed by means of electron excitations. Especially the excitation from the HOMO ("Highest Occupied Molecular Orbital") to the LUMO ("Lowest Unoccupied Molecular Orbital") (Kessler, 2006).

Commonly, UV/Vis spectra are recorded using a dual-beam construction (see Fig. 3-7). A monochromatic beam irradiates the sample and a reference. In order to record a spectrum the monochromatic wavelength is swept through the desired wavelength regime. Transmissions or absorptions spectra are obtained from the wavelength dependent intensity difference between the beam irradiating the reference and the sample.

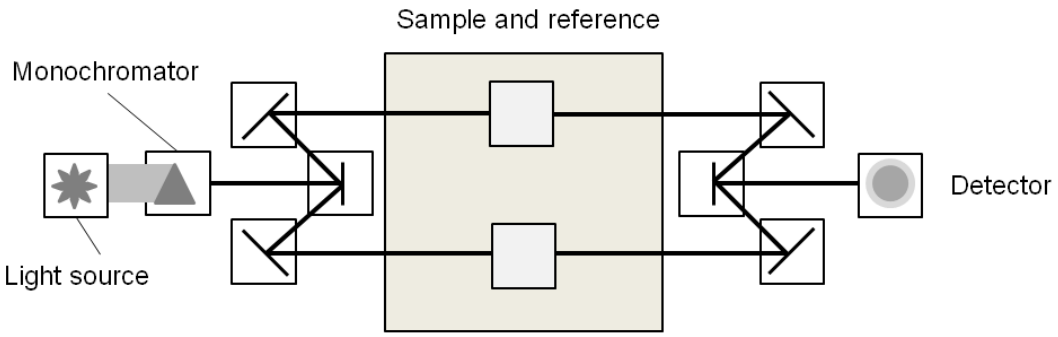

Fig. 3-7 Schematic representation of a dual-beam UV/Vis spectrometer, in accord with Kessler (Kessler, 2006)**. A monochromatic light (realized by a light source followed by a monochromator) is irradiating the sample and the reference. Subsequently both beams are routed to the detector.**

The used UV/Vis spectrometer (Perkin Elmer Lambda 950 was operated as follows (PerkinElmer, 2004):

- Principle: Double beam, double monochromator, ratio recording UV/Vis/NIR spectrophotometer with microcomputer electronics, controlled by DELL PC or compatible personal computer.
- Optical system: All reflecting optical system (SiO_2 coated) with holographic grating monochromator with 1440 Lines/mm UV/Vis blazed at 240 nm and 360 Lines/mm NIR blazed at 1100 nm, Littrow mounting, sample thickness compensated detector.
- Beam Splitting System: Chopper (46+ Hz, Cycle: Dark/Sample/Dark/ Reference, Chopper Segment Signal Correction CSSC).
- Detector: Photomultiplier R6872 for high energy in the whole UV/Vis wavelength range. Peltier cooled PbS detector for NIR.
- Source: Pre-aligned tungsten-halogen and deuterium.
- Wavelength Range (N2 purge required below 185 nm): 175 nm–3300 nm

- UV/Vis Resolution: ≤0.05 nm
- NIR Resolution: ≤0.20 nm

For each measurement the substance to measure and the reference were filled into precision cells (specimen holder) made of Quartz Suprasil (Typ 100-QS; Light Path: 10 nm).
Prior to that, the glass vessel containing the substance to measure was shaken to avoid concentrations gradients. Before each measurement, the precision cells were cleaned with water. In addition the precision cell had to be rinsed with the substance to measure once before a spectrum was recorded. Therefore about 2 mL of the substance to measure were filled in the precision cell, which was swilled in a way that the whole precision cell was flushed with the substance to measure. This procedure should guaranty that all remaining materials from previous measurements (e. g. diluting effects made by the water used for washing the precision cell) were washed away. Afterwards, about 3 mL of sample were filled into the specimen holder and put together with the reference into the measuring cell (see Fig. 3-8) of the machine.
A spectrum of ibuprofen in buffer media with buffer media as reference is shown in Fig. 3-9. Within this work, UV/Vis spectroscopy was applied to quantify the content of dissolved ibuprofen in the buffer media of the dissolution studies (see section 3.5) and an ethanolic solution used for the determination of the ibuprofen content (see Fig. 3-10) in the produced microcapsules (see section 3.4).
Two spectra were recorded for each specimen to identify irregularities and increase the accuracy of the method.

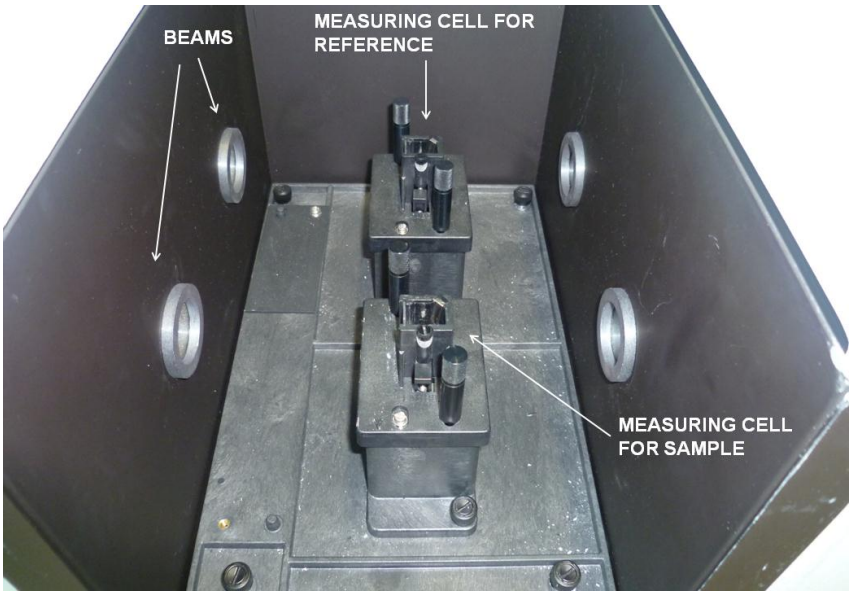

Fig. 3-8 Photograph of the used UV/Vis spectrometer. Marked are the outcome of both beams as well as the measuring cell for the reference and the sample.

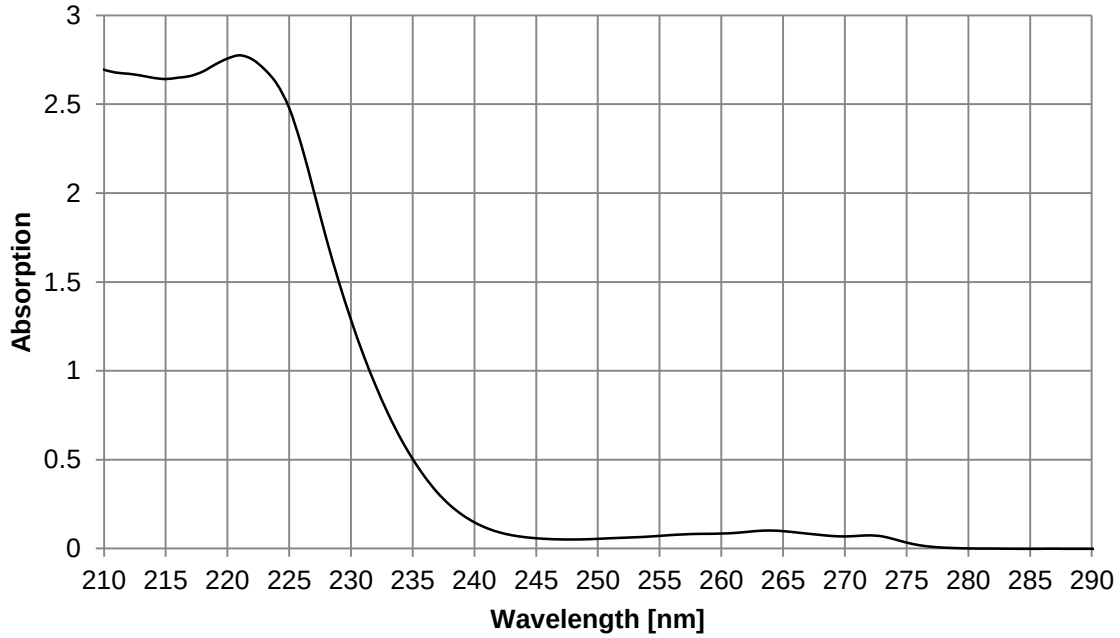

Fig. 3-9 UV/Vis spectrum in the wavelength range between 210 nm and 290 nm. 0.007 % ibuprofen dissolved in buffer media (reference: buffer media) (see section 3.5). Absorption maxima of ibuprofen are noticeable at 221 nm and 264 nm.

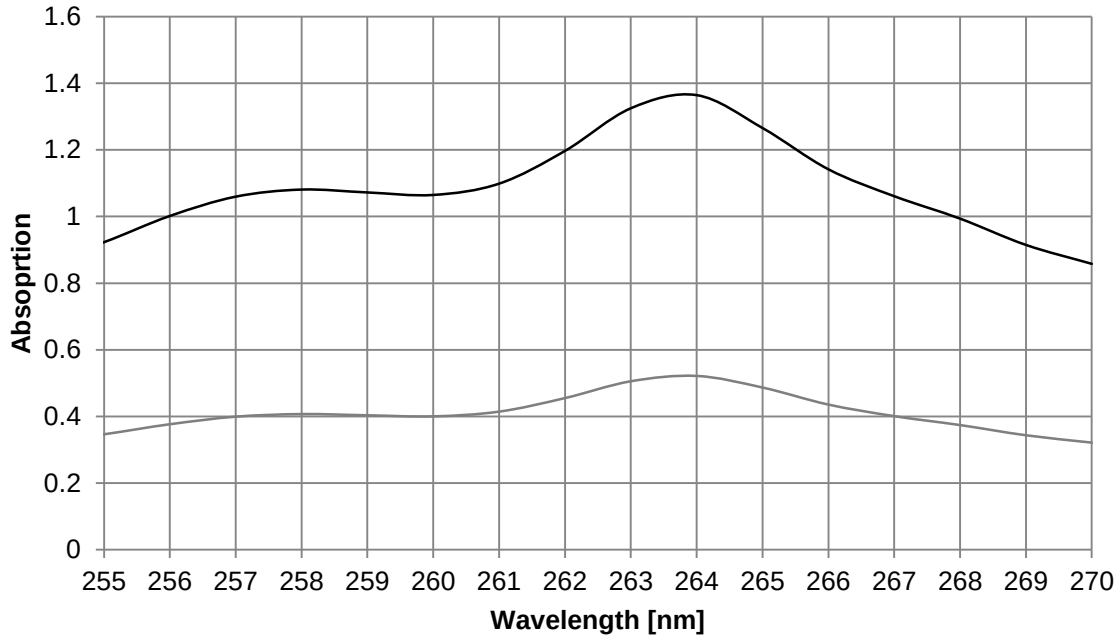

Fig. 3-10 Typical UV/Vis spectrum in the wavelength range between 255 nm and 270 nm. Ibuprofen dissolved in ethanol denaturized 99.8 % (Black line 0.13 % ibuprofen, grey line 0.05 % ibuprofen) (Reference: ethanol denaturized 99.8 %). The maximum absorption of ibuprofen is noticeable at 264 nm.

3.3.1 Quantification of the ibuprofen content in the dissolution media

The maximum solubility of ibuprofen in the buffer media is described as 71.4 mg ibuprofen per 1000 mL at 37°C (Weiß, 1991).

The calibration curve was prepared by creating a stock solution of ibuprofen dissolved in buffer media (based on mass fraction) followed by a serial dilution. This was done in duplicate. All dilutions were measured in triplicate, hence every concentration, i.e. value on the calibration curve, was measured six times.

To investigate possible influences of other chemicals used during the coating process on the UV/Vis spectra of ibuprofen, separate spectra were recorded beforehand (see Fig. 3-12). The concentrations of the chemicals used for the recording of separate spectra were chosen sufficiently high to guaranty that quantities which might be present in the coated material have no influence on the ibuprofen quantification from absorption peaks. All spectra were recorded between 255 nm to 270 nm since it can be assumed that used chemicals have no impact on the spectrometric quantification of ibuprofen in contrast to the strong interference observed at the absorption peak at 221 nm. The concentrations of the excipients dissolved in buffer media, was based on the assumption that mass of excipient is surely less than 50 % of the mass of a microcapsule.

The calibration curve for the quantification of ibuprofen in the dissolution medium was recorded for the absorption values at 264 nm (see Fig. 3-11). The region containing negative absorption is not trustable. Therefore the ibuprofen concentrations can only be determined reasonably between 0.01 % and 0.07 %.

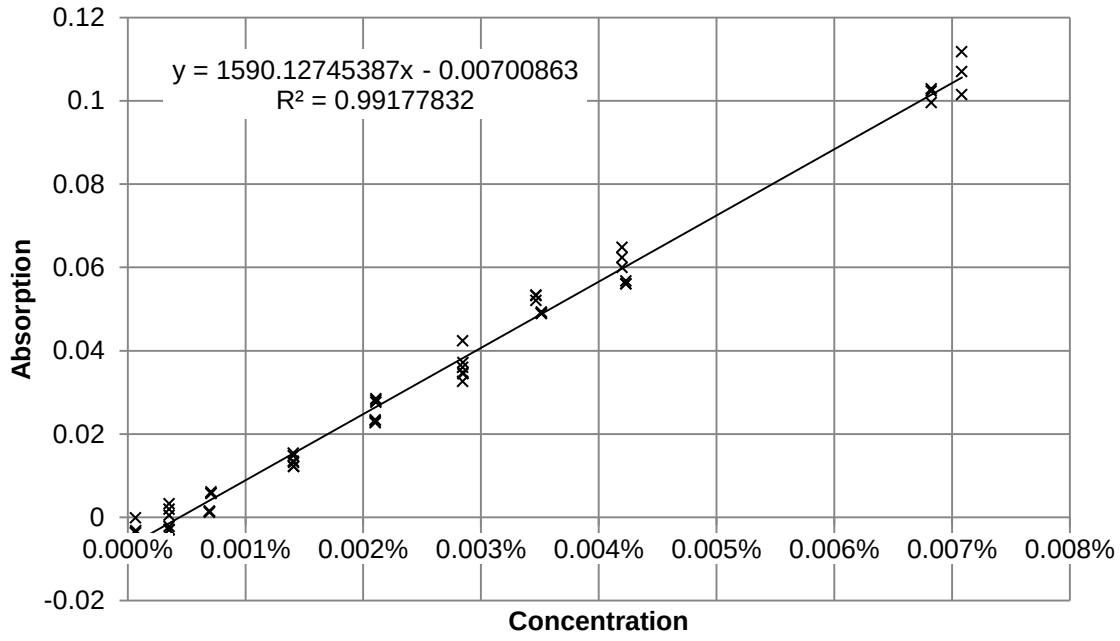

Fig. 3-11 Calibration curve at 264 nm for the calculation of the ibuprofen content (reference: pure buffer media) in the buffer media used for dissolution studies including the formula of the trendline and the coefficient of determination.

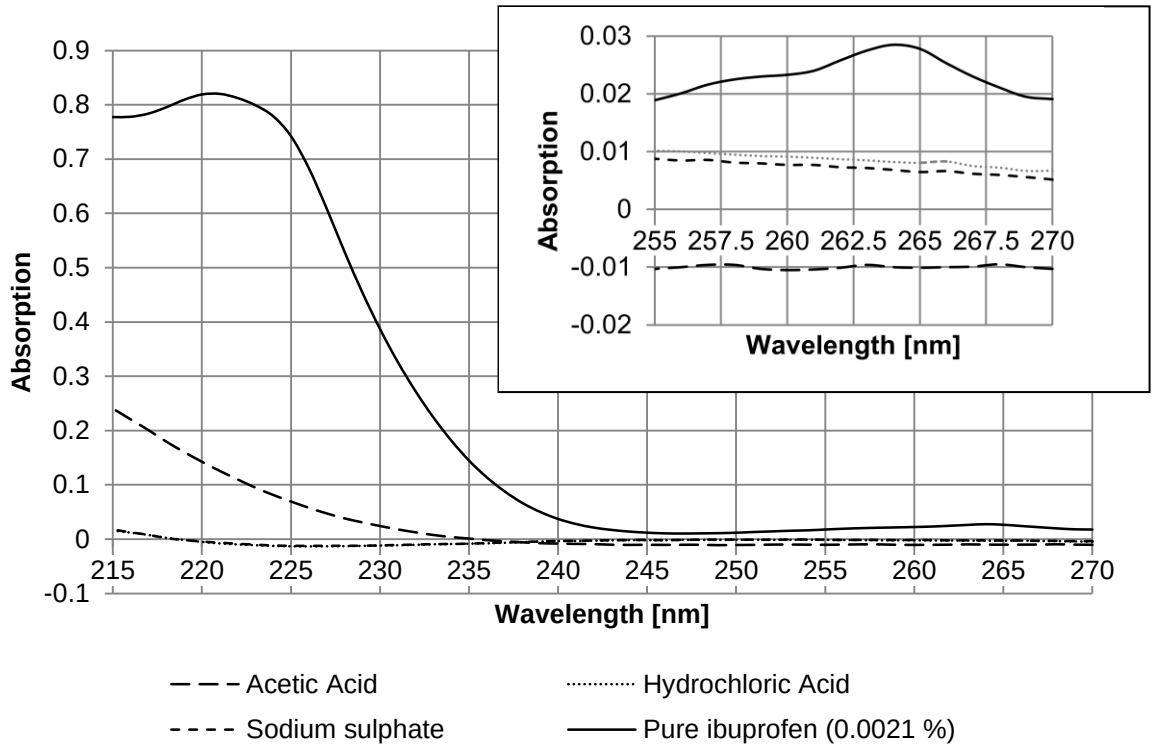

Fig. 3-12 Spectrum of all used excipients in a wavelength range of 215 nm to 270 nm dissolved in the buffer media. The concentration of pure ibuprofen was chosen at an intermediate level. Wavelength range between 255 nm to 270 nm is enlarged.

3.3.2 Quantification of the ibuprofen content in ethanol

The calibration curve was recorded for a concentration regime between 0.0026 % and 0.13 % ibuprofen dissolved in ethanol denaturized 99.8 %. Between these concentrations six additional concentrations values were measured. All of the points were measured three times but they did not show any variation.

The calibration curve for the determination of the ibuprofen content at a wavelength of 264 nm recorded as described in section 3.3 is shown in Fig. 3-13. The investigated concentration regime between 0.0026 % and 0.13 % seems trustable.

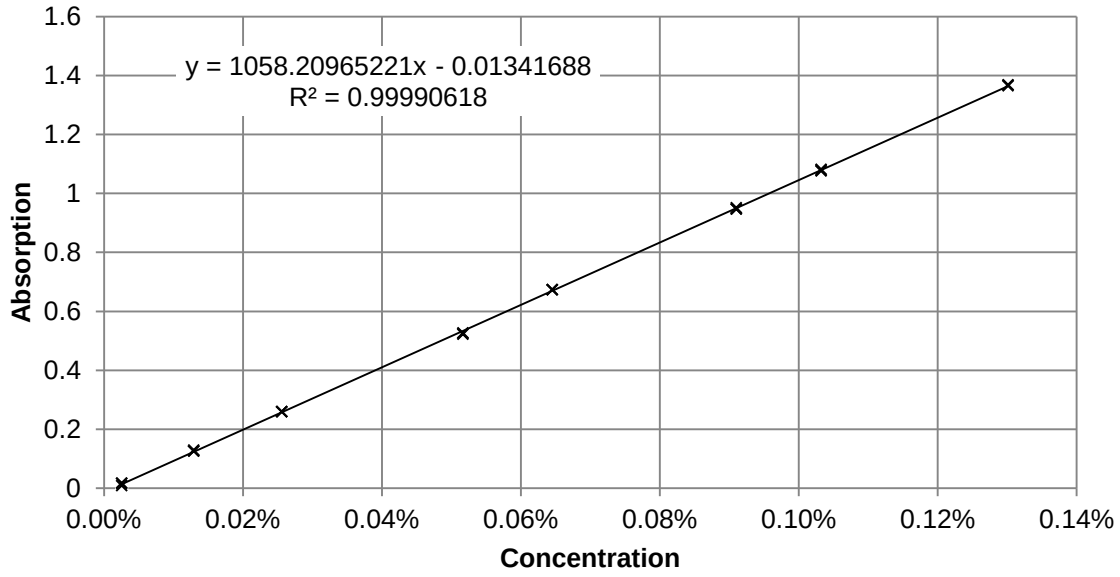

Fig. 3-13 Calibration curve of ibuprofen at 264 nm in ethanol denaturized 99.8 % expressed as absorption as a function of the concentration. It is used for the calculation of the ibuprofen content in microcapsules.

To investigate if Eudragit (which is soluble in ethanol) is affecting the method the spectrum of Eudragit was recorded and compared with the spectrum of ibuprofen (see Fig. 3-14). An impact on the method due to the presence of Eudragit can be excluded at 264 nm. The fact of an insolubility of the second used polymer (HPMCP) in ethanol denaturized 99.8 % made this experiment superfluous.

The second peak which should be found at 221 nm is overlapped by the absorption of methyl ethyl ketone added for the denaturation to the used ethanol.

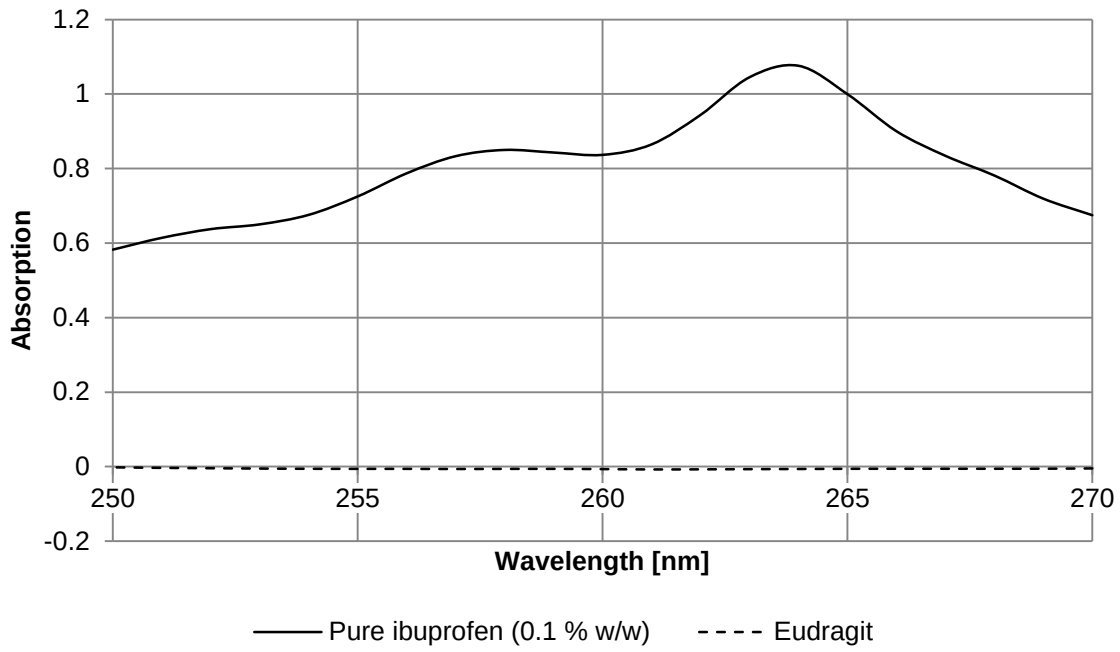

Fig. 3-14 Spectrum of Eudragit compared with the spectrum of pure ibuprofen (0.1 %) in ethanol denaturized 99.8 % (Reference: ethanol denaturized 99.8 %).

3.4 Quantification of ibuprofen content of the microcapsules

The knowledge of the correct ibuprofen content of the produced microcapsules is absolute indispensible for all further studies. Ethanol denaturized 99.8 % was chosen to determine the content of ibuprofen in the microcapsules (see also section 3.3). Therefore a sample of about 0.025 g of microcapsules with a particle size between 50 µm and 100 µm were weight in exactly and 25 mL of ethanol denaturized 99.8 % were added. Afterwards the samples were put into the ultrasonic bath for 30 minutes. After, it was put into the centrifuge for 5 minutes at 5000 rpm. A part of the supernatant was taken, passed through a syringe filter (pore size 0.20 µm) and analyzed with UV/Vis Spectroscopy.

3.5 Dissolution studies

To determine the functionality of enteric coated microcapsules dissolution studies are a suitable well established method. The ibuprofen release over time is recorded and related to a maximum possible release. A dissolution studies protocol similar to the one described by Weiß et al. (Weiß, 1991) was applied.

The addition of a wetting agent was necessary to investigate the dissolution characteristics. Preliminary experiments without wetting agent showed a floating of ibuprofen on the surface of the buffer media and the crystals were not wetted optimally with buffer media. Moreover, the addition of a wetting agent led to an increase of the dissolution rate.
Further advantages caused by adding a wetting agent could be visualized in following example (see Fig. 3-15): two separate calibration curves were created for both absorption maxima of ibuprofen (264 nm and 221 nm). Dissolution studies of ibuprofen and the calculation of the ibuprofen release over time gave absolute identical dissolution profiles in the presence of a wetting agent. In contrast, the profiles recorded in the absence of a wetting agent led to considerably variances.

The decrease of surface relating effects is realizable by the use of particles with a particle size of 50 µm to 100 µm in all measurements. All produced particles were separated to their particle sizes by a sieving tower into the fraction 50 µm to 100 µm.

The dissolution profile of the uncoated ibuprofen was recorded first to create a basis for the comparison of the microcapsules. As described, sieving of uncoated ibuprofen was necessary to inhibit surface relating effect. In this case, the sieving was very tricky because of high electrostatic interactions. Hence, sieving was realized under wet conditions followed by a drying step at room temperature. For further analysis with the uncoated ibuprofen only this fractions was used.

Dissolution studies were executed using the settings described below. The mass of ibuprofen used for dissolution studies was chosen lower than its maximum solubility in the dissolution media (71.4 mg/L at 37°C (Weiß, 1991)). The dissolution studies started by the positioning of 60 mg of ibuprofen in the dissolution vessel.

The dissolution profile of the uncoated ibuprofen which was used for all comparisons did not reach 100 % after two hours (100 % release means the release of the whole weighted ibuprofen in this case 60 mg).

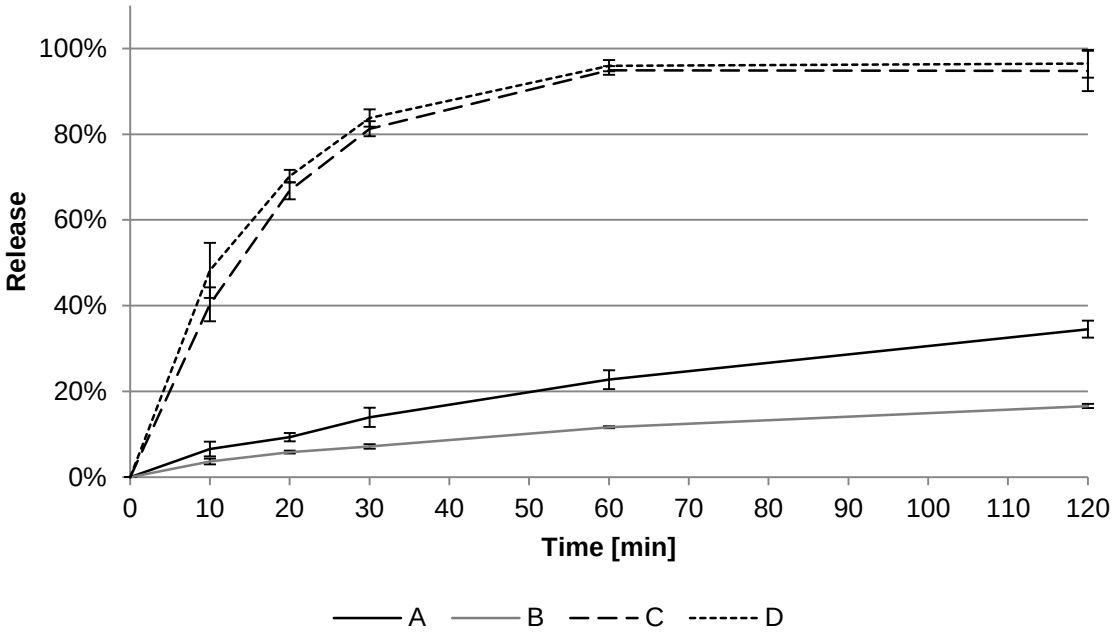

Fig. 3-15 Release of the uncoated ibuprofen over the time. This first dissolution profile was calculated using an old calibration curve based on a volumetric scale. It is the only dissolution profile in this Thesis which is not based on the calibration curve described section 3.3 and was created while developing the final procedure.
Measuring wavelength for A and C: 221 nm
Measuring wavelength for B and D: 264 nm
A and B are created without wetting agent in the dissolution studies, C and D by adding a wetting agent.

Developed procedure

As already discussed a wetting agent (Tween 20) is absolutely necessary to guarantee reproducible results. Preliminary experiments with different concentrations of wetting agent showed that a concentration of 0.05 % wetting agent in the dissolution media is sufficient. In agreement with values presented in literature a value lower 1 % is appropriately for an use as wetting agent (Rowe, Sheskey, & Owen, 2006, p. 581).

Dissolution studies were executed in a dissolution test using stirring paddles. Sample taking was tricky because of the possibility to remove ibuprofen (respectively microcapsules) out of accruing suspension. A falsification of results is reachable by a special sample taking method. Therefore a filter with a pore size of 0.45 µm was placed between a syringe and the cannula. For each dissolution vessel a separate syringe-filter-cannula was prepared before starting the recording of the dissolution profile.

For the production of the buffer media, similar to the one described by Weiß (Gerd Weiß, 1991, p. 190), 6.8 g of potassium dihydrogen orthophosphate and 0.5 g of Tween 20 had to be

dissolved in water and filled up to 1000 g. The pH-value was adjusted to pH 4 due to the addition of some drops of a 85 % phosphoric acid. Every dissolution vessel was filled with 1000 g of buffer media. The dissolution tester temperature was maintained to 37°C ± 0.5°C.

Microcapsules (correlating to 60 mg ibuprofen described in section 3.4) were put into each dissolution vessel with a time lag of 30 seconds. The rate of rotation of the paddles was defined at 100 rpm. After 10 minutes, 20 minutes, 30 minutes, 60 minutes and 120 minutes samples were taken with the special construction of a syringe, filter and cannula described above and the same time lag of 30 seconds, to warrant, that all sample had the same connection time between buffer media and particles.

Samples were taken by the pull out of 10 mL through the syringe construction. 5 mL were put into a vessel for analysis, 5 mL were pressed back to remove all particles of the filter and the cannula back to the dissolution vessel. The loss of media because of the taken sample was noted in the calculation with a value of 5 g (assumption: 1 mL = 1 g) each sample.

3.6 Scanning electron microscopy (SEM)

Electron micrographs were recorded using an acceleration voltage of 5 kV and a secondary electron detector for imaging. Samples were sputtered with a platinum palladium alloy ~ 3 nm and fixed on the specimen holder with conductive double sided adhesive tape.

3.7 Pump calibration

Concentrations in the tubular reactor could be calculated based on the pump rates of the used peristaltic pumps. To define a pump rate it is necessary to determine the transported volume. After the warm up of the pumps, the water collected over 5 minutes was weighted. Taking the mass of the collected water and the assumption that the density of water is 1000 kg per m^3 the transported volume could be calculated. This calibration procedure was implemented for all used pumps. To check the influences of pressure losses caused by the length of the tubular reactor or influences caused by the interactions of the pumps, the outlet of the whole tubular reactor was measured. In this case it was necessary to run all pumps at the same time.

A difference between the theoretical outlet of the tubular reactor (sum of the transported masses) and the real measured outlet of the tubular reactor was calculated to show variations. It is permissible to negligence this error because of its really low range caused by a small interaction of the pumps running at the same time.

4 Results and discussion

This section contains all important results. First, the results of the preliminary studies which were necessary to decide for a core-coating system are presented. The chosen systems (Ibuprofen as core material and HPMCP respectively Eudragit as coating material) are described in more detail. The resulting continuous coating processes are described precisely and the analytical results of the resulting microcapsules are presented.

4.1 Preliminary studies

The first experiment was reconstructed relating to the paper of Phares and Sperandio. There a procedure to coat acetylsalicylic acid (ASA) crystals with gelatine by coacervation is described. The coacervation is initiated by sodium sulfate solution (antisolvent) (Phares & Sperandio, 1964). Mollet and Grubenmann cited the same way for the production of microcapsules with ASA as core material and gelatine as coating material (Mollet & Grubenmann, 2000).

The second experiment was performed as described by Shimokawa et al, who described in their paper (Shimokawa et al., 2013) the possibility to coat phenacetin by coacervation. In this experiment ASA was used instead of phenacetin. The characteristic related to the solubility of ASA and phenacetin is very similar. Phenacetin as well as ASA are poor soluble in water but well soluble in ethanol. The hardening process, as described in the paper, required the use of formalin and ethanol. A modification of the hardening process was necessary because only ethanol was available.

The microencapsulation of ASA by ethyl cellulose was imitated as described from Bauer et al (Bauer et al., 2006, p. 362). To reproduce the experiment ASA crystals were suspended in a solution of ethyl cellulose. The coacervation process was induced by a temperature decrease.

All these mentioned procedures did not seem applicable for an execution in the tubular reactor. The gelatine systems for the microencapsulation of ASA crystals by the addition of sodium sulfate or ethanol were not reproducible. The system for encapsulating ASA crystals by ethyl cellulose was excluded because of the unpleasant handling of cyclohexane (toxic properties).

Based on the performed initial studies two systems were chosen for the tubular reactor. Both of these recipes containing ibuprofen as a core material while the surrounding layer is built by the two different polymers HPMCP and Eudragit. Tab. 4-1 concludes all processes currently being tried out.

Tab. 4-1 Summery of preliminary studies

API	Coating material	Process description	Comments
ASA	Gelatine	• ASA crystals get suspended in a gelatine solution at 37°C • Sodium sulfate solution is added • Hardening of microcapsules by adding ethanol	Problems while processing because of the formation of clumps and the impossibility of mixing.
ASA	Gelatine	• ASA crystals get suspended in a gelatine solution at 50°C • Sodium sulfate solution is added • Hardening of microcapsules by cooling	Problems while processing because of the formation of clumps and the impossibility of mixing.
ASA	Ethyl cellulose	• Cubic ASA crystals get suspended in an Ethyl cellulose solution at 80°C • Hardening of microcapsules by cooling	Problems because of necessary temperatures at the boiling point of cyclohexane used for ethyl cellulose solution.
Ibuprofen	Eudragit	• Ibuprofen crystals get suspended in an Eudragit-isopropanol solution • Sodium sulfate solution is added • Hardening of microcapsules by the addition of hydrochloric acid	Simple process which was absolutely replicable in the batch process.
Ibuprofen	HPMCP	• Ibuprofen crystals get suspended in a HPMCP solution • Sodium sulfate solution is added • Slowly heating up to 50°C • Hardening of microcapsules by the addition of acetic acid	Simple process which was absolutely replicable in the batch process.

First, it was necessary to modify the chosen systems to operate them in the tubular reactor. The tubular reactor was operated in axial direction this means that all reactants passed the tube in axial direction. At the tubing's inlet the polymer solution, the core material and the salt solution were mixed while the products and side products respectively unused educts were collected at the end of the tube.

Many batch experiments were necessary to find out essential parts of the experiments which had to be adapted to the tubular reactor.

By changing concentrations and rates and observing the process under the microscope it was possible to reduce the process steps to the most important. The batch experiments were based

on two papers which are presented in detail below (Weiß, Knoch, Laicher, Stanislaus, & Daniels, 1995b) (Weiß, Knoch, Laicher, Stanislaus, & Daniels, 1993).

4.2 Batch process for HPMCP microencapsulation

Based on the work of Weiß et al. (Weiß et al., 1995b) a HPMCP coating process operated continuously was developed. In this section the batch process as described by Weiß et al. is presented in detail. As a core material ibuprofen was used.

Preparation of HPMCP solution

4 g of disodium phosphate dihydrate were dissolved in 186 g of demineralized water. Afterwards, 10 g of HPMCP were dissolved in the solution. Stirring the solution for 10 hours at room temperature led to a little bit gleaming solution with a pH-value of 5.45 (± 0.05).

Preparation of the microcapsules

100 g of the prepared HPMCP polymer solution were filled into a beaker. 16.5 g of ibuprofen were suspended in the solution at room temperature and stirred for approximately 15 minutes. While stirring the suspension with a magnetic stirrer at 350 rpm, 60 g of 20 % sodium sulfate solution (antisolvent) were added drop wise over a time of 15 minutes. Afterwards, the suspension was heated up to 50°C (0.5°C/min) in a temperature regulated thermostatic bath to enhance the phase separation.

Heating up the suspension to 50°C was the first part of the hardening step. After, the microcapsules were put into a second beaker and washed three times with 100 g of 8.5 % sodium sulfate solution at 50°C. At the end of the process the microcapsules were harden by the addition of 75 g of 5 % acetic acid and stirred for 30 minutes.

To clean the microcapsules they were washed three times with 100 g of diluted acidic acid. Subsequently, the microcapsules were filtered and air-dried for 48 hours. After the drying process they were strained through a 500 µm sieve to remove agglomerates and coarse particles.

Observation during the batch process – microencapsulation by HPMCP

For a better understanding of coacervation by HPMCP the every step of the process described by Weiß et al. (Weiß et al., 1995b) was observed.

Samples were taken after the addition of 15 mL, 20 mL, 25 mL, 30 mL, 40 mL, 45 mL and 50 mL of 20 % sodium sulfate solution and observed under the microscope. Also some samples were taken during the heating process at 30°C, 35°C, 40°C, 45°C and 50°C. After every washing step with 8.5 % sodium sulfate solution, after the hardening process with 5 % acetic acid and after the washing with diluted acetic acid a sample was taken.
Just in this one case exceptionally not the described raw material ibuprofen 25 (see section 3.2.1) was used. The used ibuprofen was not specified exactly but because of much bigger crystals size, the observation of the process was easier.

Fig. 4-1 shows many small parts of crystals. This crystal parts were maybe formed by a milling effect of magnetic stirring. Till to the addition of 15 mL of 20 % sodium sulfate solution no phase separation was observable.

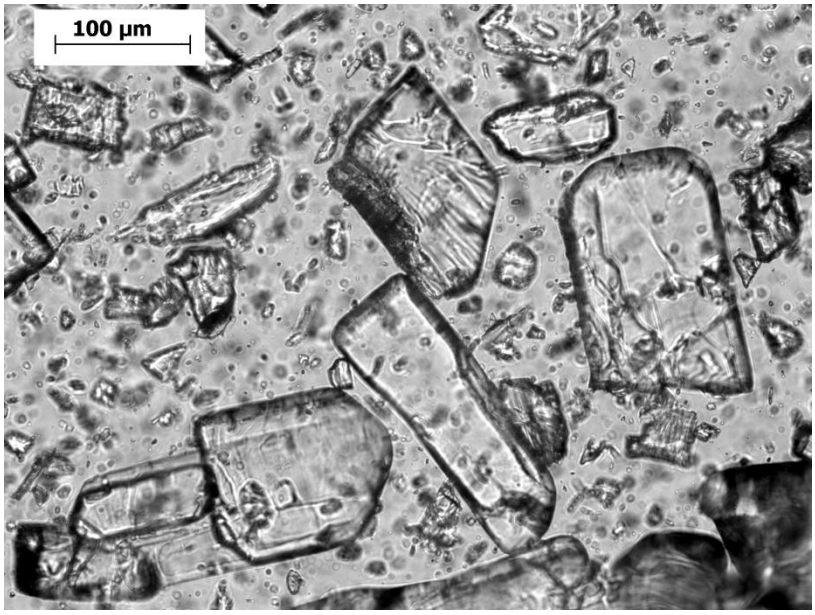

Fig. 4-1 Micrograph of the coacervation process after addition of 15 mL of 20 % sodium sulfate solution.

The addition of 35 mL of 20 % sodium sulfate solution led not to a phase separation. This is noticeable in Fig. 4-2.

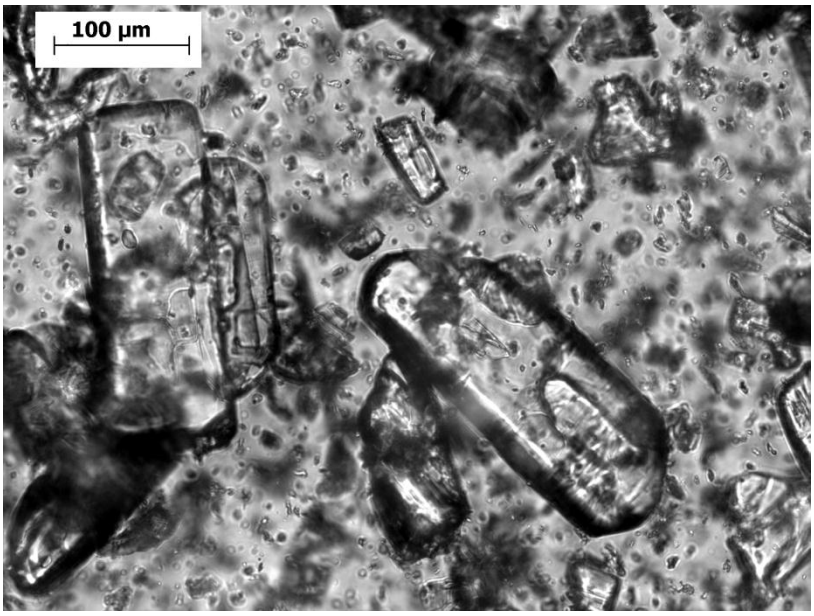

Fig. 4-2 Micrograph of the coacervation process after the addition of 35 mL of 20% sodium sulfate solution.

After the addition of 45 mL of 20 % sodium sulfate solution a phase separation in the form of emulsion drops in the background was recognizable (see Fig. 4-3).

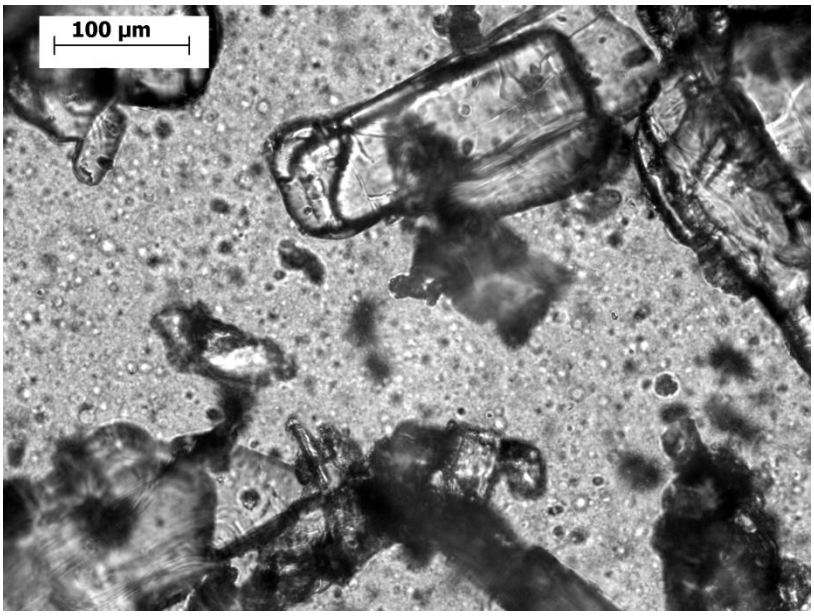

Fig. 4-3 Micrograph of the coacervation process after the addition of 45 mL of 20 % sodium sulfate solution.

As shown in Fig. 4-4 the addition of 50 mL of 20 % sodium sulfate solution led to bigger emulsion drops and the formation of the coacervate layer started. The mark shows the formation process of the coacervate layer around an ibuprofen crystal.
Fig. 4-5 shows the encapsulation by the polymer rich phase around the crystal before starting the heating process.

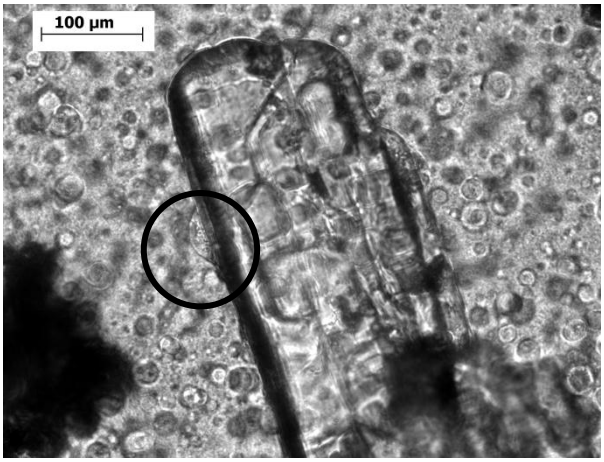

Fig. 4-4 Micrograph of a sample of the coacervation process after the addition of 50 mL of 20 % sodium sulfate solution. The mark shows the formation of the surrounding coacervate layer.

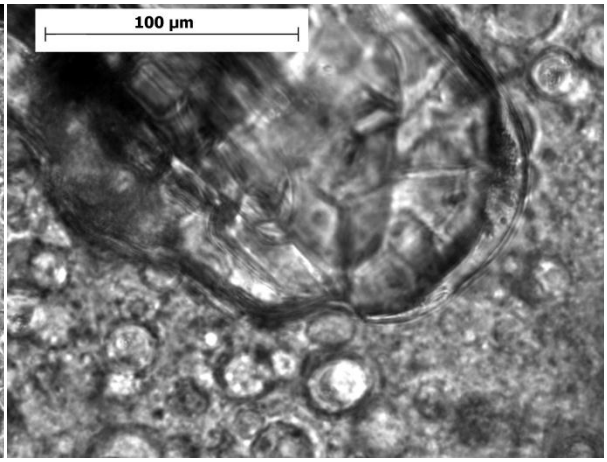

Fig. 4-5 Micrograph of a sample of the coacervation process after the addition of 50 mL of 20 % sodium sulfate solution.

At 30°C the coacervate layer became more definite. Fig. 4-6 shows an example of a fully encapsulated ibuprofen crystal. This sample contained also many agglomerates. It was noticeable that many emulsion drops (the polymer rich phase) were not included in the coacervate phase around the crystal.

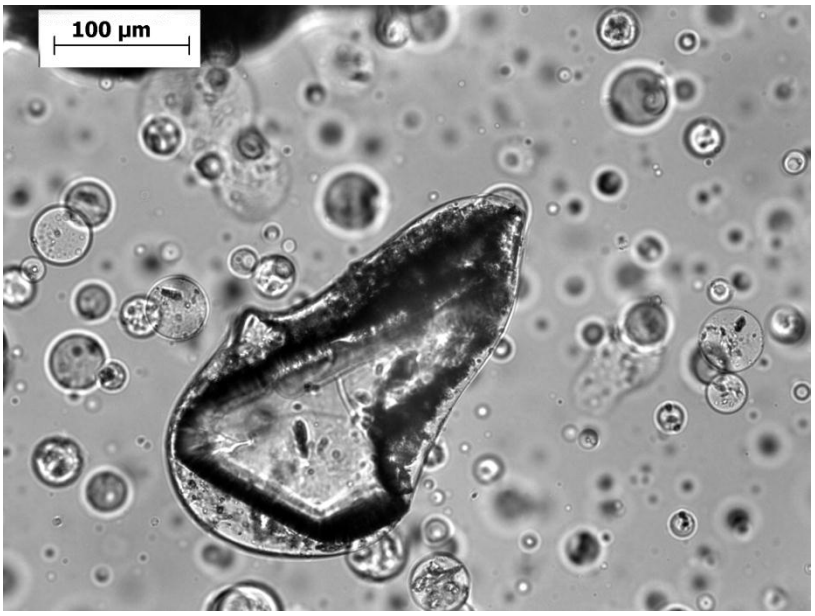

Fig. 4-6 Micrograph of a sample of the coacervation process after heating up to 30°C. In the background are many emulsion drops recognizable.

In Fig. 4-7 it is possible to see one of the biggest problems of the coacervation process. Agglomeration became obvious and for that reason an encapsulated crystal adheres to another one. Also noticeable is the increasing of the thickness of the coacervate layer.

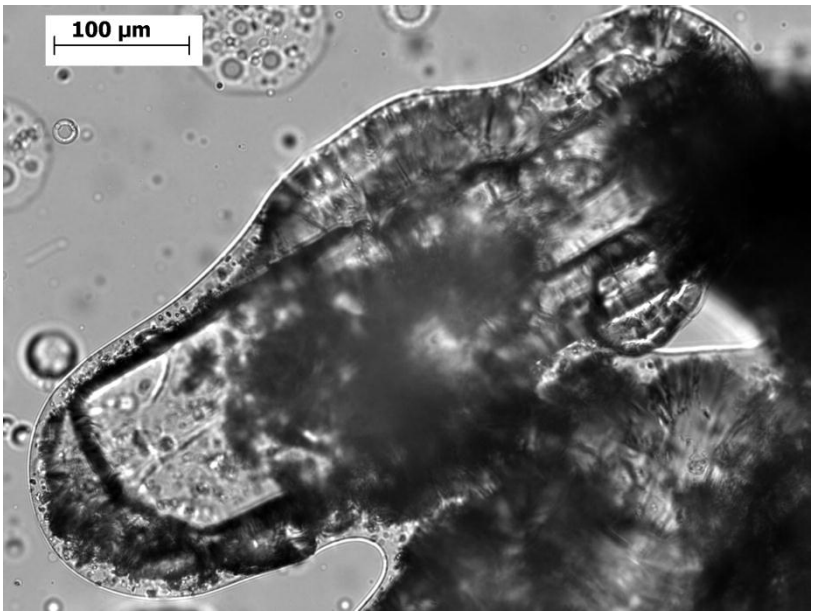

Fig. 4-7 Micrograph of the coacervation process after heating up to 35°C.

A very well encapsulated ibuprofen crystal is shown in Fig. 4-8. Recognizable was the lower amount of emulsion drops. The size of the emulsion drops increased or they were included in the coacervate layer around the ibuprofen crystals.

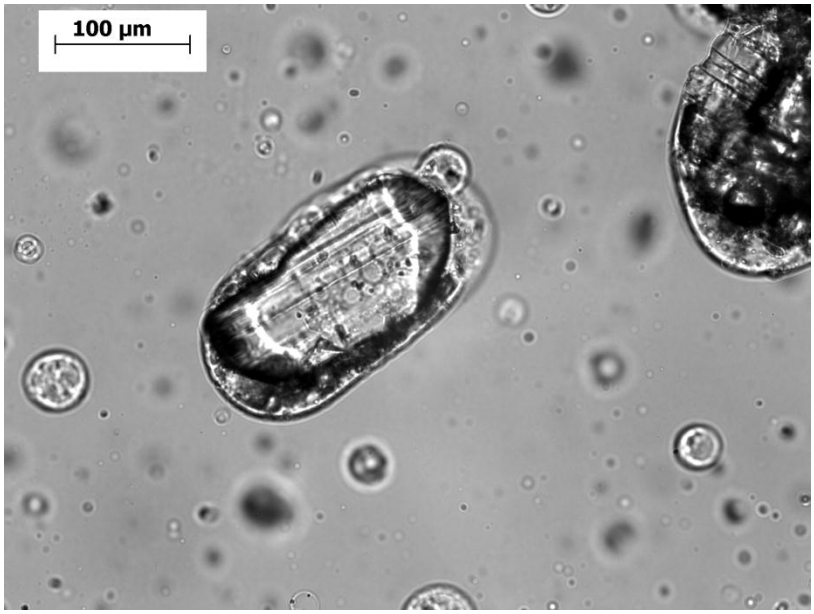

Fig. 4-8 Micrograph of the coacervation process of after heating to 40°C.

In Fig. 4-9 agglomerated crystals are shown. A different appearance of the coacervate layer as in Fig. 4-8 is recognizable. The layer seems to be lesser swollen.

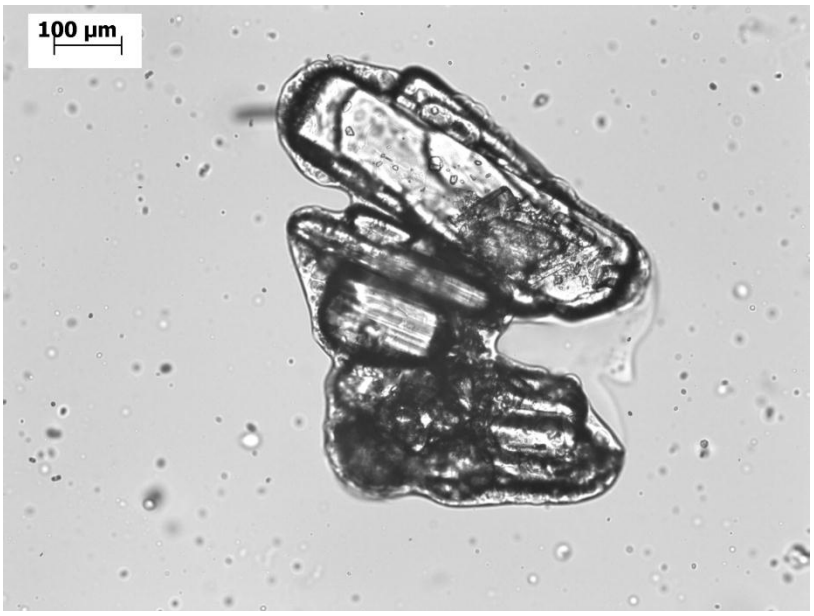

Fig. 4-9 Micrograph of a sample of the coacervation process after heating up to 45°C.

After the heating process, the appearance of the coacervate layer was cloudy. The special shape of the coacervate layer because of centrifugal force, induced by stirring, is observable in Fig. 4-10.

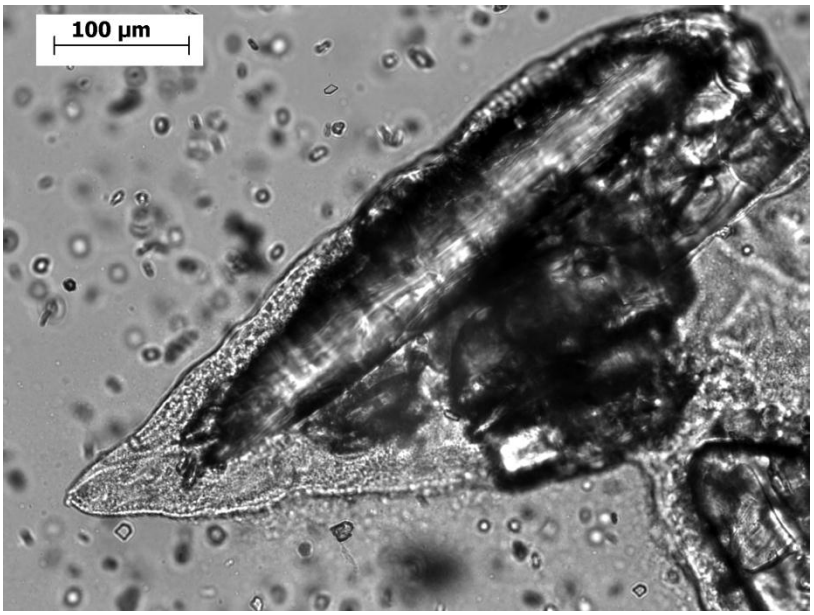

Fig. 4-10 Micrograph of the coacervate phase of the coacervation process after the heating process at 50°C.

Subsequently, the microcapsules were washed three times with 8.5 % of sodium sulfate solution. It is noticeable that most of redundant polymer was removed what is caused by the washing steps. Fig. 4-11 presents a typically example for the produced microcapsules. A high level of agglomeration is recognizable.

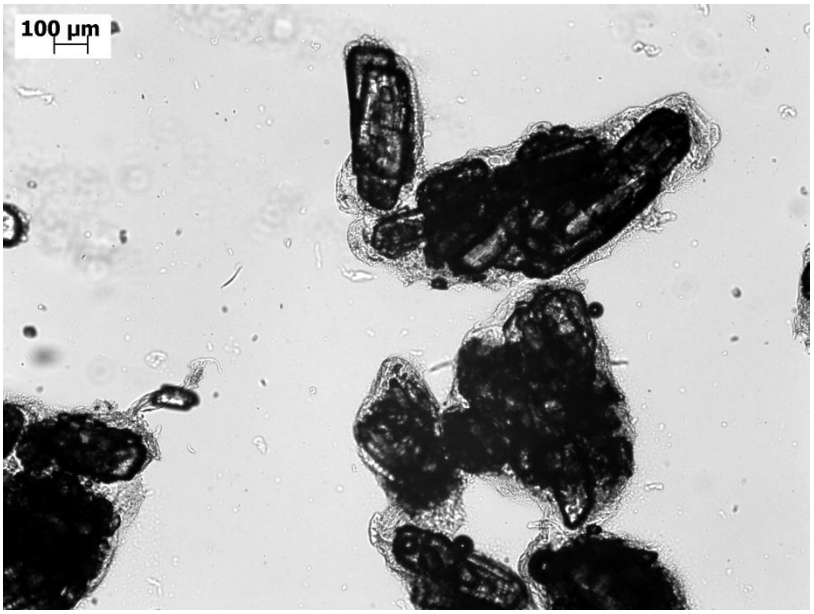

Fig. 4-11 Micrograph of the coacervation process after three times washing with 8.5 % sodium sulfate solution.

A good example for a produced microcapsule is shown in Fig. 4-12. The figure shows the microcapsule after washing the microcapsules three times with diluted acetic acid.

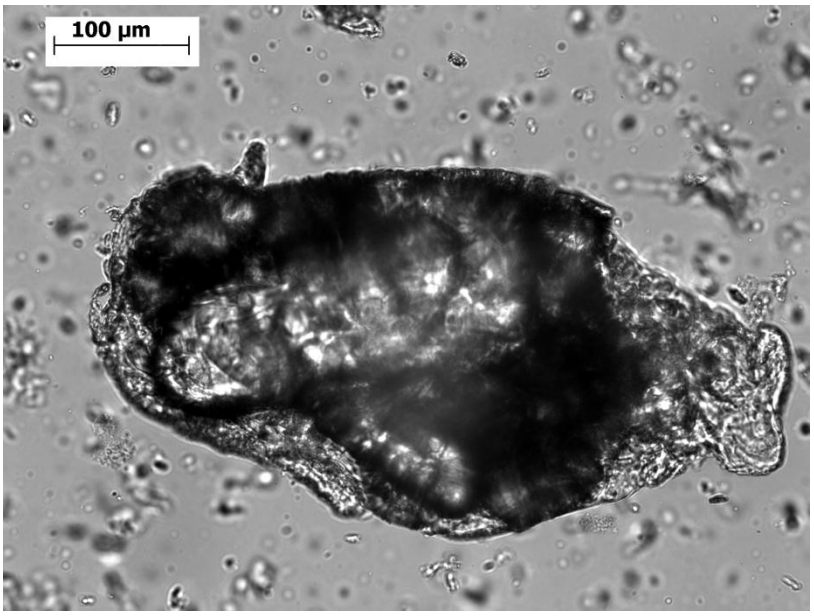

Fig. 4-12 Micrograph of the coacervation process after hardening with 5 % acetic acid and washing three times with diluted acetic acid.

4.3 Batch process for Eudragit microencapsulation

The coacervation system of ibuprofen and Eudragit was tested using the recipe described in the paper of Weiß et al. (Weiß, Knoch, Laicher, Stanislaus, & Daniels, 1993).

Preparation of the Eudragit-solution

10 g of Eudragit were suspended in 450 g of demineralized water. Then 17.5 mL of a 1 N sodium hydroxide solution were added. The solution was filled up to 500 g by water and stirred for 5 hours until it became a clear solution with a pH-value of 5.85 ± 0.05.

Preparation of the microcapsules

30.6 g of 2-propanol was mixed with 100 g of the Eudragit solution. 6.6 g of ibuprofen were suspended afterwards at least 15 minutes before the experiments were executed. Afterwards, 21.35 g of a 20 % sodium sulfate solution (antisolvent) were added dropwise to induce the phase separation. Then the mixture was poured dropwise into 0.8 L of a diluted hydrochloric acid (pH-value: 3) for 10 minutes. The capsules were rinsed three times with diluted hydrochloric acid to remove the residual polymer. The capsules were hardened by decantation in 30 g of a 0.1 N hydrochloric acid for 30 minutes. The microcapsules were washed with a 0.25 % acetic acid solution to remove residual polymer material and the antisolvent from the

shell. Then, the capsules were filtered and air-dried at room temperature for 48 hours. At least, the processed capsules were passed through a 500 μm sieve.

4.4 Continuous process for HPMCP microencapsulation

Following sections describe the developed continuous coating process for the HPMCP microencapsulation

4.4.1 Setup and Experiments

For the continuous coating process a tubular reactor was built up using polysiloxane tubes. Three peristaltic pumps were used, termed as P I, P II and P III. Connections between the tubes in the pumps and the feeding tubes were made by straight fittings. Y-fittings were applied to mix the solutions etc. within the tubular reactor. To enhance mixing and avoid agglomeration of the particulate phase "Crossers" were integrated in the tubing. Two thermostatic B I and B II were used to temper the tubing. Two magnetic stirrers, S I and S II, were used for stirring and heating. A microscope was applied to investigate the microencapsulation behavior during the process development. Dried microcapsules were sieved by a sieve tower.

First, the HPMCP solution was prepared as described for the HMPCP microencapsulation batch process (see section 4.2) and (Weiß et al., 1995b).
The stock suspension was prepared by suspending 40 g of ibuprofen in 400 g of the HPMCP solution (=440 g stock suspension) at least 15 minutes before experiments were executed. Beforehand, the used ibuprofen powder was passed through a 300 μm sieve to loosen ibuprofen clumps of the purchased ibuprofen powder.

The schematic draft of the developed continuous HPMCP microencapsulation in the tubular reactor is shown in Fig. 4-13. P I was used to feed the stock suspension into the tubular reactor with a pumping rate of 11.9 mL/min. The stock suspension was stirred during the entire process in a 1 L beaker placed on the magnetic stirrer S I. The two slots of the second pump P II (2 X 2.0 mL/min) were used to add the 20 % sodium sulfate solution, i.e. the antisolvent, in two steps. Two Y-fittings, placed 1.75 m and 2.75 m after P I, were applied to mix the 20 % sodium sulfate solution with the stock suspension. Between both Y-fittings 1 m of tubing tube was installed to enable sufficient mixing. After the second Y-fitting the

antisolvent concentration was sufficient to induce coacervation. This part of the tubular reactor was tempered at 21.5°C in a thermostatic bath (B I). The 20 % sodium sulfate solution was stirred at 50°C (S II) to guarantee that the entire sodium sulfate remains dissolved. The 50°C hot 20 % sodium sulfate solution was precooled in B I by a 0.9 m of tube before entering the tubular reactor.
To provoke further phase separation and therefore microencapsulation it was necessary to heat up the mixture (prehardening). For this reason the successive part of the tubular reactor was tempered at in the thermostatic bath (B II). Three of the "Crossers", were integrated approximately every 0.7 m. Further three "Crossers" were built in shortly before the outlet. In total, 4.4 m of tubing were installed after the second Y-fitting used for the antisolvent addition.

The hardening of the HPMCP microcapsules was realized in two different ways. The hardening step was executed outside the tubular reactor (hereafter referred as "external hardening") or inside the tubular reactor (hereafter referred as "internal hardening").
In the case of external hardening, the microcapsules were collected at the reactor's outlet. The collecting vessel was tempered at 50°C (Beaker, 1 L, located in B II) to maintain current state of phase separation in the tubular reactor. After the whole run, i.e. the entire stock suspension was processed, the supernatant was decanted and the capsules were hardened by adding 300 g of 5 % acetic acid (as described in section 4.2). Subsequently, the microcapsules were stirred for 30 minutes and filtrated by a pleated filter. The microcapsules were dried for 48 hours at room temperature under the fume cupboard.

In the case of internal hardening 1.3 m of tube followed the prehardening step in B II. By means of a third pump (P III, 34 mL/min) a 7.5 % acetic acid solution was fed into the tubular reactor via a third Y-fitting. After additional 0.5 m of tubing, the hardened microcapsules were collected in a 1 L beaker. Afterwards, the supernatant was decanted and the microcapsules were filtered by a pleated filter. The microcapsules were dried for 48 hours at room temperature under the fume cupboard.

All washing steps described in the batch process for HPMCP microencapsulation (see section 4.2) and (Weiß et al., 1995b) were excluded for the continuous tubular process. The pumping rates of P I and P II, the temperatures and tube lengths were tuned in order to find process settings that enable a good encapsulation behavior of the core material as well as a minimum

of agglomeration. An exact tuning of the pumping rates was impossible because of the interplay between the pumps (see section 3.7).

1 g of the microcapsules produced in the tubular reactor with internal hardening was washed with 100 mL of a 0.25 % acetic acid solution and stirred for 15 minutes. This additional washing step was done to test if the purification leads to different results in the microencapsulation quality and dissolution studies.

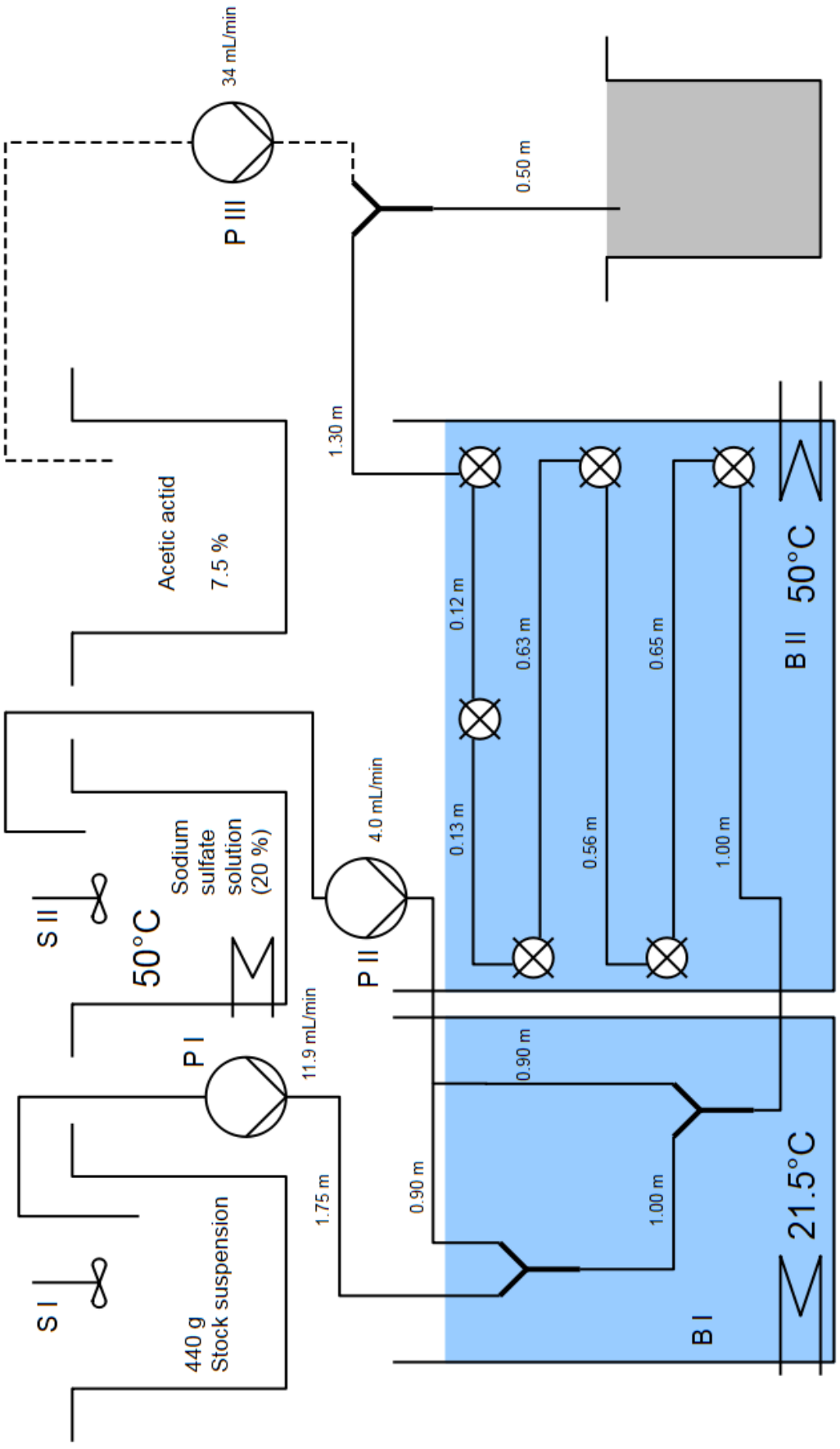

Fig. 4-13 Schematic draft of the coating process containing the whole process described in section 4.4. The broken line shows the production of microcapsules by internal hardening.

4.4.2 Analysis of microcapsules microencapsulated by HPMCP

The quality of the produced HPMCP microcapsules was investigated due to three different techniques. Optical as well as electron micrographs were recorded. In addition dissolution studies were performed in acidic pH 4 buffer media to quantify the release of ibuprofen coated with HMPCP, i.e. an enteric polymer. The microcapsules were produced as described in section 4.4 (internal hardening, external hardening and internal hardening including an additional washing step).

The optical micrographs of the unsieved uncoated ibuprofen as well as the produced microcapsules are depicted in Fig. 4-14 - Fig. 4-17.

Microcapsules depicted in Fig. 4-15 were produced by external hardening. Although the figure shows a large number of microcapsules, the micrograph indicates as well that some of the ibuprofen crystals are not encapsulated completely. Furthermore, fractions of hardened polymer material are apparent beside the microcapsules. Fig. 4-16 evidences that most of the microcapsules produced with the internal hardening procedure are encapsulated. Nevertheless, a lot of residual polymer is present beside the microcapsules. Fig. 4-17 shows that microcapsules produced using the internal hardening including an additional washing step are well encapsulated as well. Only minor amounts of residual polymer, probably due to the additional washing as described above, are present.

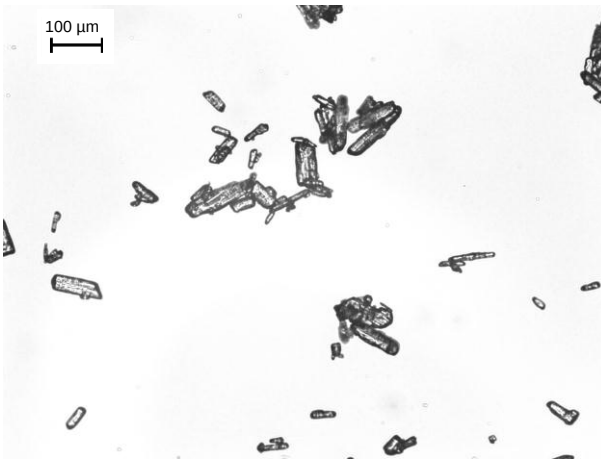

Fig. 4-14 Micrograph of the uncoated ibuprofen (characterization see section 3.2.1).

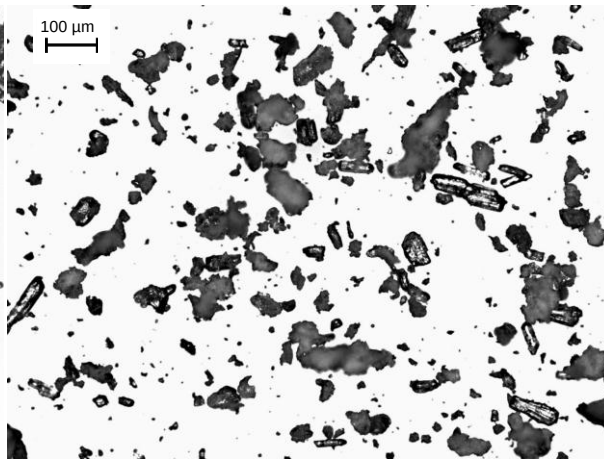

Fig. 4-15 Micrograph of microcapsules encapsulated by HPMCP. Microcapsules were produced (see section 4.4.1) with external hardening.

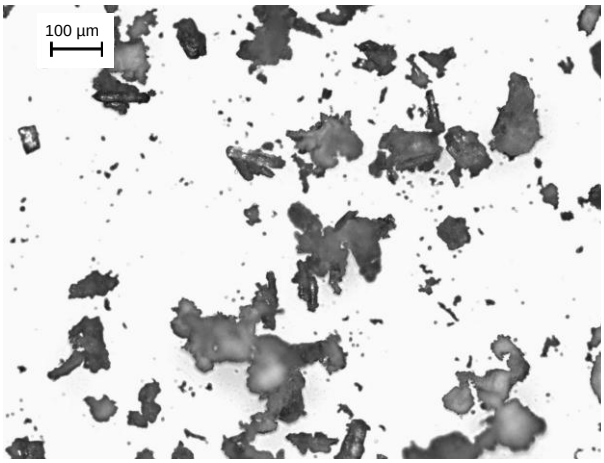

Fig. 4-16 Micrograph of microcapsules encapsulated by HPMCP. Microcapsules were produced by internal hardening (see section 4.4.1).

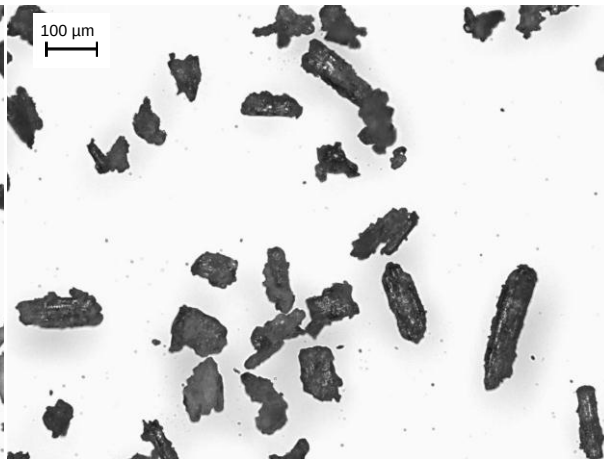

Fig. 4-17 Micrograph of microcapsules encapsulated by HPMCP. Microcapsules were produced with internal hardening (see section 4.4.1). An additional washing step with 0.25 % acetic acid was performed as described in section 4.4.1.

Tab. 4-2 delineates a summary of the produced microcapsules as described in section 4.4. The determined ibuprofen contents of the microcapsules (see section 3.4) and the weights of microcapsules needed for the dissolution studies (see section 3.5) are summarized.

Tab. 4-2 Summary of the ibuprofen contents of the HPMCP microcapsules and the weights of microcapsules for the dissolution studies (referring to 60 mg uncoated ibuprofen).

Process	Ibuprofen content [%]	Weight for dissolution studies [g]
External hardening	75.40 ± 4.14	0.0630*
Internal hardening	53.80 ± 2.00	0.1115
Internal hardening and additional purification with 0.25 % acetic acid	75.02 ± 0.27	0.0800

*This calculation was based on a wrong ibuprofen content of 95.2 % which was evaluated in a second ibuprofen content determination.

Fig. 4-18 shows the results of the dissolution studies of the microcapsules produced with external hardening (see section 4.4.1). The release measurement after 10 minutes was excluded from the analysis because of inconclusive UV/VIS spectra. The inconclusive spectra might originate from the presence of acetic acid and the low ibuprofen concentrations (signal to noise ratio). After a rapid increase in the ibuprofen release, the dissolution profile, i.e. release over time, flattens. The dissolution study lasted two hours and a final ibuprofen release of 72.9 % was determined. The microcapsules show a slower ibuprofen release than uncoated ibuprofen crystals. Hence a retardation effect can be observed.

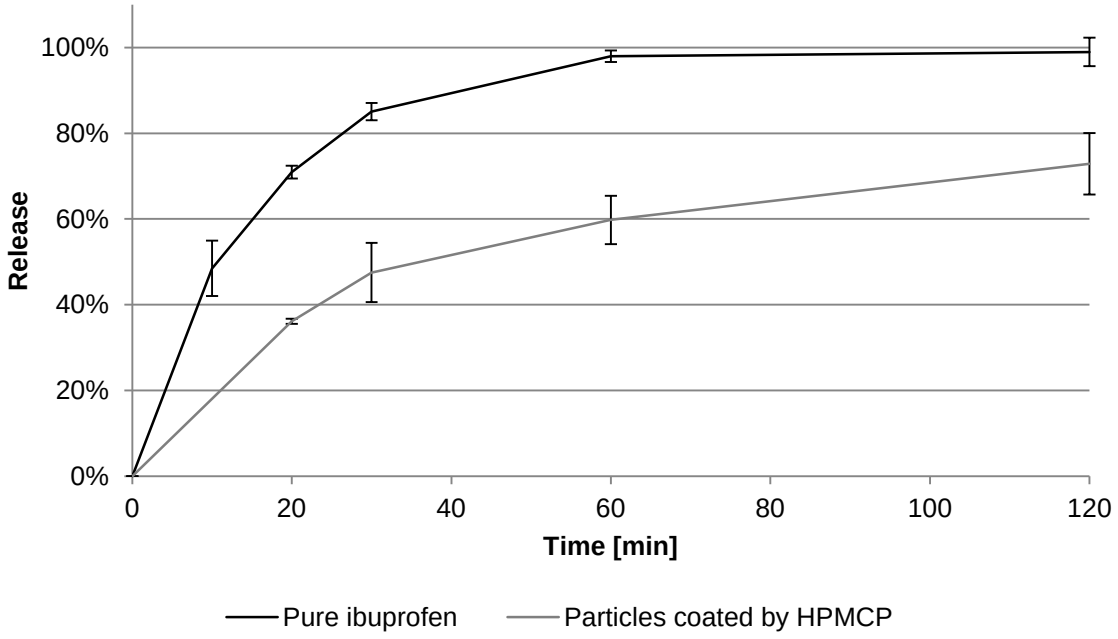

Fig. 4-18 Result of the dissolution study. The ibuprofen release of microcapsules encapsulated by HPMCP in comparison to the uncoated ibuprofen is depicted. The microcapsules were produced as described in section 4.4 with external hardening. The release at 10 minutes was excluded because of an inconclusive spectrum.

Fig. 4-19 shows the dissolution profile of the microcapsules produced with the internal hardening step (see section 4.4.1) in comparison to the uncoated ibuprofen crystals. The dissolution profile of the microcapsules and the uncoated ibuprofen is very similar. A clear retardation effect could not be observed. The missing retardation effect could be a reason of a failed quantification of the ibuprofen content in the microcapsules. There is the idea that an esterification is possible under these conditions. If this proposition is right, impurities of acetic acid in the shell of the microcapsules, reacts with the ethanol used for the quantification of the ibuprofen content. The resulting esters could maybe influence the quantification of the

ibuprofen content. Higher ibuprofen contents would lead to an absolutely different dissolution profile due to a change of the maximum ibuprofen release. There are no conclusive reasons why two of three measured spectra at 30 minutes were inconclusive. Maybe there was an error in UV/Vis measurement or in sample taking.

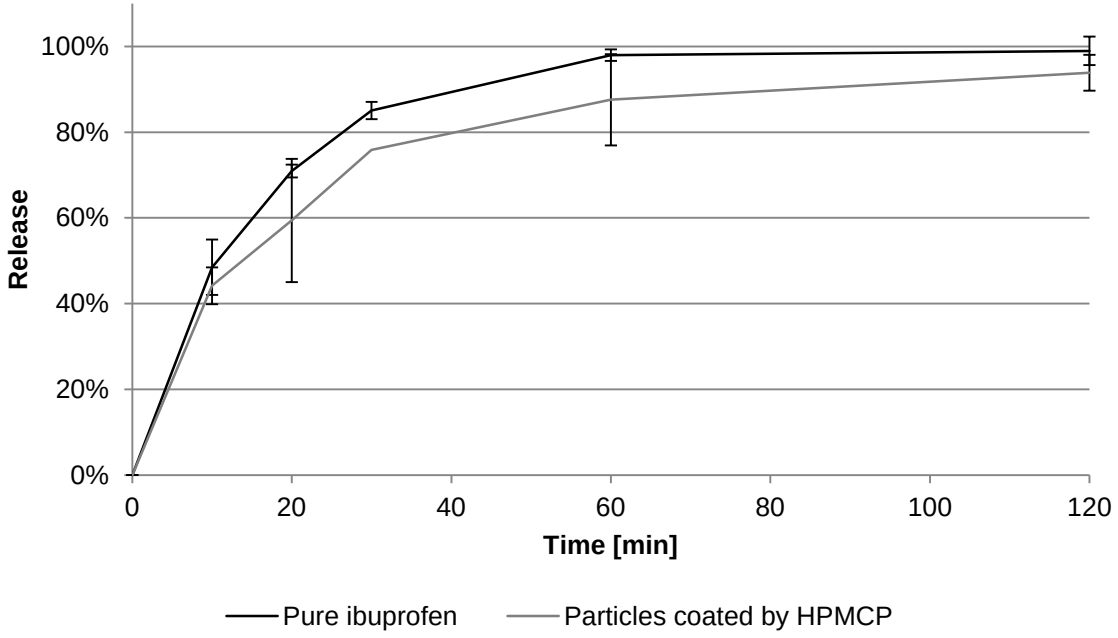

Fig. 4-19 Result of the dissolution study. Release of microcapsules encapsulated by HPMCP in comparison to the uncoated ibuprofen. The error bar at 30 minutes is missing because just one measuring point was evaluable (inconclusive spectra). The microcapsules were produced (see section 4.4.1) with internal hardening.

The dissolution profile of produced microcapsules (see section 4.4.1) in comparison with the uncoated ibuprofen is represented in Fig. 4-20. These microcapsules were produced with internal hardening and an additional washing step with 0.25 % acetic acid. The ibuprofen release of microcapsules washed by acetic acid show more retarding effect then the microcapsules without washing (see Fig. 4-19). This fact supports the theory of esterification described in the paragraph above. The washing of microcapsules leads to a lower level of acetic acid in the shells of microcapsules and reduce the influences on the quantification of the ibuprofen content. Due to inconclusive spectra at 10 minutes two of three measuring points had to be excluded.

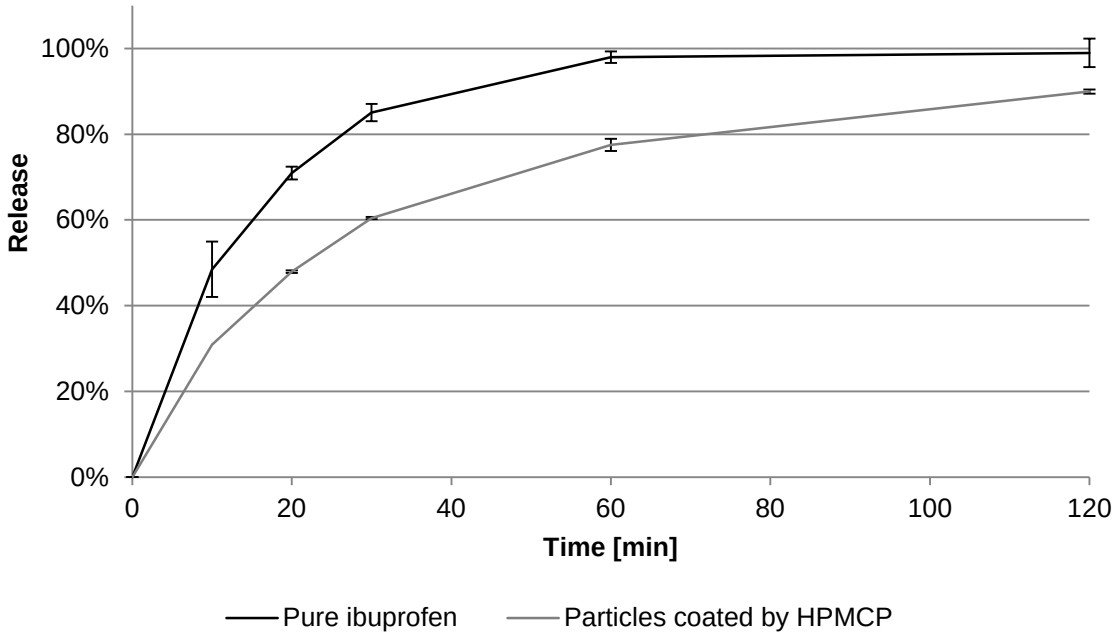

Fig. 4-20 Result of the dissolution study. Depicted is the ibuprofen release of microcapsule encapsulated by HPMCP in comparison to the uncoated ibuprofen. The microcapsules were produced with internal hardening and an additional purification of the resulting microcapsule with 0.25 % acetic acid (see section 4.4.1).The error bar at 10 minutes is missing because only one measuring point was evaluable.

Micrographs of processes material evidence a good microencapsulation of the core material, i.e. ibuprofen crystals. Nevertheless, dissolution studies exhibit a good retardation effect only if the hardening step was performed externally. The presented continuous HPMCP coating process and especially the hardening step requires further development to ensure a sufficient enteric coating of the core material. However, the achieved coating seems appropriate for sustained release applications and to protect an API from environmental influences.

The third technique to investigate the quality of the produced HPMCP microcapsules was scanning electron microscopy. Electron micrographs of the produced microcapsules were taken at several magnifications (see Fig. 4-21). The uncoated ibuprofen is characterized by its nearly rectangular shaped crystals (B) and the special wavy surface (A). The microcapsules produced with external hardening (see section 4.4.1) show a much more irregular surface (C). Even the general expression of the microcapsules is irregular shaped. Beside the microcapsules no residual polymer is noticeable (D). Microcapsules produced in the tubular reactor with internal hardening (see section 4.4.1) lead to rugged surfaced crystals (E) and much more residual polymer beside the microcapsules (F). Residual polymer is washed away (H) by the use of 0.25 % acetic acid (see section 4.4.1) and also the surface becomes cleaner (G).

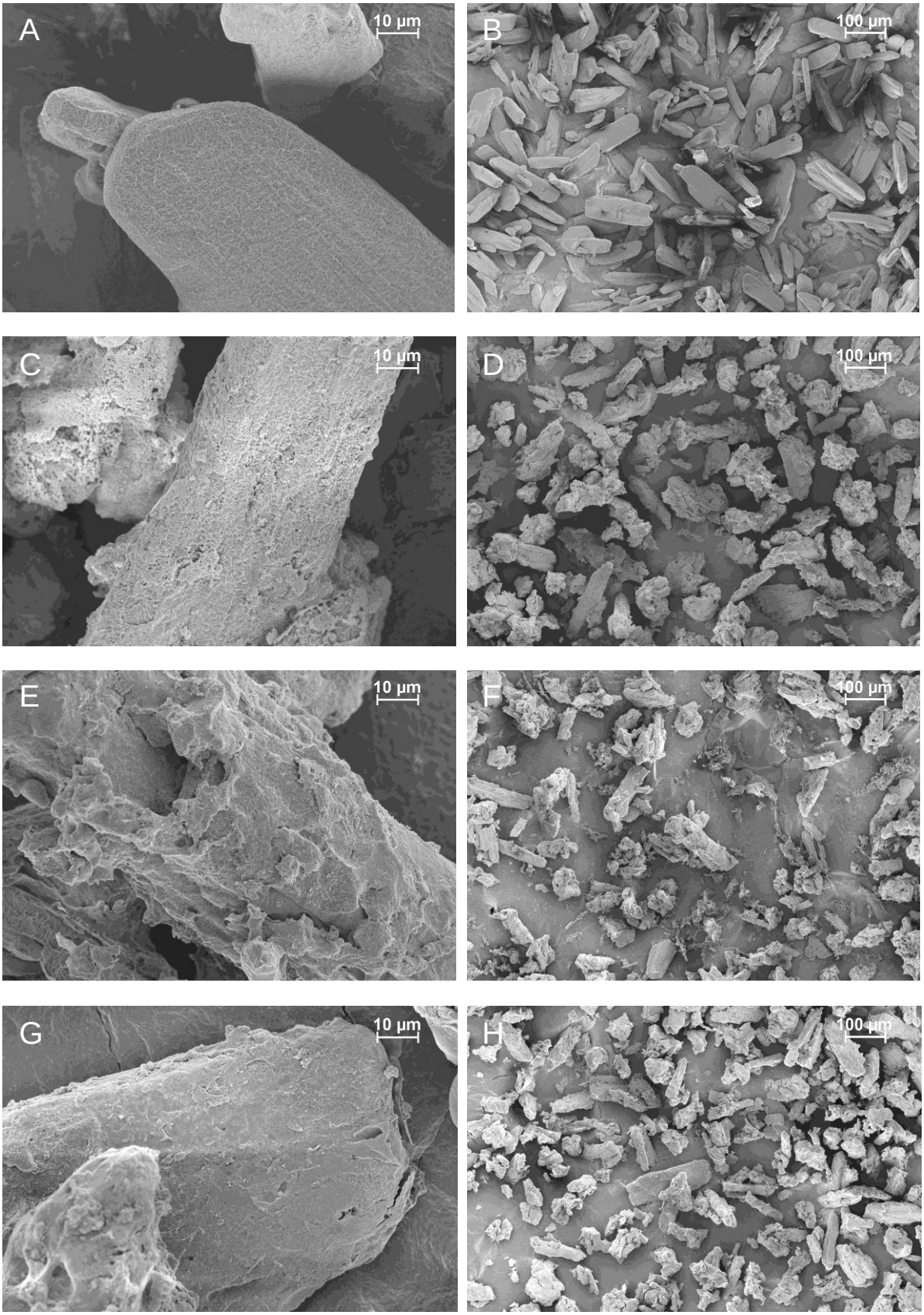

Fig. 4-21 Electron micrographs of the uncoated ibuprofen and the produced microcapsules. A, B: Uncoated ibuprofen characterized in section 3.2.1. C, D: Microcapsules produced with external hardening (see section 4.4.1). E, F: Microcapsules produced with internal hardening (see section 4.4.1). G, H: Microcapsules produced with internal hardening and an additional washing step by diluted acetic acid (see section 4.4.1).

By comparing the surfaces of the produced microcapsules (see Fig. 4-22) it is recognizable that the surface of the uncoated ibuprofen (I) is regular wavy while the surface of the produced microcapsules is full of bubbles (J, K, L). Microcapsules produced in the tubular reactor (see section 4.4.1) with external hardening show a regular surface containing different layers (J). Differences to the microcapsules produced with internal hardening are noticeable especially related to the homogeneity of the surface (K) which looks much more rugged. In the picture (K) also crystals of a third substance are visible. It can be assumed that this third substance is either an acetate crystal built by the impurities of acetic acid or a sodium sulfate crystal built by impurities of the antisolvent. The microcapsules washed by diluted acetic acid (see section 4.4.1) show a more regular bubbled surface (L) than microcapsules without the washing step. The lack in the coating layer (L) is probabilistic created by a defect made by the electron microscope.

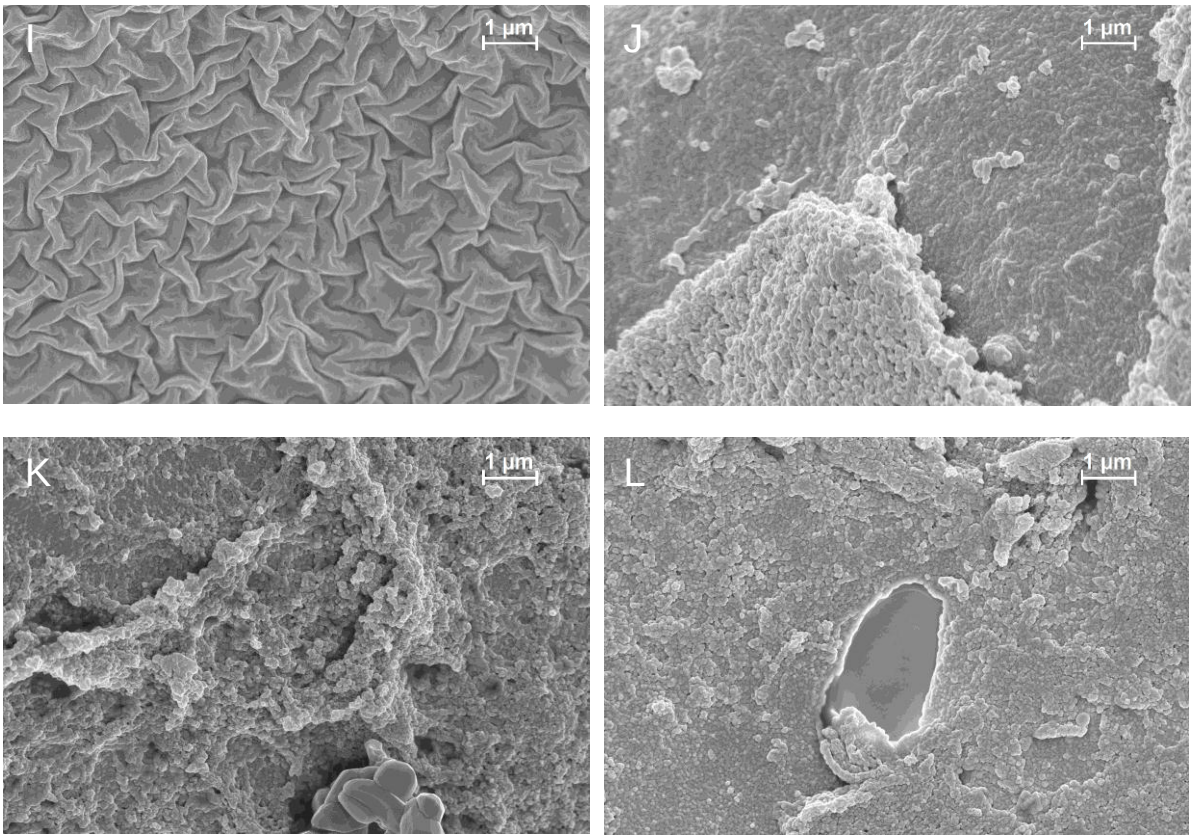

Fig. 4-22 Electron micrographs of the surfaces of the uncoated ibuprofen and the produced microcapsules. I: uncoated ibuprofen. J: Microcapsules produced with external hardening (see section 4.4.1). K: Microcapsules produced with internal hardening (see section 4.4.1). L: Microcapsules produced with internal hardening and washed by diluted acetic acid (see section 4.4.1).

A good illustration for residual polymer lying beside the microcapsules in the case of internal hardening is show in Fig. 4-23. A third substance (maybe an acetate crystal or a sodium sulfate crystal) which can also be found in Fig. 4-22 (K) is noticeable in the polymer.

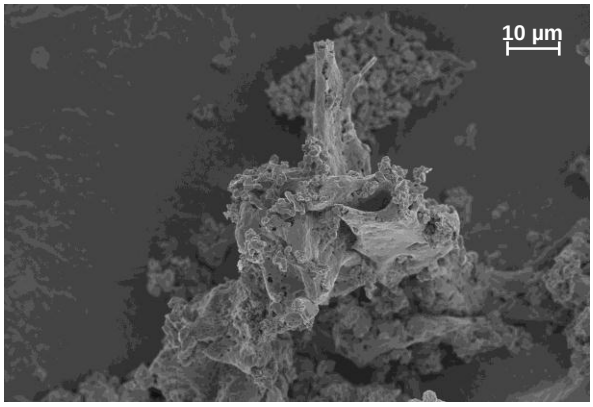

Fig. 4-23 Polymer without ibuprofen crystal inside. Side product while producing microcapsules in the tubular reactor with internal hardening (see section 4.4.1).

4.4.3 Appearance of the coacervate layer – temperature dependency

The polymer content in the coacervate phase is temperature dependent in a high level. As a result the viscosity (and therefore agglomeration) and the encapsulation behavior can vary impressive even for minor changes in temperature. An experimental setup to demonstrate this dependency was realized by a modification of the setup described in section 4.4. The coacervate phase was observed under the microscope before the heating step. The process was executed in a thermostatic bath at various temperatures between 17°C and 24°C (see Fig. 4-24). Afterwards, the microcapsules were collected and observed under the microscope.

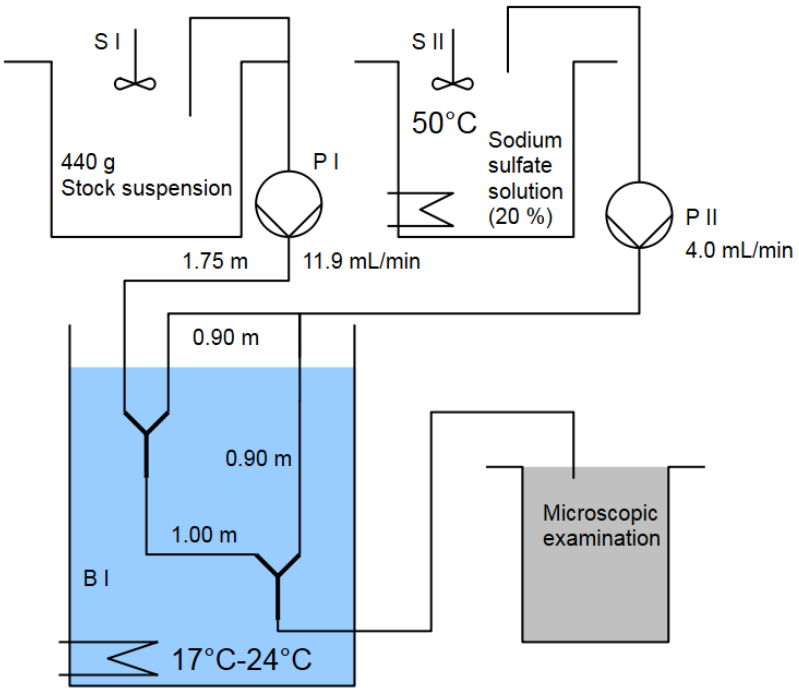

Fig. 4-24 Schematic draft of the microscopic examination of the coacervate layer to observe the temperature dependency

Fig. 4-25 shows the temperature dependency of the coacervate layer. If the process is executed at 17°C no coacervate layer is recognizable. This is changing if the processing temperature is increased to 19°C where a first thin coacervate layer is formed. When adding 20 % sodium sulfate solution at 21°C the resulting coacervate layer is thicker but the polymer layer is very translucent and instable. A much more firm layer is reachable by the addition of 20 % sodium sulfate solution at 22°C. All temperatures higher than 22°C cause a higher tendency to agglomeration. This fact can be also reflected in the image at 24°C where built agglomerates are depicted.

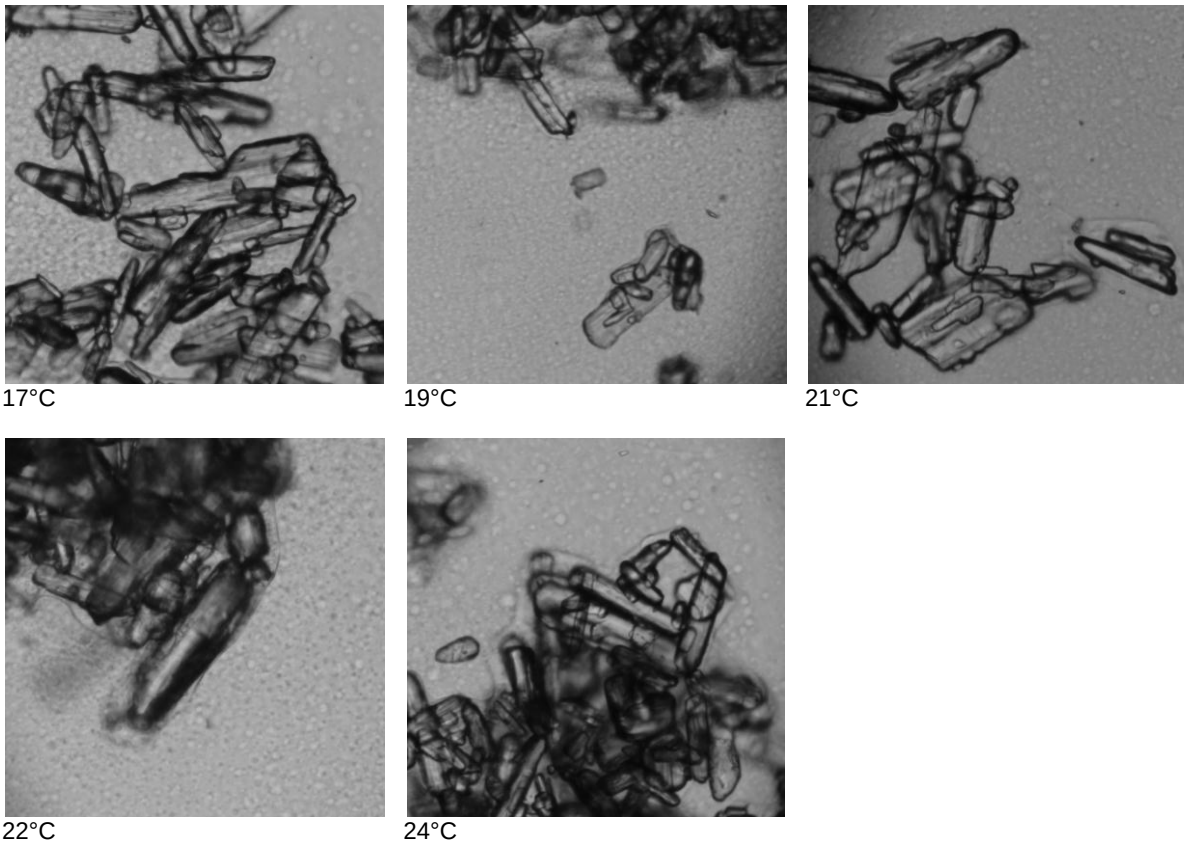

Fig. 4-25 Micrograph of ibuprofen crystals and the surrounding coacervate layer. Each image shows the coacervate layer which is built at current temperatures induced by the addition of 20 % sodium sulfate solution at this temperature. Differences in appearance are noticeable brought about by the different temperatures. Low temperatures cause a loose coacervate layer. Rising temperatures affect a much more jelly coacervate layer.

4.5 Continuous process for Eudragit microencapsulation

Following sections describe the developed continuous coating process for the Eudragit microencapsulation.

4.5.1 Setup

For the continuous coating process a tubular reactor was built up using polysiloxane tubes. Three peristaltic pumps were used, labeled as P I, P II and P III. Connections between the tubes in the pumps and the feeding tubes were made by straight fittings. Y-fittings were applied to mix the solutions etc. within the tubular reactor. To enhance mixing and avoid agglomeration of the particulate phase "Crossers" were integrated in the tubing. Two thermostatic B I and B II were used to temper the tubing. Two magnetic stirrers, S I and S II, were used for stirring and heating. A microscope was applied to investigate the microencapsulation behavior during the process development. Dried microcapsules were sieved by a sieve tower.

Eudragit solutions were prepared as described for the Eudragit microencapsulation batch process in section 4.3 (Weiß et al., 1993).
For the stock suspension 91.8 g of isopropanol were mixed with 300 g of the produced Eudragit solution. 15 g of ibuprofen were passed through a 300 µm sieve to loosen ibuprofen clumps. Afterwards, the ibuprofen was suspended in the Eudragit solution at least 15 minutes (=406.8 g stock suspension).

The process (schematic draft see Fig. 4-26) started by feeding (P I = 8.7 mL/min) the stock suspension (which was stored in a 1 L beaker and stirred the whole time by S I) into the tubular reactor. The 20 % sodium sulfate solution (which was stored in a 1 L beaker, stirred by S II and tempered to 50°C) was added by the two slots of P II (2 x 0.65 mL/min) in two steps via two Y-fittings, placed 1.75 m and 2.75 m after P I. Between both Y-fittings 1 m of tubing tube was installed to enable sufficient mixing. The 50°C hot 20 % sodium sulfate solution was precooled in B I by a 0.9 m of tube before entering the tubular reactor. After the second Y-fitting the antisolvent the concentration was sufficient to induce coacervation. Next, time and mixing were necessary to increase the coacervate layer and reduce agglomeration. Three of the "Crossers", were fitted approximately every 0.7 m of tube. Shortly before the outlet, another three of the "Crossers" were built in. After the second Y-fitting used for the antisolvent addition, 4.4 m of tubing were installed in total.

Relating to Weiß et al. (Gerd Weiß, 1991, p. 62) it was necessary to implement the process at 25°C. At this temperature the solubility of ibuprofen in isopropanol can be reduced and the solubility of sodium sulfate in water is still high enough. To guarantee this temperature during the whole process, the tubular reactor was tempered in a thermostatic bath (B I).

A prehardening step, realized by a pH 3 hydrochloric acid, followed after the last "Crosser". P III (Pump rate of 73.2 mL/min) fed the pH 3 solution via a third Y-fitting into the tubular reactor.

The hardening of the Eudragit microcapsules was realized in two different ways. The hardening step was executed outside the tubular reactor (hereafter referred as "external hardening") or inside the tubular reactor (hereafter referred as "internal hardening").

In the case of external hardening, 1.1 m of tube followed the prehardening step. The reactors output, i.e. the entire stock suspension, was collected in a beaker (1 L). Afterwards, the supernatant was decanted and the microcapsules were hardened by adding 90 g of a 0.1 N hydrochloric acid (equal to the batch experiment in section 4.3). Subsequently, the microcapsules were stirred for 30 minutes and filtrated by a pleated filter. The microcapsules were dried for 48 hours at room temperature under the fume cupboard.

In the case of internal hardening, 1.1 m of tube followed the prehardening step. P I (8.7 mL/min) fed 1 N hydrochloric acid via a Y-fitting into the tubular reactor (concentration of hydrochloric acid in the tubular reactor was approximately 0.1 N).
After further 0.5 m of tubing the harden microcapsules were collected in a beaker. Then the supernatant were decanted and the microcapsules were filtered by a pleated filter. The microcapsules were dried for 48 hours at room temperature under the fume cupboard.

All washing steps which were executed in the batch process for Eudragit microencapsulation (see section 4.3) (Weiß et al., 1993) were excluded for the continuous tubular process. The pumping rates of P I and P II were chosen by the calculation of the concentration of sodium sulfate at the end of the batch process (see section 4.3) and the calculation of equal pumping rates. The pumping rate of the P III was determined by the ratio of resulting mixture to pH 3 solution (Mixture : pH 3 solution = 1:5) (Weiß et al., 1993). While processing it became apparent that a little higher pump rate is easier to handle (Mixture : pH 3 solution = 1:7).

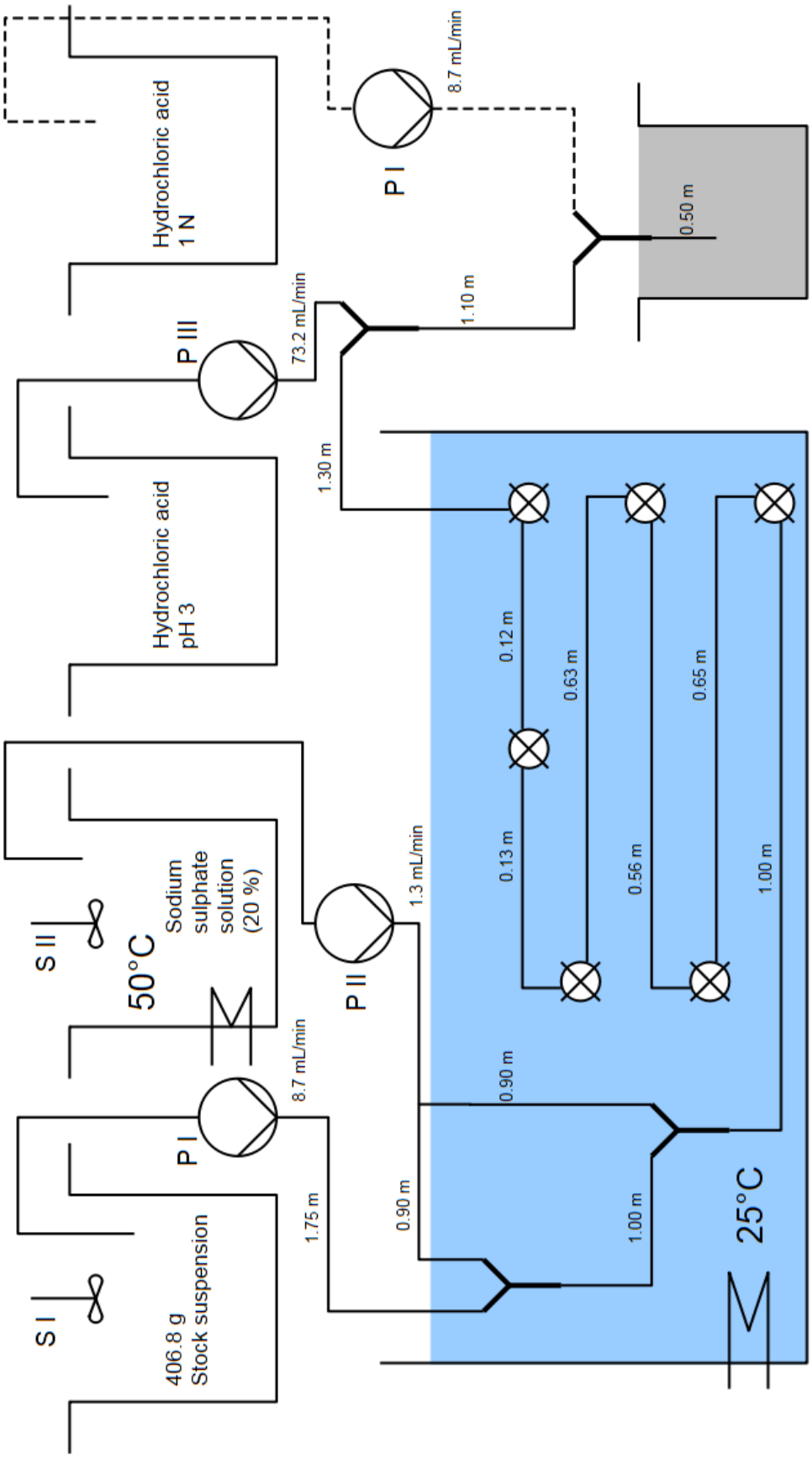

Fig. 4-26 Schematic draft of the process containing the whole process described in section 4.5. The broken line indicates the additional hardening step (internal hardening section 4.5.1). For a better understanding, this hardening process is illustrated with an extra pump but in reality it is just a second pumping tube of P I)

4.5.2 Additional batch experiment

A comparison of the continuous tubular reactor process with an equal batch process was realizable just for the Eudragit microencapsulation process. All concentrations for the additional batch experiment were calculated out of the flow rates of the pumps. Ibuprofen was suspended in the Eudragit/isopropanol solution and 20 % sodium sulfate solution was added. After mixing the mixture was dropped into the pH 3 hydrochloric acid. The hardening step was realized by the addition of 0.1 N of hydrochloric acid and mixing for 5 minutes. Afterwards, the microcapsules were filtered by a pleated filter and dried for 48 hours at room temperature under the fume cupboard.

4.5.3 Analysis of microcapsules encapsulated by Eudragit

The quality of the produced Eudragit microcapsules was investigated due to micrographs as well as electron micrographs. Additionally, dissolution studies were implemented to quantify the release of ibuprofen of the Eudragit microcapsules. In the dissolution study an acidic pH 4 buffer media was used. The microcapsules were produced as described in section 4.5 (internal hardening, external hardening and additional batch experiment).

Optical micrographs of the used unsieved uncoated ibuprofen as well as the produced microcapsules are depicted in Fig. 4-27 - Fig. 4-30.
In Fig. 4-28 microcapsules produced with external hardening are depicted. The figure shows that practically all ibuprofen crystals are encapsulated completely. Just a very small number of crystals which are less encapsulated are detectible in the figure. There is nearly no hardened residual polymer beside the microcapsules. Microcapsules produced with internal hardening are presented in Fig. 4-29. The figure indicates more residual polymer beside the microcapsules than figure Fig. 4-28. However, almost all ibuprofen crystals are completely encapsulated. All microcapsules produced in the batch process are completely encapsulated and depicted in Fig. 4-30. In this figure only minor amounts of residual polymer are present.

Generally, all figures lead to the conclusion that the continuous coating process was successful.

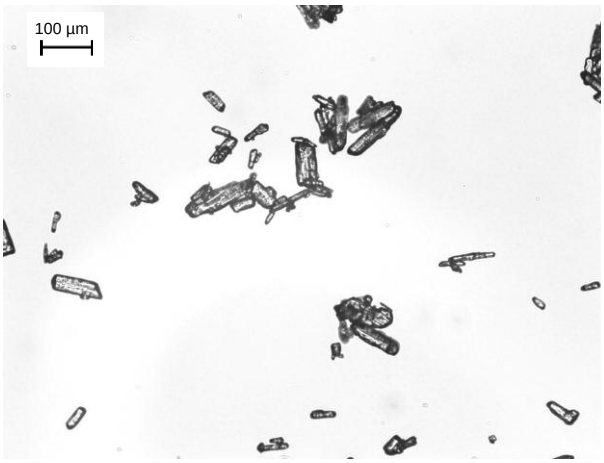

Fig. 4-27 Micrograph of the uncoated ibuprofen (Characterization see section 3.2.1).

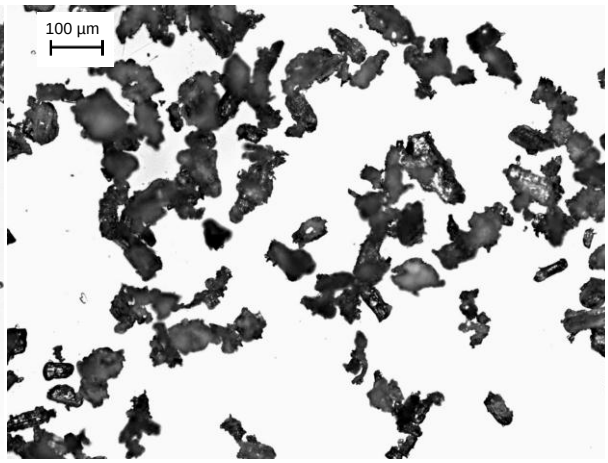

Fig. 4-28 Micrograph of Eudragit microcapsules. Microcapsules were produced in the tubular reactor as described in section 4.5.1 with external hardening.

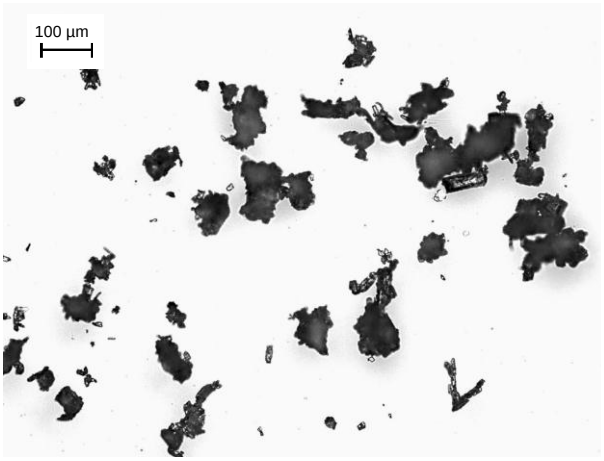

Fig. 4-29 Micrograph of Eudragit microcapsules. Microcapsules were produced in the tubular reactor as described in section 4.5.1 with internal hardening.

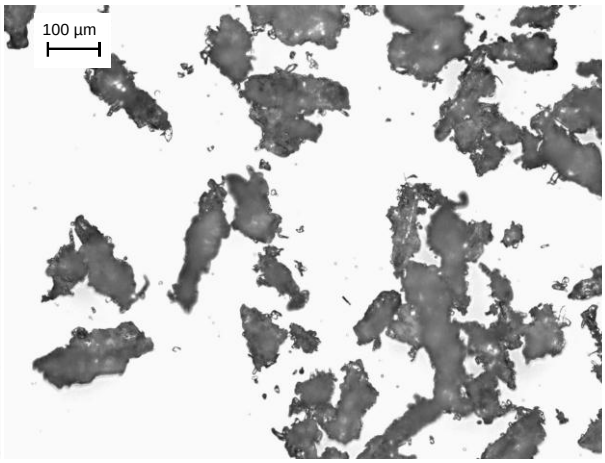

Fig. 4-30 Micrograph of Eudragit microcapsules. Microcapsules were produced in an additional batch experiment as described as described in section 4.5.2.

Tab. 4-3 delineates a summary of the produced microcapsules as described in section 4.5. The determined ibuprofen contents of the microcapsules (see section 3.4) and the weights of microcapsules needed for the dissolution studies (see section 3.5) are summarized.

Tab. 4-3 Summary of the ibuprofen contents of the Eudragit microcapsules and the weights of microcapsules for the dissolution studies (referring to 60 mg uncoated ibuprofen).

Process	Ibuprofen content [%]	Weights for dissolution studies [g]
External hardening	84.3 ± 1.8	0.0710
Internal hardening	79.2 ± 5.0	0.0758
Batch process	74.0 ± 1.2	0.0811

Fig. 4-31 presents the results of the dissolution studies of the microcapsules produced with external hardening (see section 4.5.1). The release measurement after 10 minutes was excluded from the analysis because of inconclusive UV/VIS spectra. After a rapid increase in the ibuprofen release up to 27.7 % the dissolution profile, i.e. release over time, flattens. This rapid increase could be explained by the release of uncoated ibuprofen which is recognizable also in the micrographs (see Fig. 4-28). The dissolution study lasted two hours and a final ibuprofen release of 44.9 % was determined. The investigated microcapsules exhibit a distinct retardation of the ibuprofen release.

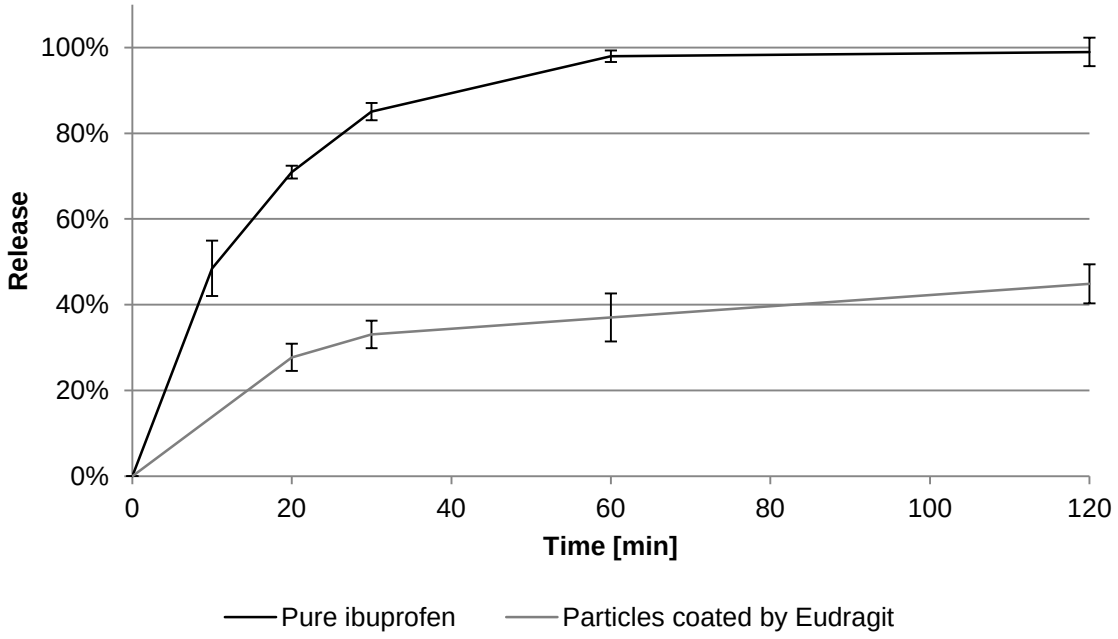

Fig. 4-31 Result of the dissolution study of Eudragit microcapsules produced in the tubular reactor with external hardening (see section 4.5.1). The ibuprofen release of Eudragit microcapsules is compared to the uncoated ibuprofen crystals. The release at 10 minutes was excluded because of the inconclusive spectrum.

Fig. 4-32 shows the ibuprofen release of microcapsules produced in the tubular reactor with internal hardening (see section 4.5.1) in comparison to the uncoated ibuprofen. The release measurement at 10 minutes and 20 minutes had to be discarded because of inconclusive UV/Vis spectra (no clear ibuprofen peak was identifiable) and excluded of the figure. Nevertheless, a clear retardation effect can be observed. The dissolution study lasted two hours and a final ibuprofen release of 35.7 % was determined.

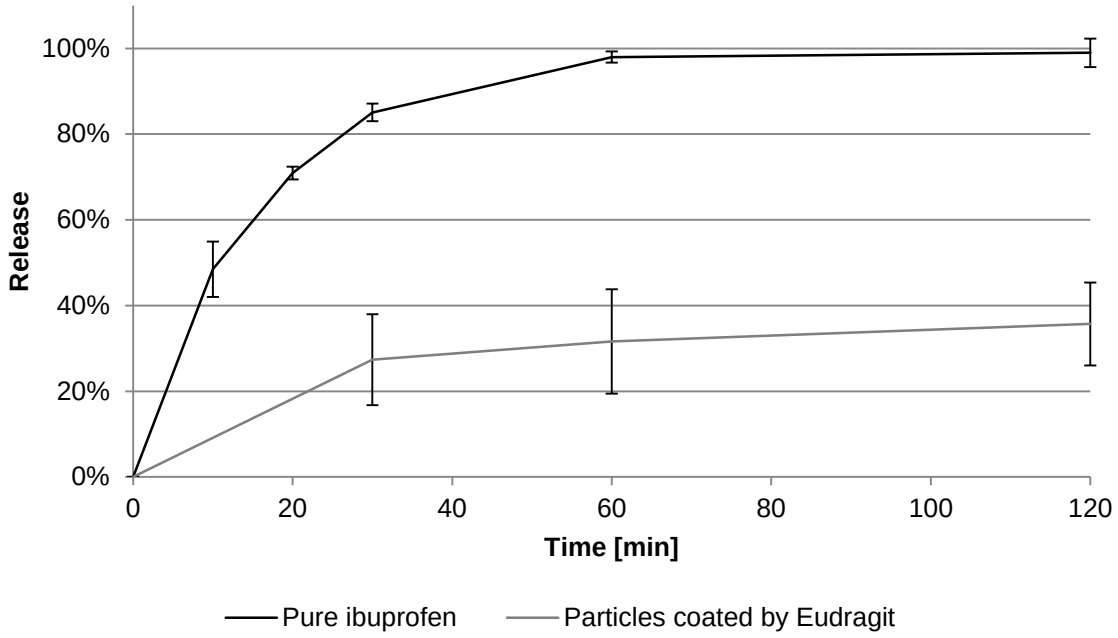

Fig. 4-32 Result of the dissolution study of Eudragit microcapsules produced in the tubular reactor with internal hardening (see section 4.5.1). The diagram is showing the ibuprofen release of microcapsules in comparison to the uncoated ibuprofen. The release at 10 minutes and 20 minutes were excluded because of the inconclusive spectrum.

Fig. 4-33 compares the release of the ibuprofen of microcapsules produced in the additional batch experiment (see section 4.5.2) and the uncoated ibuprofen. The release measurement after 10 minutes was excluded from the analysis because of inconclusive UV/VIS spectra. At a release of 40 % the curve flattens. After 60 minutes it reaches a nearly constant level. The plateau of the dissolution profile might be caused in two reasons. First, it is possible that the determination of the ibuprofen content failed because of an incorrect quantification of the ibuprofen content in the microcapsules. It is also conceivable that there is a mixture of not encapsulated ibuprofen (which dissolves first) and very well encapsulated microcapsules. An absolute confidence to this result should be avoided due to the singlet determination.

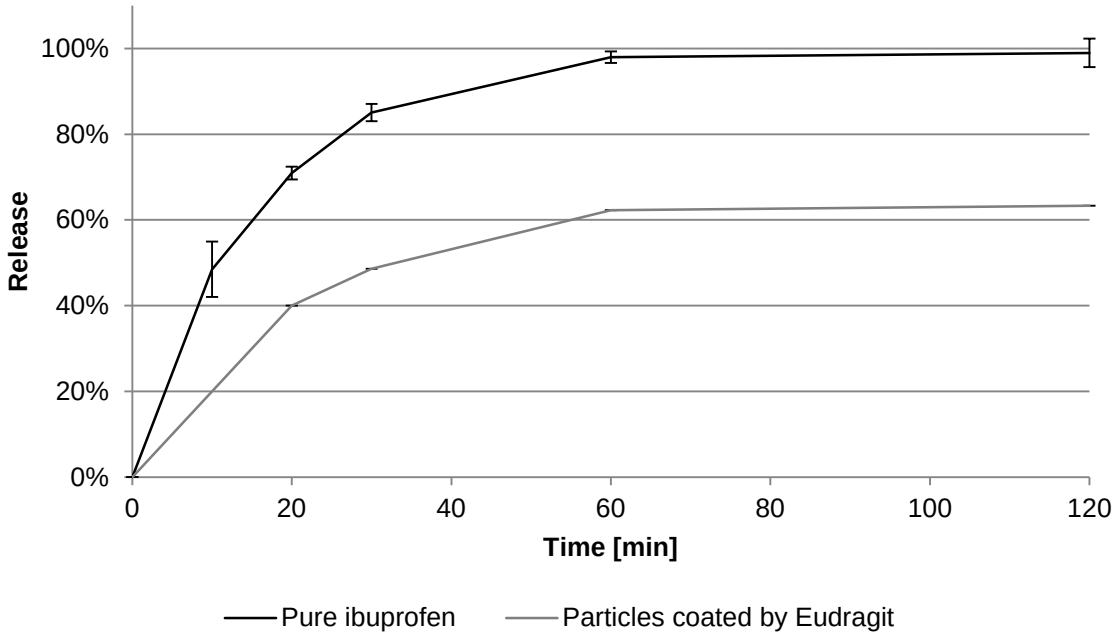

Fig. 4-33 Result of the dissolution study of the microcapsules produced in an additional batch experiment (see section 4.5.2). The ibuprofen release of the Eudragit microcapsules in comparison to the uncoated ibuprofen is depicted. In contrast to all other measurements this dissolution study was performed only once. The release at 10 minutes was excluded because of the inconclusive spectrum.

For further investigation of the coating layer scanning electron micrographs were recorded (see Fig. 4-34). The nearly rectangular shape of the uncoated ibuprofen crystals (B) and the wavy surface (A) are characteristics of the uncoated ibuprofen. Eudragit microcapsules produced with external hardening show a smooth ribbed shape which contains irregular clumps onto the surface (C). There is no significant difference between the microcapsules produced in the tubular reactor with external (C) and internal hardening (E). Microcapsules produced in the additional batch experiment (see section 4.5.2) (G) exhibit a smoother surface compared to the microcapsules produced in the tubular reactor (C) (E). In contrast to microcapsules produced in the tubular reactor there is a less amount of residual polymer beside the microcapsules produced in the additional batch experiment (H).

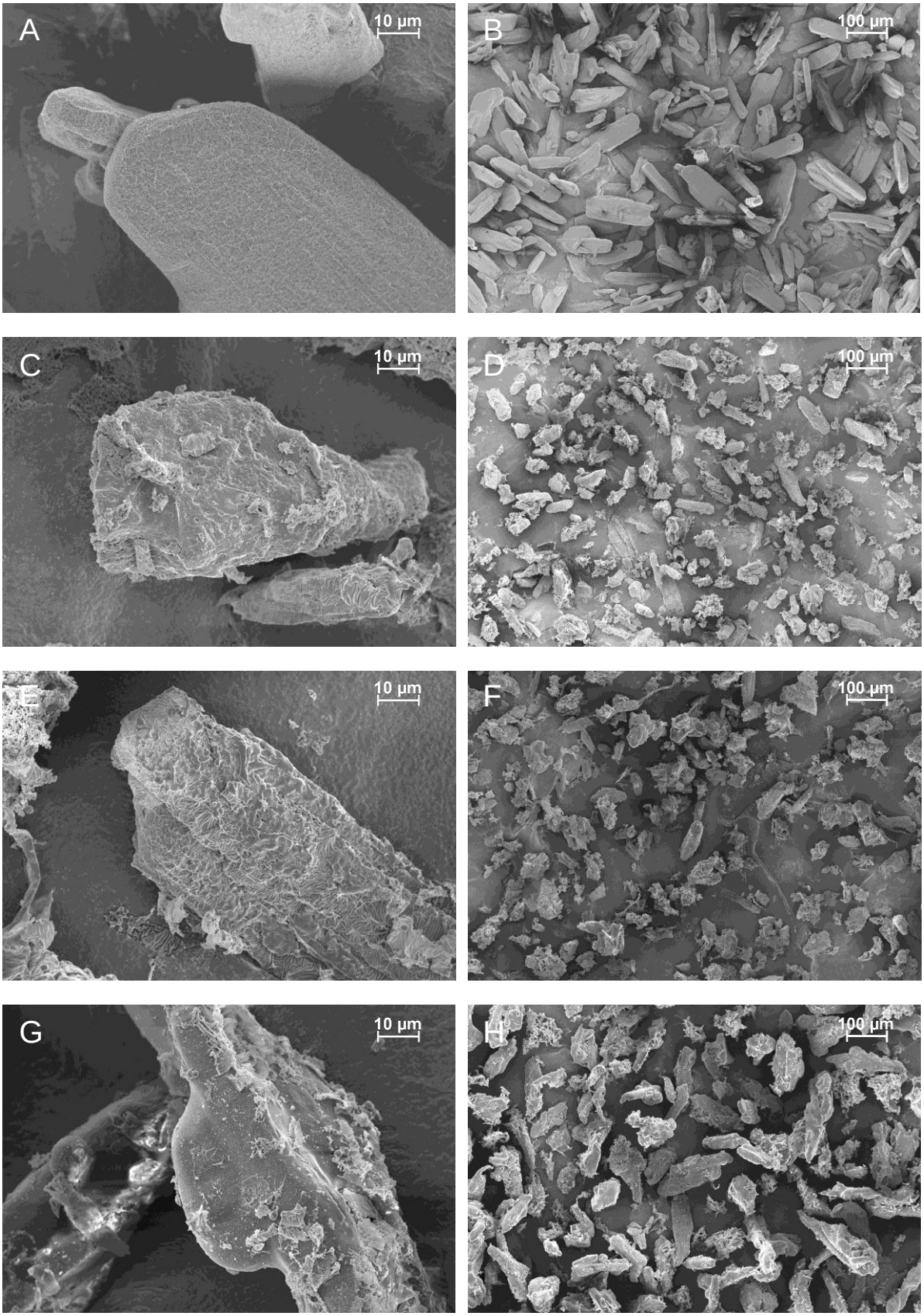

Fig. 4-34 Electron micrographs of Eudragit microcapsules. A, B: Uncoated ibuprofen. C, D: Microcapsules produced in the tubular reactor with external hardening (see section 4.5.1). E, F: microcapsules produced in the tubular reactor with internal hardening (see section 4.5.1). G, H: Microcapsules produced in the additional batch experiment (see section 4.5.2).

The surface of uncoated ibuprofen (I) looks more regular shaped in comparison to the produced microcapsules (J, K, L). So it can be suggested that there is polymer on the surface of the ibuprofen crystals. All in all, there is no significant difference in the surface appearance between the produced microcapsules. All surfaces show parts of bubbled polymer, polymer formed as a net and a crinkled polymer. The surface of microcapsules produced with internal hardening have more netlike surface (K) than the microcapsules produced with external hardening (see section 4.5.1) (J) or microcapsules produced in the additional batch experiment (see section 4.5.2) (L).

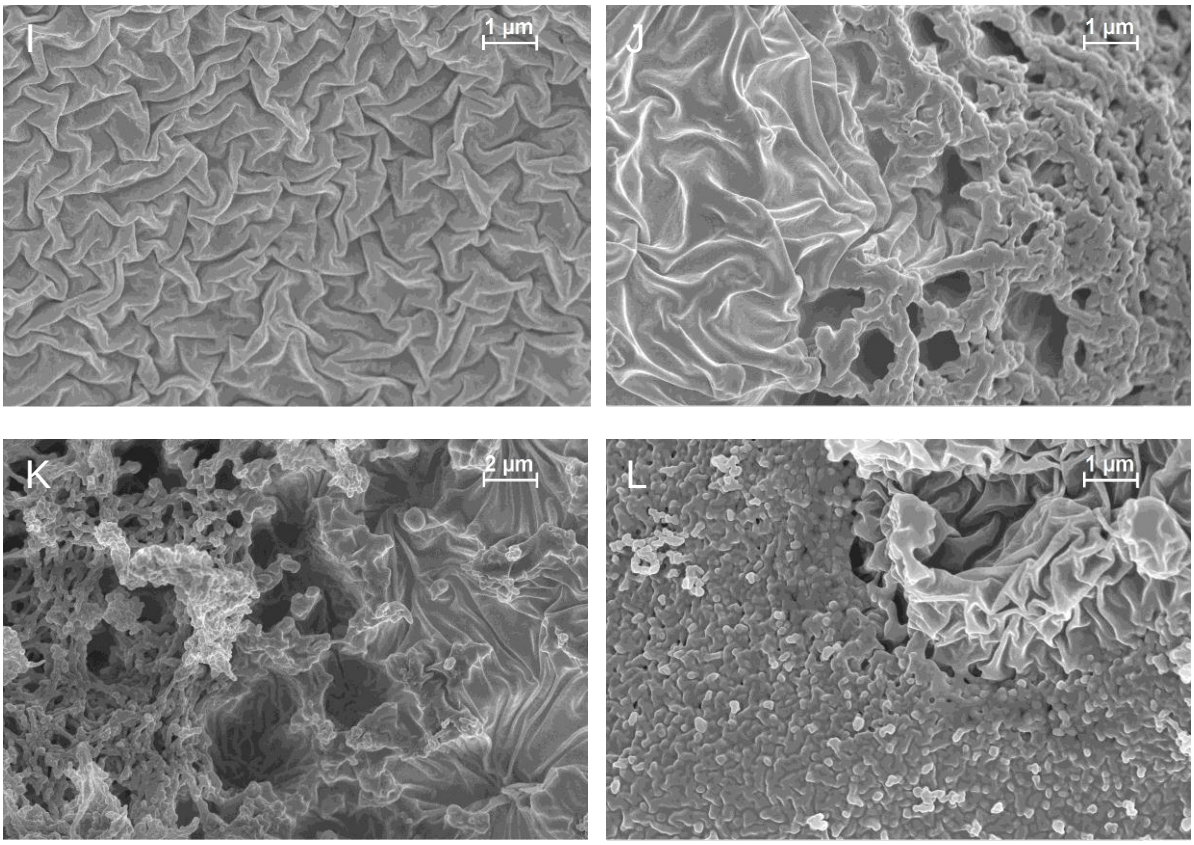

Fig. 4-35 Electron micrographs of Eudragit microcapsules. I: Uncoated ibuprofen . J: Microcapsules produced in the tubular reactor using external hardening (see section 4.5.1). K: microcapsules produced in the tubular reactor with internal hardening (see section 4.5.1). L: Microcapsules produced in the additional batch experiment (see section 4.5.2).

Fig. 4-36 shows an example of an Eudragit microcapsule produced in the tubular reactor with internal hardening. A homogeneous smoothen surface of the microcapsule and the absence of defects in the shell are noticeable in the figure.

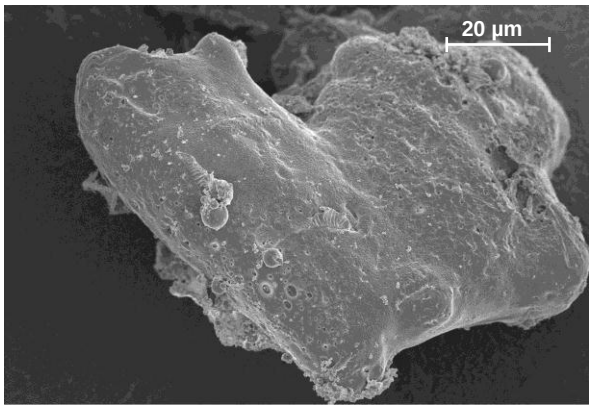

Fig. 4-36 Electron micrograph of an example of an Eudragit microcapsule produced in the tubular reactor with internal hardening (see section 4.5.1).

5 Conclusion and outlook

This Thesis presents the proof of principle of a continuous coating process operated in a tubular reactor. Two different processes were developed to coat the model core (ibuprofen crystals) with either hydroxypropylmethylcellulose phthalate (HPMCP) or Eudragit®. Both polymers are relevant for pharmaceutical coatings due to their enteric properties. The developed continuous coating process was based on microencapsulation by the means of simple coacervation.

Several experiments were executed in order to reproduce published batch processes which use coacervation as a microencapsulation technique. Based on these initial studies two processes for the production of microcapsules (ibuprofen crystals surrounded by polymer (HPMCP or Eudragit)) were established.

To implement the processes described by Weiß et al. (Weiß et al., 1995b), (Weiß et al., 1993) in a tubular reactor, some process steps had to be modified. The final process can be briefly summarized as follows.

1. Coacervation process (induced by a sodium sulfate solution)
2. Prehardening (induced by temperature (HPMCP) or diluted acid (Eudragit))
3. Hardening (induced by acetic acid (HPMCP) or hydrochloric acid (Eudragit))

The hardening step was executed in two different procedures to investigate the influence of this step. The produced microcapsules were hardened within the tubular reactor (internal hardening) or externally (external hardening).

The optical micrographs and electron micrographs as well as dissolution studies of the produced microcapusles are summarized in Fig. 5-1 and Fig. 5-2.

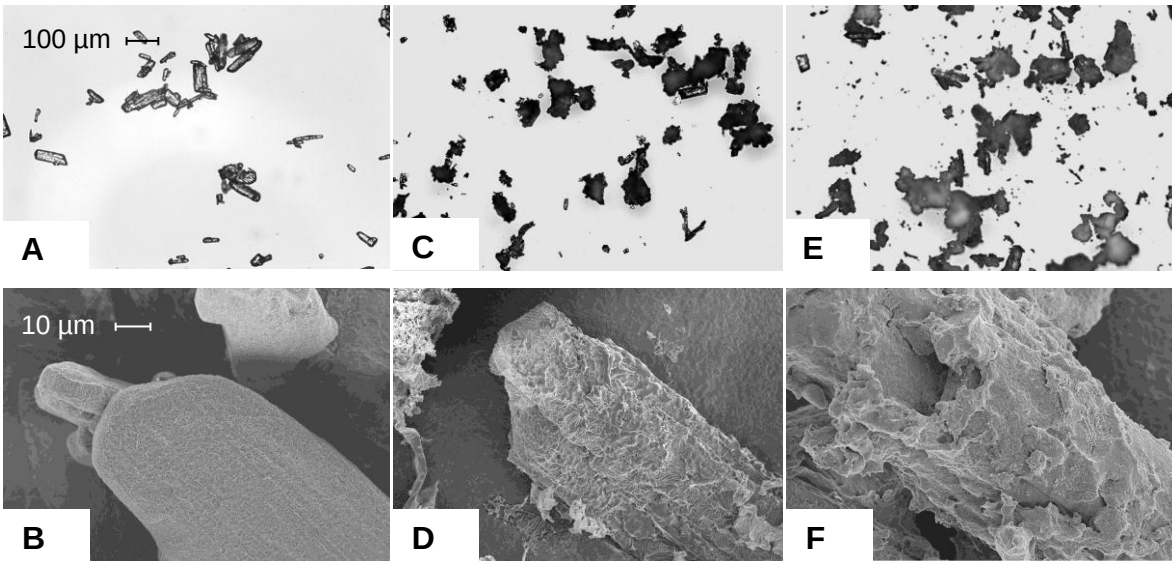

Fig. 5-1 Summary of the main results of the analysis of the optical micrographs (A, C, E) and electron micrographs (B, D, F) of produced microcapsules in the tubular reactor with internal hardening and the uncoated ibuprofen. A, B: uncoated ibuprofen. C, D: Eudragit microcapsules. E, F: HPMCP microcapsules.

In the case of the developed continuous HPMCP process the micrographs and electron micrographs of the produced microcapsules evidenced a good microencapsulation of the model cores. Nevertheless, the dissolution studies exhibit a retardation effect if the hardening step was performed externally

Microcapsules produced by the continuous Eudragit process revealed not only good microencapsulation of the model cores, also the dissolution studies demonstrate its feasibility for enteric coating applications.

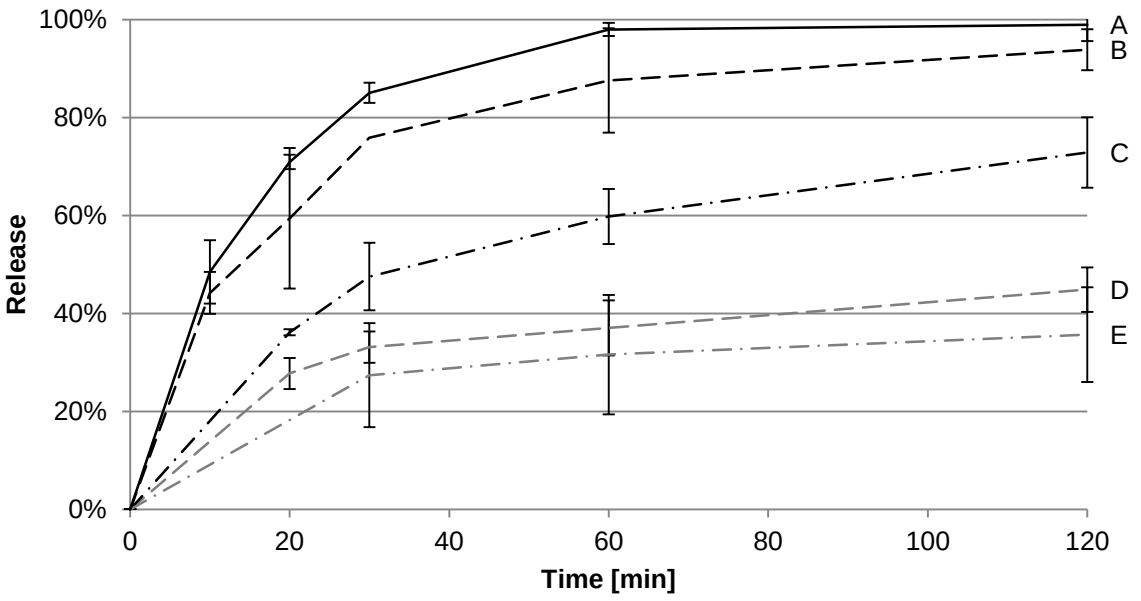

Fig. 5-2 Summary of the main results of the dissolution studies of the uncoated ibuprofen and the produced microcapsules. Ibuprofen release of the microcapsules encapsulated by Eudragit and HPMCP produced in two different ways meaning external and internal hardening. Some of the results had to be excluded because of their inconclusive spectrum.
A: uncoated ibuprofen; B: HPMCP microcapsules (internal hardening); C: HPMCP microcapsules (external hardening); D: Eudragit microcapsules (external hardening); E: Eudragit microcapsules (internal hardening).

The continuous process developed in this Thesis highlighted a lot of benefits of the tubular reactor design. Reduced process time and therefore lower costs are reachable by a low residence time (see Tab. 5-1).

Tab. 5-1 Comparison of residence times in the tubular reactor and the batch processes. The residence time of the HPMCP process is calculated for the tubular reactor process with external hardening because of the much better results in dissolution studies. For further information to the calculation of the residence times see appendix.

	Eudragit		**HPMCP**	
	Tubular reactor	**Batch process**	**Tubular reactor**	**Batch process**
Antisolvent induced coacervation	~ 2 min	~ 10 min	~ 1 min	~ 15 min
Prehardening		~ 10 min		~ 60 min
Hardening		~ 30 min	~ 30 min	~ 30 min
Sum	**~ 2 min**	**~ 50 min**	**~ 31 min**	**~ 105 min**

The Eudragit batch process (which was modified within this Thesis), is not relevant for industrial applications. According to Weiß (Weiß, 1991) a necessary change of medium during

the batch process it is impracticable for industrial scale. The realization in a tubular reactor as presented here overcomes this obstacle since no change of medium is needed.
Another disadvantage of the batch process is a microscopically control needed for every single batch. For the continuous process the microscopically control can be reduced to a minimum while defining the settings.

This Thesis demonstrates the potential of a tubular reactor design for continuous coating processes based on a coacervation technique.

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6 Appendix

EUDRAGIT

	D [mm]	D[m]
Diameter	2	0.002

	Length [m]	Flow rate [cm³/min]	Flow rate [m³/min]	Volume [m³]	Residence time [min]
Part 1	1	9.35	0.00000935	0.000003	0.34
Part 2	4.39	10	0.00001	0.000014	1.38
Part 3	1.1	83.2	0.0000832	0.000003	0.04
Part 4	0.5	91.9	0.0000919	0.000002	0.02
	6.99			Sum	**1.77**

HPMCP

	Length [m]	Flow rate [cm³/min]	Flow rate [m³/min]	Volume [m³]	Residence time [min]
Part 1	1	13.9	0.0000139	0.000003	0.23
Part 2	4.39	15.9	0.0000159	0.000014	0.87
	5.39			Sum	**1.09**