In situ encapsulation of liquids by means of crystallization

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1. Introduction

The encapsulation of liquids is a common approach for sensitive products, like volatile liquids or active pharmaceutical ingredients. Such capsules can enhance the water-solubility or even the bioavailability and therefore improve the quality of pharmaceutical products. The most common encapsulation techniques include spray drying and filling of precast hard or soft capsules. Both processes involve limited particle sizes, a big loss of material and thus high processing costs [Col08, Día06, Joh86].

The in situ encapsulation represents, due to its few process steps, an effective, low energy consuming and economic procedure for the inclusion of different volumes of liquids. It combines the well-known techniques of pastillation and crystallization to a new encapsulation process. The resulting products consist of a crystalline shell and a liquid core whereas the size of the capsules as well as the volume of the included liquid can vary [Har16a].

The proof of concept should be given on three examples of liquid-filled xylitol capsules. Xylitol was chosen because this pentavalent sugar alcohol has many different benefits like its applicability for diabetic products due to its insulin independent metabolism. Furthermore, it has an anticariogenic effect that was proven by the reduction of plaque and tooth decay while applying xylitol products. Those products, like tooth paste or chewing gum, also profit by the negative heat of solution of xylitol which creates a refreshing taste during the application of the products [Row06].

The influence of different additives and solvents on the thermodynamic and kinetic properties of a xylitol solution were investigated. Due to changes in solubility, nucleation and crystal growth, the added substances have to be seen as additives or co-solvent [Ulr04]. Based on these properties, the optimal production conditions can be found. By varying the concentration of the solution, the process temperatures and the cooling rate, the products can be optimized regarding their shape, stability and layer thickness of the crystalline shell.

The production and evaluation of the three tested capsules give the proof of concept for the in situ encapsulation process. A general guideline including a detailed decision tree should be derived from the experimental results. The process and the products

should therefore be optimized for new materials, if the decision tree is followed carefully. This way, it should be shown, that only a few process requirements have to be fulfilled for the application of this encapsulation technique and that the in situ encapsulation process represents a good alternative to already established encapsulation methods.

2. State of the art

2.1 Crystallization

Crystallization is a thermal separation and purification technique in which a substance is transformed from an amorphous, gaseous or liquid state to the crystalline state. It may be defined as a phase change in which a crystalline product is obtained from a solution or melt [Mer05, Mye02]. The terms solution and melt developed historically and their differentiation was discussed by Ulrich et al. [Ulr03, Ulr88]. One approach is to focus on the heat and mass transfer. If the heat transfer is predominant compared to the mass transfer, the system can be called a melt. In contrast, if the mass transfer is predominant, it can be called a solution [Ulr88]. The presented work will be focused on the crystallization from a solution.

2.1.1 Solubility and metastable zone

A homogenous solution is formed by dissolving a solid solute in a solvent. Only a certain amount of solute can be dissolved in the solvent at a given temperature. The solution is saturated when the maximum amount of solute is dissolved in the solvent. Thus, solubility is defined as the required amount of solute to get a saturated solution at given conditions [Mor15, Mye02].

Fig. 2.1-1 shows the concentration plotted against the temperature and represents a typical solubility curve. On the solubility curve the solution is in a saturated state. Below the solubility curve, the stable zone, the solution is undersaturated which means that it is less solute dissolved than maximum possible. Above the solubility curve, the labile zone, the solution is supersaturated which means it is more solute dissolved than maximum possible for the given conditions. The second curve that can be found in this diagram is the nucleation curve. It is defined by the spontaneous nucleation of the solid phase. The area between solubility and nucleation curve is the metastable zone in which crystal growth can occur, but no nucleation [Hof04, Mul01].

To start the crystallization and initiate the nucleation, the thermodynamic equilibrium of the saturated state has to be disturbed so that the solution is supersaturated [Sat01].

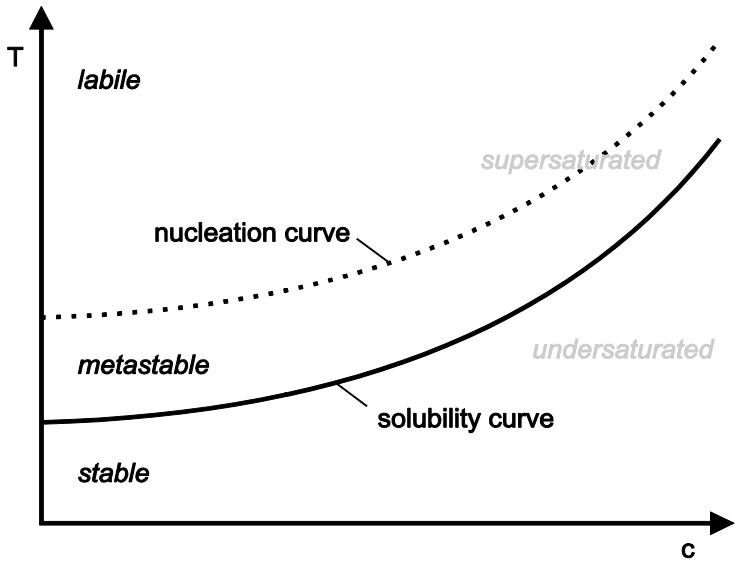


Fig. 2.1-1: Solubility diagram including the metastable zone [Hof04].

That can be realized by cooling down the solution, evaporating the solvent, a combination of both or supplanting one of the components of the solution [Sat01].

2.1.2 Nucleation and seeding

If a supersaturated state is reached, the solution tries to recreate the thermodynamic equilibrium by the formation of solid particles (nucleation) and their growth [Hof04]. Before crystals can develop, a certain number of minute solid bodies, nuclei or seeds must exist to act as a center of crystallization. Nucleation can occur spontaneously or may be induced artificially. The different types of nucleation can be seen in Fig. 2.1-2 (a) [Mul01].

Primary nucleation occurs in systems which do not contain any crystal matter. In case of primary homogeneous nucleation, the crystals will be formed spontaneously which requires the most energy and therefore the highest supersaturation of the system (Fig. 2.1-2 (b)). Primary heterogeneous nucleation will occur in the presence of foreign particles in the solution, e.g. dust or other impurities. If the nucleation is induced by abrasion of already existing crystals it is called secondary nucleation. It may also be induced artificially by adding seed crystals to the supersaturated solution [Hof04, Mer05, Mul01].

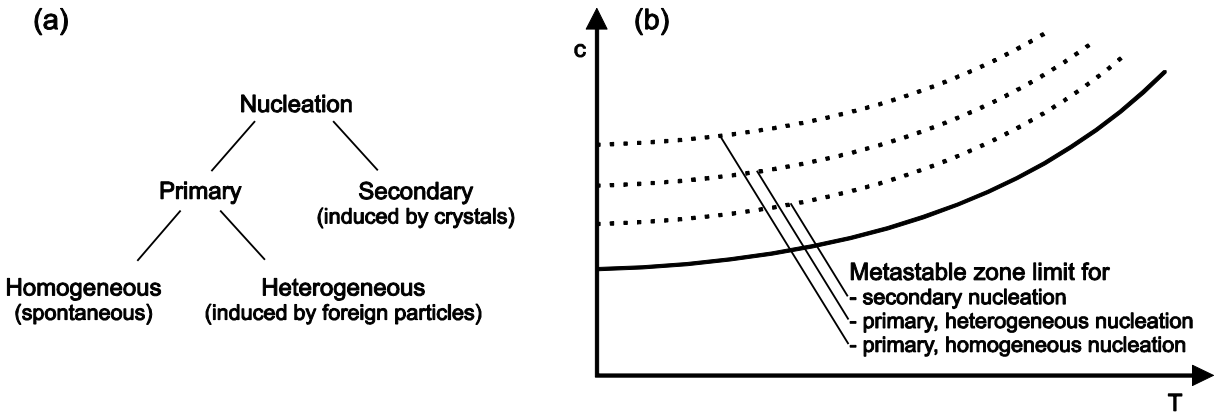


Fig. 2.1-2: (a) Types of nucleation [Mul01],
(b) Nucleation curves for different types of nucleation [Mer05].

This so-called seeding has the advantage that it requires a lower supersaturation to initiate the crystallization and makes the nucleation much easier to control [Hof04, Mer05, Mul01].

2.1.3 Growth rate dispersion

Individual crystals with the same initial size and growing under identical growth conditions grow in most cases at different rates. This phenomenon is called growth rate dispersion. It was first identified by White and Wright in 1971 during a batch crystallization of sucrose and can be explained by different surface effects of the crystals. One reason is a random surface adsorption or incorporation of impurities which leads to the development of different crystallographic faces and thus different growth rates. It could also be caused by different degrees of lattice strain and deformation in the individual crystals. Crystal deformation can be induced by mechanical stress caused by fluid shear, the agitator in the crystallizer and physical contact to other crystals or other parts of the equipment. The growth rate dispersion is now a generally accepted behavior during crystallization and has to be considered for planning crystallizers or growth rate experiments [Mul01, Ulr89].

2.1.4 Influence of additives and solvents

Additives and solvents can influence the properties of a solution and the behavior of their components. The effect strongly depends on the amount of added substance. If small amounts of a substance have an effect on the kinetic properties of the system,

like nucleation or crystal growth rate, but no significant effect on the thermodynamics, e.g. solubility, it can be considered as additive. But if a substance exists in larger amounts in the solution and it is affecting the kinetic as well as the thermodynamic properties, it has to be considered as a third component. In general, the addition of solvents or additives can have an apparent effect on the system in terms of changing the solubility, metastable zone, nucleation and crystal growth and as a result also changing the shape, size and particle size distribution of the crystalline product. The actual effect of an additive strongly depends on the substance itself and has to be considered for each individual case [Hao06, Mee02, Ulr04].

2.1.5 Solidification of drops

The solidification of a drop proceeds from the outside towards the inside of the liquid drop. If the drop has contact to a cooling surface and seed crystals, maybe even from the top and bottom, many nuclei will occur on the surface and a thin crystalline shell can be formed. This thin layer can grow thicker towards the center of the drop. The heat of crystallization will be mainly released outwards to the surface of the drop and as a result a temperature gradient develops inside the drop. Therefore, the solidification depends on the properties of the solution as well as on the temperatures in and around the drop [Ulr94].

Three different models for the solidification of drops by surface nucleation, mainly categorized by the optical appearance of the solid drops, can be distinguished (Fig. 2.1-3).

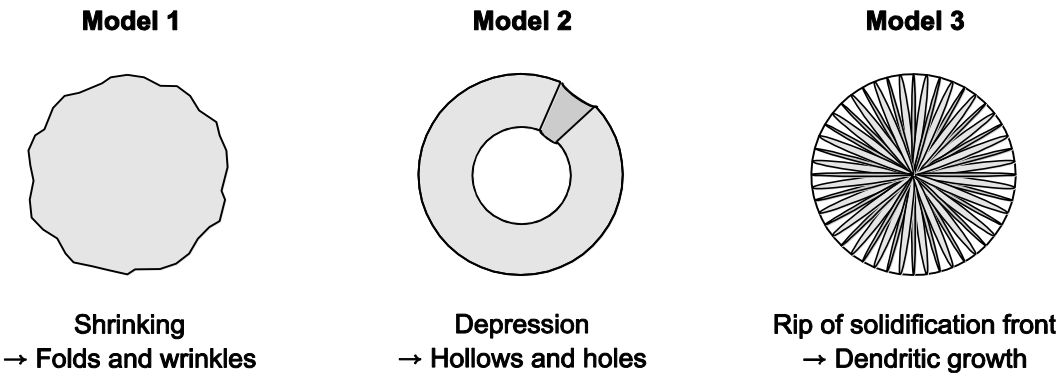


Fig. 2.1-3: Solidification models [Ulr94].

The different appearances are caused by the density difference between solid and liquid phase during the solidification. Model 1 describes the shrinking of the particle. If the liquid drop is cooled down, the volume decreases and if the outer crystalline shell

is too thin, the drop will shrink and the surface will have folds and wrinkles. If the crystalline shell is thicker and thus more stable, a deformation is not possible anymore. In this case (model 2), the depression in the liquid core will lead to hollows or even holes in the crystalline shell. The third model leads to a dendritic crystal growth from the surface towards the center of the drop. This happens due to a rip of the solidification front and leads to solid drops with rough surfaces [Ulr94].

2.2 Pastillation

Pastillation is a process for the automatized disintegration of liquids which then solidify to solid particles and was developed by the companies BASF (Ludwigshafen) and Gebr. Kaiser (Krefeld) [Bül03, Kai70]. It is a simple, effective and economic technique which can be applied for liquids with a viscosity between 0 and 30000 mPas. The resulting products are roundly shaped, dust free and thus ideal for packaging and transport. Furthermore, products with defined quality and properties can be obtained. In the fields of pharmacy and food industry, the application of pastillation can enhance the bioavailability and storage stability as well as improve the color and taste of the products [Kai08, Tei03].

The pastillation of a liquid can be realized by using rotating or non-rotating systems. Examples for rotating systems are the systems Rollomat®, Rollosizer® [Kai08] and Rotoform [San16]. The GS-system (piston and cylinder) and ZN-system (needle and nozzle) are non-rotating pastillation systems. Since the ZN-system was used in this work, it is shown in Fig. 2.2-1 and will be explained in the following [Bül03, Kai08, Kai70].

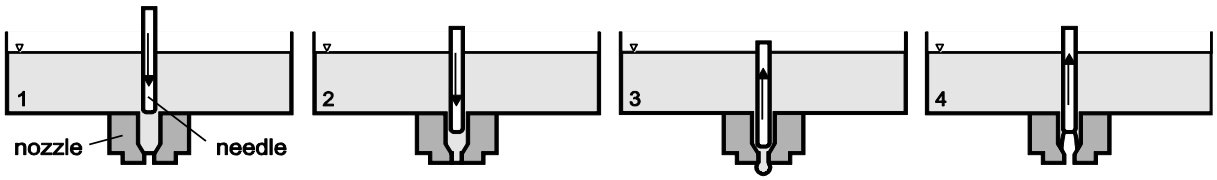


Fig. 2.2-1: Non-rotating ZN-system [Bül03].

The ZN-system can be used for low viscous liquids with a viscosity below 1000 mPas. The basis of this work principle is the gravity draining the liquid out of the nozzle. In position 1 (Fig. 2.2-1) the needle is at its highest point and the nozzle is already filled with liquid. When the needle is moving downwards (position 2 and 3), it is pushing

liquid out of the nozzle. At its lowest position (position 3), the needle brakes the jet of liquid so that a single drop is deposited on a cooling surface. Afterwards, the needle is moving upwards again and is thus inhibiting the liquid to flow out of the nozzle (position 4). At the highest position of the needle the cycle starts again [Bül03, Kai70].

2.3 Encapsulation processes

The encapsulation of liquids is often used in food industry for various reasons. It can protect sensitive materials from the environment, stabilize food ingredients, decrease degradation of volatile substances like aroma, mask a bad taste or smelling and thus allow aroma differentiation [Día06, Gha07, Ned11, Röm07]. Furthermore, encapsulation processes play a major role in pharmaceutical industry as well. The encapsulation of active pharmaceutical ingredients or bioactive molecules can enhance their water solubility and thus improve the delivery and bioavailability [Col08, Día06, Ned11].

In the food industry spray drying is the most common applied encapsulation technique. Due to the very limited and small particle size of the products (down to a few nanometers in diameter) it is also called microencapsulation. Spray drying involves four steps which are the preparation of the dispersion or emulsion, homogenization of the dispersion, atomization of the infeed emulsion and dehydration of the atomized particles. However, it also includes a big loss of material during the spraying process itself [Ned11, Sha93].

Another possibility for the encapsulation of liquids, especially in the pharmaceutical industry, is the filling of hard or soft capsules which mainly consist of gelatin or other suitable polymers. Soft capsules are ovally shaped single unit solid dosage forms that need to be formed, filled and sealed. Hard capsules are single unit dosage forms as well which are manufactured separately and are provided empty for filling. Their shape is cylindrical and they consist of a body and a cap. All these filling techniques include many separate process steps which leads to high production costs. Furthermore, these precast capsules are limited in size as well as flexibility [Cad96, Col08, Joh86].

3. Aim of the work

The in situ encapsulation represents an effective, low energy consuming and economic procedure for the inclusion of different volumes of liquids. It combines the well-known techniques of pastillation and crystallization to a new encapsulation process. The resulting products consist of a crystalline shell and a liquid core whereas the size of the capsules as well as the volume of the included liquid can vary. The aim of the work is the introduction and proof of concept of this new and innovative encapsulation technique as an alternative to already established processes.

The production of liquid-filled capsules by in situ encapsulation requires less process steps compared to other encapsulation techniques (Fig. 3-1) [Har16a].

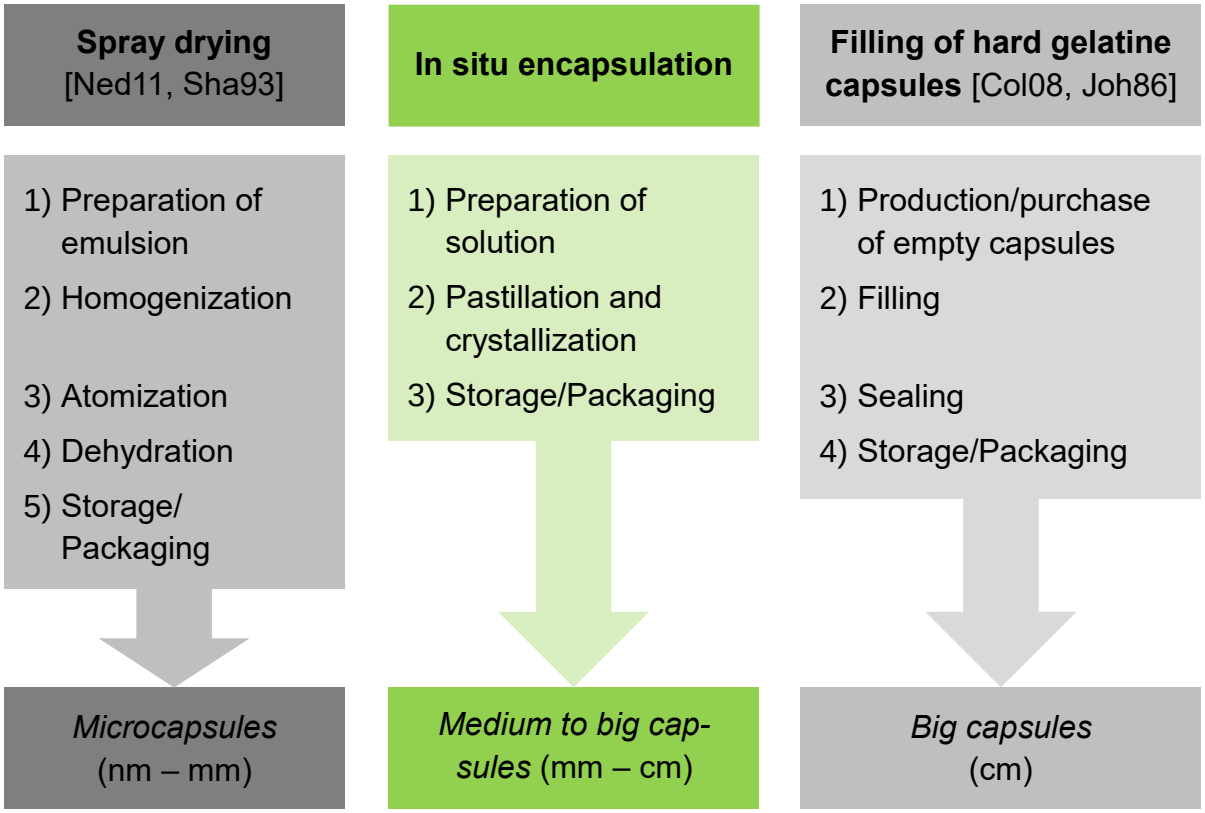


Fig. 3-1: Comparison of different encapsulation processes.

After the core and shell material are dissolved in a solvent, the solution has to be cooled down to a certain temperature, depending on the used materials (1). The shaping and solidification of the capsules happens in only one step by combining pastillation and crystallization (2). The prepared solution is divided into drops and solidifies on the

temperature-controlled conveyer belt which allows a continuous production of the capsules. As a last step, the capsules can be packed and stored under suitable conditions (3). By adjusting the manufacturing parameters properly, it is possible to produce capsules that vary in size and composition for each application case according to the needs.

This is the theoretical understanding of the in situ encapsulation process. The proof of concept and a general guideline on how to optimize the process and how to apply the productions conditions on different substances are needed. Therefore, different requirements have to be fulfilled before the in situ encapsulation process can be applied to a system. After the definition of the desired product properties, the following questions have to be answered:

- → Are the chosen components suitable for the in situ encapsulation process? Which properties of the system are required to achieve a good product?
- → Which are the ideal manufacturing parameters for the production of optimal capsules?
- → Which characteristic properties of the capsule have to be obtained to ensure a product of good quality?

The answers to this questions and the proof of concept for the in situ encapsulation process should be shown by three case studies of xylitol capsules. These three different systems vary in their composition, their physical and chemical properties as well as the size and properties of the resulting capsules. From these experimental results, a general guideline for the application of the in situ encapsulation process should be derived.

4. Materials and methods

4.1 Materials

The materials used for the experiments, their source of supply and their usage are summarized in Tab. 4.1-1. The main substances are explained more detailed in the following paragraphs.

Tab. 4.1-1: Summary of used materials.

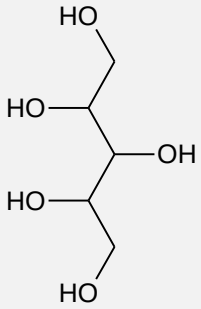
Material	Company	Usage
Xylitol (98.5 %)	DHW Deutsche Hydrierwerke, Rodleben, Germany; Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Main component for encapsulation
Lime flavor	Symrise AG, Holzminden, Germany	Additive
Food coloring	Dr. Oetker GmbH, Bielefeld, Germany	Additive
Ascorbic acid (≥ 99.9 %)	Carl Roth GmbH & Co. KG, Karlsruhe, Germany	Additive
Ethanol (≥ 99.8 %)	Carl Roth GmbH & Co. KG, Karlsruhe, Germany	Solvent
L-Menthol	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Additive
Parafilm	Bemis Flexible Packaging, Neenah, Wisconsin, USA	Cover for cooling surface

4.1.1 Xylitol

Xylitol is a pentavalent sugar alcohol that can be found in traces in many fruits and vegetables. Its physical properties and structure can be seen in Tab. 4.1-2. Industrially, xylitol is produced by hydrogenation of xylose which can be obtained from hemicelluloses of different hardwoods [Eco16, Gre15].

Xylitol has different fields of application. Due to its sweetness, that is almost as high as the sweetness of sucrose, it is often used as a sugar substitute in food industry. In pharmaceutical industry, xylitol is applied as sweetening agent, for the production of chewable tablets and as resistant and durable coating material [Bon06].

Tab. 4.1-2: Physical properties and structure of xylitol [Bon06].

Physical properties		Structure
Density	1.52 g/cm³	
Solubility in water at 20 °C	62.5 wt%	
Solubility in ethanol at 20 °C	1.25 wt%	
Melting point	92-96 °C	
Boiling point	215-217 °C	

Only 50 to 75 % of xylitol is absorbed in the gastrointestinal system. Therefore, it has a lower caloric value (2.4 kcal/g) than sucrose (4 kcal/g). Due to its insulin independent metabolism it is also used for the production of diabetic products. Another characteristic of xylitol is the negative heat of solution of -157.1 J/g [Bon06]. The consumption of a xylitol product will create a cooling effect in the mouth while it is dissolving and results in a very refreshing taste. Therefore, it is already used, often in combination with menthol or mint flavor, for the production of chewing gum, tooth paste and mouth rinse [Bon06, Gre15, Mus12].

One major benefit of xylitol is its positive impact on the dental health. The chewing of xylitol-containing chewing gum decreases plaque and increases salvation which promotes the remineralization of the teeth. Furthermore, many studies have revealed an anticariogenic effect. It could be shown that xylitol inhibits the metabolism and growth of *streptococcus mutans* and thus inhibits the production of lactic acid which results in less caries. Most studies recommend to chew a chewing gum with at least 5 g xylitol three to five times a day to achieve a proper antimicrobial effect [Gre15, Hil00, Huj99, Rob02].

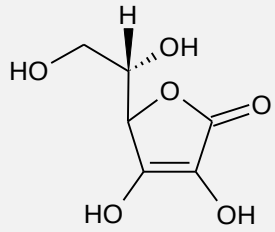
The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluates the intake of xylitol through food stuff as harmless, also high dosages are nontoxic. But due to the laxative effect of sugar alcohols, an excessive consumption of xylitol products is

not recommended. About 100 g intake per day is tolerated by a majority of people [Bon06, Gre15, Wor83].

4.1.2 L-Ascorbic acid

L-Ascorbic acid, also known as vitamin C, is present in all animal and plant cells, in free form as well as bound to proteins. Fruits and vegetables containing large amount of vitamin C are rose hips, red and black currants, strawberries, parsley, citrus fruits, potatoes and a variety of cabbages. Its physical properties and the structure can be seen in Tab. 4.1-3 [Bel09].

Tab. 4.1-3: Physical properties and structure of L-ascorbic acid [Kib06].

Typical properties		Structure
Density	1.65 g/cm³	
Solubility in water at 20 °C	28.6 wt%	
Solubility in ethanol at 20 °C	4.0 wt%	
Melting point	190 °C (decomposition)	
Boiling point	-	

The majority of the commercial manufactured L-ascorbic acid is produced with the seven-step Reichstein process using glucose as starting component. This process involves six chemical steps and one bacterial fermentation step for the oxidation of sorbitol to sorbose. As alternative, bacterial fermentation processes have been established. All processes lead to the same stable direct precursor of vitamin C, 2-keto-L-idonic acid (also called 2-keto-L-gulonic acid). This precursor substance is then, under very acidic and alcoholic conditions, converted chemically to the final product [Bou90, Han02].

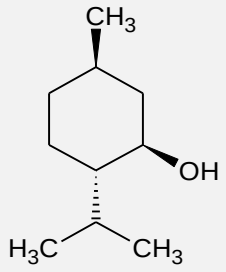
About 50 % of the synthetic L-ascorbic acid is used in vitamin supplements and pharmaceutical preparations. Due to its antioxidant properties and its potential to stimulate collagen production, vitamin C is increasingly used as additive in cosmetic products. Its antioxidant impact is also beneficial in food industry to prevent pigment discoloring and enzymatic browning, protect flavor and aroma and enhance nutrient content [Han02, Kib06].

Vitamin C is an essential part of the human diet. The recommended daily intake for adults in Germany is about 100 mg. High doses may cause diarrhea or other gastrointestinal disturbances and may be damaging the teeth as well. However, no harmful effect could be found if L-ascorbic acid is applied as additive in food and pharmaceutical industry [Deu16, Kib06].

4.1.3 L-Menthol

L-Menthol is a cyclic monoterpene that is mainly used as flavoring agent. Its physical properties and structure can be seen in Tab. 4.1-4 [Lan06].

Tab. 4.1-4: Physical properties and structure of L-menthol [Lan06].

Typical properties		Structure
Density	0.90 g/cm³	
Solubility in water at 20 °C	practically insoluble	
Solubility in ethanol at 20 °C	95 wt%	
Melting point	34 °C	
Boiling point	212 °C	

In contrast to the D-isomer, the naturally-occurring L-menthol has a very refreshing taste and creates a cooling sensation during consumption. Therefore, it is a main component of peppermint flavor which is used in the production of mouth hygiene products, food stuff and tobacco. Furthermore, L-menthol enhances the skin penetration and is applied in cosmetics and pharmaceutical products [Lan06].

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has set a daily intake up to 4 mg per kg bodyweight as acceptable dose. Higher doses, taken orally or inhalatively, can cause tiredness, nausea, vertigo and ataxia [Lan06, Org03].

4.2 Methods

The devices used for the experiments are summarized in Tab. 4.2-1. The main experimental methods are explained more detailed in the following paragraphs.

Tab. 4.2-1: Summary of used devices.

Device	Company	Usage
Ultrasonic probe: LiquiSonic 30	SensoTech GmbH, Magdeburg, Germany	Determination of metastable zone
Viscometer: Viscotester®550	Thermo Haake GmbH, Karlsruhe, Germany	Viscosity measure-ments
One-drop pastillation device	KAISER Process and Belt Technology GmbH, Willich, Germany	Pastillation
Digital microscope: VHX-500F	Keyence Deutschland GmbH, Neu-Isenburg, Germany	Analysis of layer thick-ness
DSC 204 “Pheonix®”	NETZSCH Gerätebau GmbH, Selb, Germany	Analysis of purity of the capsule’s shell
Climatic chamber: ICH 110	Memmert GmbH & Co. KG, Schwabach, Germany	Analysis of storage sta-bility

4.2.1 Metastable zone

The solubility of the tested systems was measured gravimetrically and the nucleation points were determined by means of an ultrasonic probe.

4.2.1.1 Gravimetric analysis

For the gravimetric analysis of the solubility, supersaturated solutions were prepared in a temperature-controlled double-walled beaker. After stirring the suspension mag-netically for one hour at a constant temperature, the stirrer was switched off so that the crystals can settle on the bottom of the beaker. After another hour the clear saturated solution was removed and dried in a compartment dryer. With the resulting mass of the dried crystals the solubility of the system could be determined for the investigated temperature. This experiment was repeated for different temperatures ranging from 20 to 50 °C to obtain the complete solubility curve.

4.2.1.2 Ultrasound measurement

The metastable zone width of xylitol in water was gathered by means of an ultrasonic device, which was previously described by e.g. Omar et al. [Oma99]. The ultrasonic probe includes a sonic transmitter and receiver. The sonic velocity depends on the density and the adiabatic compressibility of the system. Since the distance between transmitter and receiver is fixed and known, the ultrasound velocity can easily be calculated by measuring the travel time of the sonic signal [Sen16].

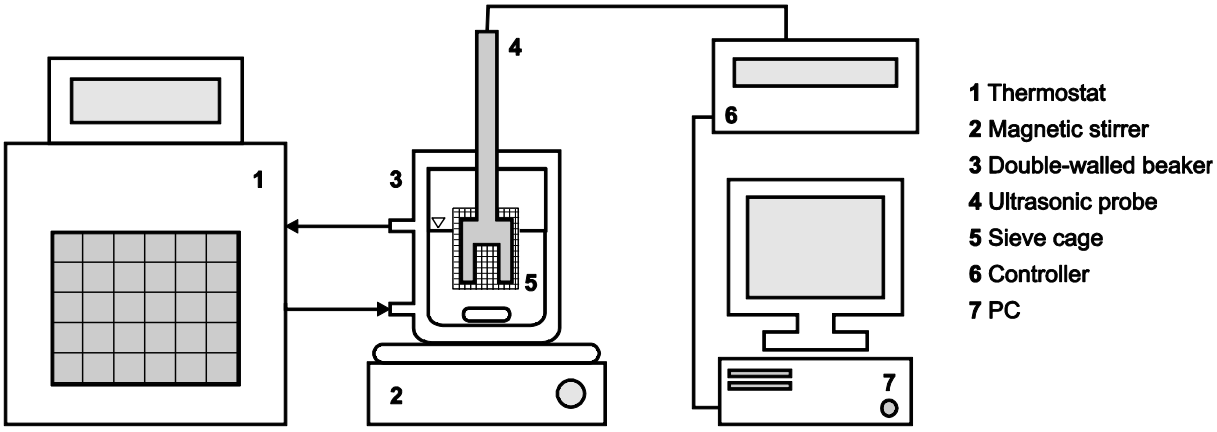


Fig. 4.2-1: Experimental set up for the determination of the nucleation curve.

The experimental set up is shown in Fig. 4.2-1. For the experiments, the solutions were prepared in a double-walled beaker (3) which was temperature controlled by a thermostat (1). The crystallization was initiated through secondary nucleation [Ulr02] by adding 500 mg xylitol seed crystals with a particle size between 500 and 1000 µm. The crystals were added 2 K below the saturation temperature and then the solution was cooled and heated up again with the same rate of 2 K/h. The differences in ultrasound velocity as a function of the temperature were measured by the ultrasonic probe (4). To prevent a disturbance of the detected signal by the seed crystals, the probe was enclosed by a sieve cage (5). Thus only the nucleation and not the seed crystals themselves could be registered.

4.2.2 Crystal growth

Previous growth experiments were often carried out using a microscopic cell as described by e.g. Niehörster et al. [Nie95]. The crystal growth rates were calculated as the length increase of a growing crystal face as function of time. Even though a large

number of crystals has been investigated, this experiment led to very high standard deviations and thus incomparable results [Har15]. This method was proven to be inaccurate due to the varying growth rates of each individual crystal, called growth rate dispersion (see Chap. 2.1.3).

To bypass this problems, the crystal growth rates were determined by batch experiments considering a high quantity of crystals. Therefore, 50 mL of a xylitol solution was saturated at 25 °C in a double-walled beaker. Supersaturated states were achieved by cooling the solution to 24, 22 and 20 °C, respectively. After that, 500 mg xylitol crystals with a size between 355 and 400 µm were added and magnetically stirred for five minutes. After a seed growth period, filtering and washing with ethanol (purity ≥ 99.8 %), the crystals were dried at 60 °C in a compartment dryer. The growth rates were calculated as linear surface growth rates (Eq. 4-1) referring to Garside [Gar71]. This relation derives from the linear length growth of the crystals related to their mass increase over time.

$$G = \frac{L_1}{t}\left(\left(\frac{m_2}{m_1}\right)^{\frac{1}{3}} - 1\right) \qquad \text{(Eq. 4-1)}$$

G is the averaged crystal growth rate, L_1 is the arithmetic mean of the seed crystal size, *t* is the retention time in the batch crystallizer, m_2 is the crystal mass after their growth and m_1 is the initial seed crystal mass.

4.2.3 Viscosity

Viscosity is the property of liquids to offer opposition to the flow. The dynamic viscosity (η) depends on the temperature, pressure and composition of the investigated solution and was determined by means of the viscometer shown in Fig. 4.2-2 [Mor15, The16].

This rotational viscometer consists of two coaxial cylinders where the liquid is filled in the resulting gap. A rotational speed is present and the flow resistance is measured. Therefore, the torque required to maintain the set speed is proportional to the viscosity [The16].

Regarding the flow behavior liquids can be differentiated between Newtonian and non-Newtonian liquids. The viscosity of Newtonian materials may depend on the temperature but is independent of the shear rate whereas non-Newtonian liquids are influenced

by the shear rate. Thus a shear-rate scan was carried out before each measurement [The16].

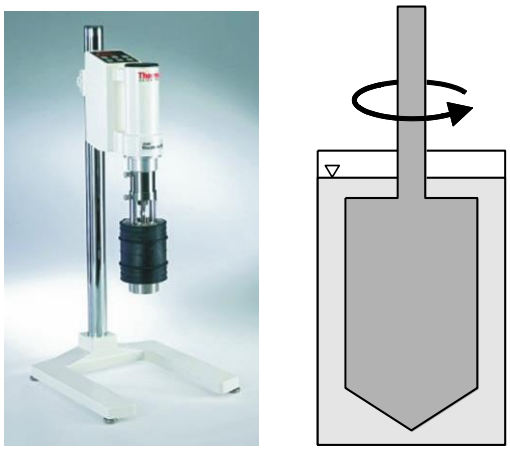


Fig. 4.2-2: Viscosotester®550 and measurement cell [The16].

For the measurements, solutions with different concentrations were prepared and measured at the same temperature to obtain the concentration dependency of the viscosity. Furthermore, a solution with a fixed concentration was measured at different temperatures to gather the temperature dependent viscosity data.

4.2.4 Pastillation

The production of the capsules in lab scale was carried out by means of a one-drop pastillation device (Fig. 4.2-3) previously described by e.g. Wendt et al. [Wen14].

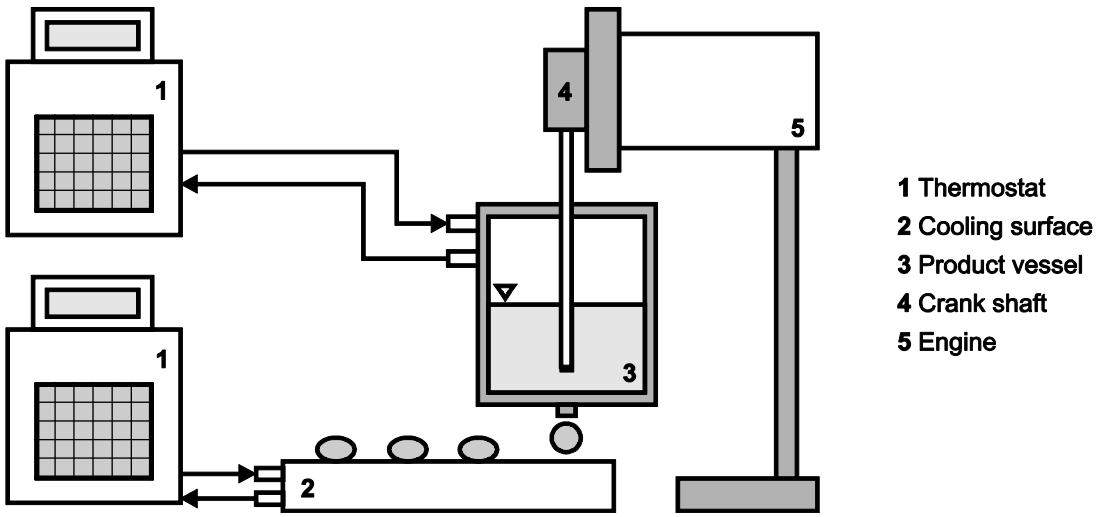


Fig. 4.2-3: One-drop pastillation device.

The prepared aqueous solution was filled in the temperature-controlled product vessel and divided by the pastillation unit into separate drops. The drops were deposited on a cooling surface which was covered with Parafilm to enhance the roughness of the surface. Xylitol (< 200 µm) was used as seed crystals to cover the cooling surface and the liquid drops after the pastillation. By controlling the temperatures properly, the drops will start crystallizing from the outside towards the inside and form a solid capsule with a liquid core.

During the optimization of the pastillation process, parameters like temperature of cooling surface and product vessel, type and amount of seeding as well as storage conditions were changed and the effects on the product were investigated.

4.2.5 Analysis of the capsules

For the evaluation of the capsules, the layer thickness of the crystalline shell was measured microscopically. The stability of the products was determined by means of a stability measurement device and the storage stability was tested in a climatic chamber.

4.2.5.1 Microscopic analysis

For the evaluation of the capsules, the layer thickness of the crystalline shell was measured using a digital microscope.

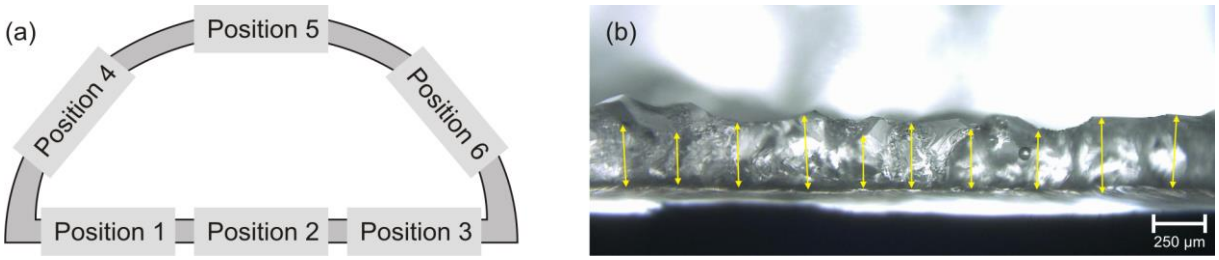


Fig. 4.2-4: (a) Schematic picture of the microscopic analysis, (b) Analysis of a cross section.

To get a representative average value, six different positions of the cross-section of the capsule were analyzed (Fig. 4.2-4 (a)). The layer thickness of this six sections was determined by means of the software analySIS measuring at least ten thicknesses per image (Fig. 4.2-4 (b)).

4.2.5.2 Stability measurement

The stability of the capsules was determined by means of a stability measurement device (Fig. 4.2-5) similar to the miniature load cell described by Scoffin [Sco15].

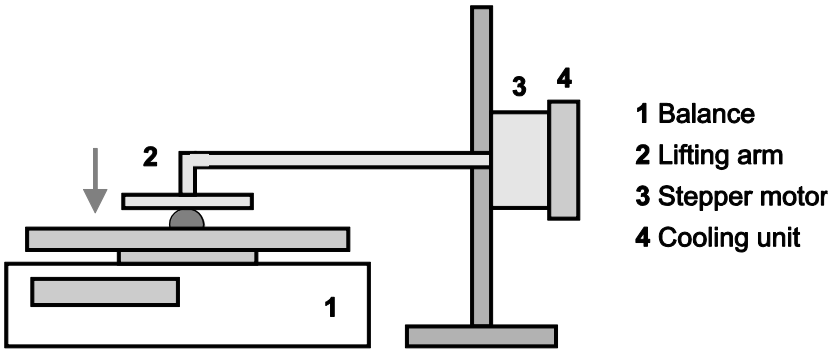


Fig. 4.2-5: Stability measurement device [Har16a].

The experimental set-up consist of a balance, which is connected to a PC and is registering the data all the time, and a stepper motor, which can also be controlled by a PC. A weight is pushed down automatically on the capsules and the corresponding mass is registered by the connected balance. The measured mass is increasing due to the pressure of the weight until the capsules break and is dropping again after the capsules broke. This way, the maximum pressure the capsules can resist is determined and the gathered data are used to calculate the crushing force and stability in respect to the capsule's size [Har16a].

The raw data gathered with this method is the maximum mass (m_{max}) before the capsules break. By multiplying this mass with the gravitational acceleration (g), the crushing force (F_{cr}) can be calculated (Eq. 4-2).

$$F_{cr} = m_{max} \cdot g \qquad \text{(Eq. 4-2)}$$

$$p_{st} = \frac{F_{cr} \cdot 4}{\pi \cdot d^2} \qquad \text{(Eq. 4-3)}$$

The stability (p_{st}) is the relation of the crushing force to the capsules area and thus can also be considered as a pressure. Due to the circular shape of the capsules, the diameter (d) can be used to calculate the area and stability as can be seen in Eq. 4-3.

4.2.5.3 Differential scanning calorimetry (DSC)

The differential scanning calorimetry (DSC) is an established and widely used analytical method. It is applied in various research areas to determine e.g. melting points, phase diagrams, metastable zones, solubility and polymorphism. The measurement principle of the used heat flux DSC is based on the difference in heat flow rate between the sample and a reference [Hai08, Moh02]. The schematic setup of a differential scanning calorimeter can be seen in Fig. 4.2-6.

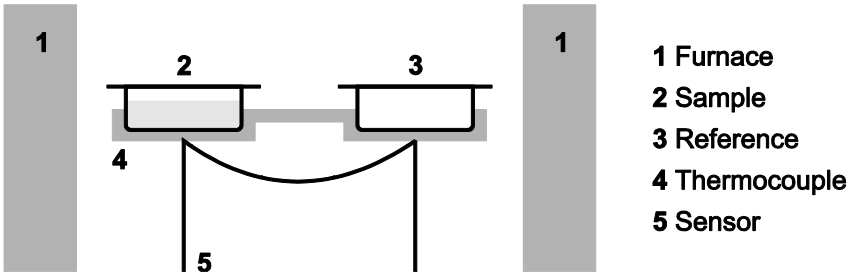


Fig. 4.2-6: Schematic setup of a differential scanning calorimeter [Net16].

The reference (3) and sample (2) are heated in a furnace (1) with a defined temperature program. The difference in temperature between reference and sample is registered by the sensor (5) which is connected to the thermocouple (4). At the beginning of the measurement this temperature difference is zero. When the sample is physically changing, e.g. during phase transition, the heat exchanged with the surrounding environment changes and a temperature difference can be observed. This will result in a corresponding peak in the diffractogram which then can be analyzed [Mar03].

For the measurement, about 7 mg of the capsule's shell or the pure components were taken in an aluminum crucible and sealed with an aluminum lid. To avoid an overpressure due to decomposing samples or evaporating water, a small hole was punched into the lid. The scan was performed in a temperature range between 25 and 210 °C with a heating rate of 5 K/min. The DSC cell was purged with nitrogen at a rate of 30 mL/min. After each measurement, the diffractogram was analyzed with Proteus Analysis software and the heat of fusion as well as the onset temperatures were determined.

4.2.5.4 Storage stability

The storage stability of the produced capsules was investigated by means of a climatic chamber. The capsules were stored at different temperatures and humidity and the stability and layer thickness were analyzed by means of the explained methods.

This method is based on the guideline Q1A (R2) of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) which describes stability tests for new pharmaceuticals. For short time studies, the ICH recommends a measurement period of at least six months. The thermodynamic equilibrium between liquid core and crystalline shell can be reached much faster. Therefore, the capsules were exposed to the different conditions for 24 hours [Int03].

The investigated conditions were chosen to be close to real condition that can be found during production, transport and storage at the costumer's place. Therefore, the temperatures -10, 10, 25, 40 and 60 °C were investigated, simulating storage in the fridge and at room temperature as well as transporting processes in summer and winter. Additionally to the temperature, the humidity was varied in the range between 10 and 80 %.

5. Results

5.1 Metastable zone

The metastable zones, including solubility and nucleation data, of the three tested systems and a pure xylitol solution for comparison are shown in Fig. 5.1-1.

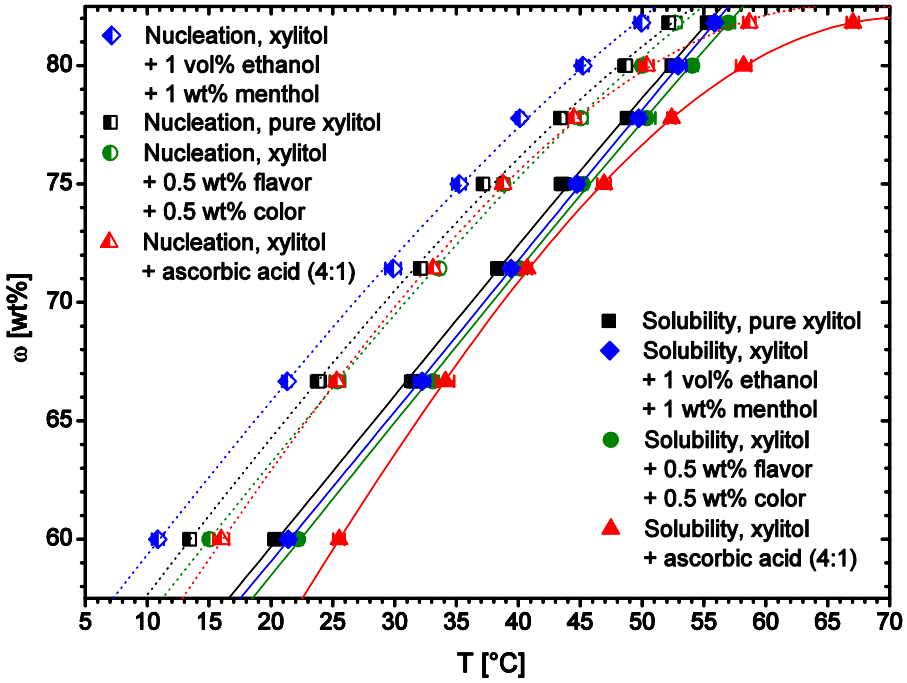


Fig. 5.1-1: Solubility and nucleation data of the three systems.

The solubility as well as the nucleation temperatures are increasing with increasing concentration for all the tested systems. Looking at the solubility data, it can be seen that the solubility curves of the pure xylitol solution, the ethanolic xylitol solution with menthol and the colored and flavored xylitol solution show the same progression. However, the pure xylitol solution has the highest solubility, followed by the xylitol-menthol solution and the flavored and colored xylitol solution. The solution containing xylitol and ascorbic acid in a ratio of 4:1 shows the lowest solubility. Furthermore, the progress of this curve is different. At higher temperatures the solubility is lower than the solubility of the other systems. This results in a more curved shape compared to the other solubility curves.

The nucleation curves of the systems show the same progress as the corresponding solubility curves. In general, the metastable zone gets smaller at higher temperatures

but the metastable zone widths vary. The metastable zone widths (MSZW) and the corresponding standard deviations (SD) can be seen in Tab. 5.1-1.

Tab. 5.1-1: Metastable zone widths of the three systems.

System	MSZW [°C]	SD [°C]
Pure xylitol	5.63	1.54
Xylitol + 0.5 wt% flavor + 0.5 wt% color	5.93	1.30
Xylitol + ascorbic acid (4:1)	8.31	0.61
Xylitol + 1 vol% ethanol + 1 wt% menthol	9.11	1.60

The metastable zone width of the xylitol-ascorbic acid solution is over all larger than the metastable zone of a pure xylitol solution. The addition of the investigated small amounts of flavor and color to the pure xylitol solution doesn't affect the metastable zone width significantly, it is just shifting the metastable zone to higher temperatures. An addition of 1 vol% ethanol and 1 wt% menthol is clearly widening the metastable zone.

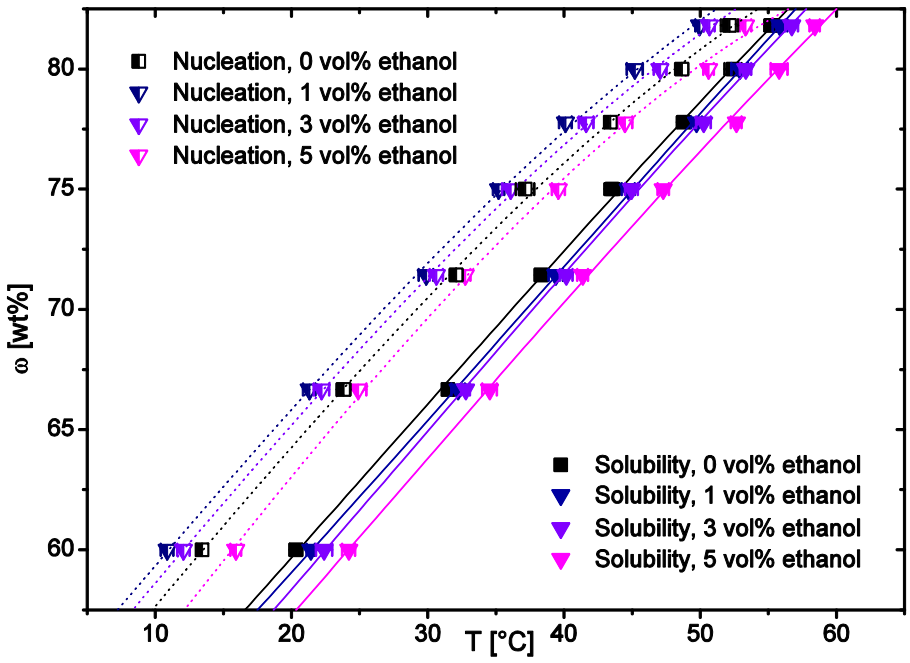


Fig. 5.1-2: Solubility and nucleation data of xylitol depending of the ethanol content.

Due to this large impact of ethanol on the metastable zone, further experiments were carried out using different ethanol amounts. The results can be seen in Fig. 5.1-2.

Relatively low ethanol amounts up to 5 vol% were investigated due to the capsule's potential applicability in food and pharmaceutical industry. The solubility of xylitol is decreasing with increasing ethanol amount. The highest applied ethanol amount is shifting the solubility curve of xylitol about 3.5 °C to higher temperatures.

Tab. 5.1-2: Metastable zone widths of xylitol solutions with different ethanol content.

System	MSZW [°C]	SD [°C]
Pure xylitol	5.63	1.54
Xylitol + 1 vol% ethanol	9.11	1.61
Xylitol + 3 vol% ethanol	8.61	1.68
Xylitol + 5 vol% ethanol	7.52	1.61

Furthermore, it is clearly recognizable that the addition of different amounts of ethanol has different effects on the nucleation points and thus on the metastable zone width. To clarify the differences, the metastable zone widths are summed up in Tab. 5.1-2.

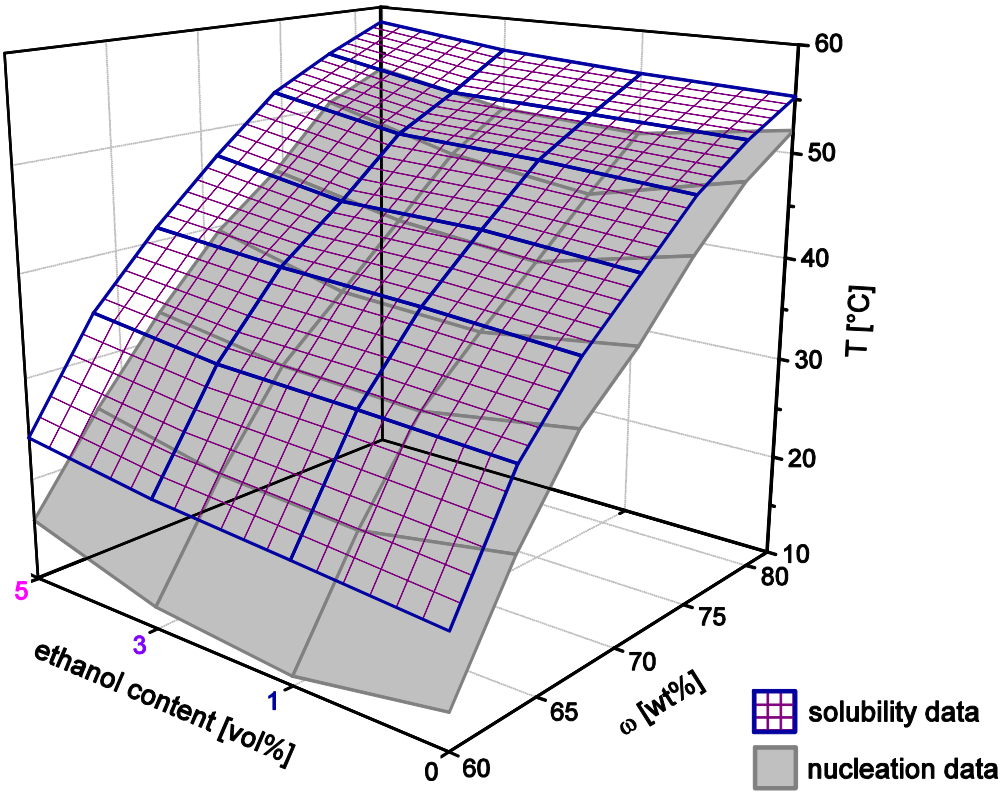


Fig. 5.1-3: Three-dimensional plot of solubility and nucleation data of xylitol as function of concentration and ethanol content.

Additionally, the solubility and nucleation data were plotted in a three dimensional diagram as a function of concentration and ethanol content and are shown in Fig. 5.1-3. Overall it can be seen that the metastable zone becomes smaller with increasing temperature and concentration, independent of the ethanol content. However, by adding ethanol the metastable zone width increases in all three cases.

It was found that the lowest investigated ethanol amount of 1 vol% is enlarging the metastable zone from 5.63 to 9.11 °C. As can be seen in Fig. 5.1-3 and Tab. 5.1-2, respectively. This represents a local maximum of the metastable zone width as function of the ethanol content. Increasing the ethanol amount to 3 and 5 vol% is decreasing the metastable zone width but not below the metastable zone width of a pure xylitol solution.

5.2 Crystal growth rate

To determine a suitable retention time for the seed crystals in the batch experiment, the crystal growth experiment for xylitol in water was carried out over a time period of 50 minutes.

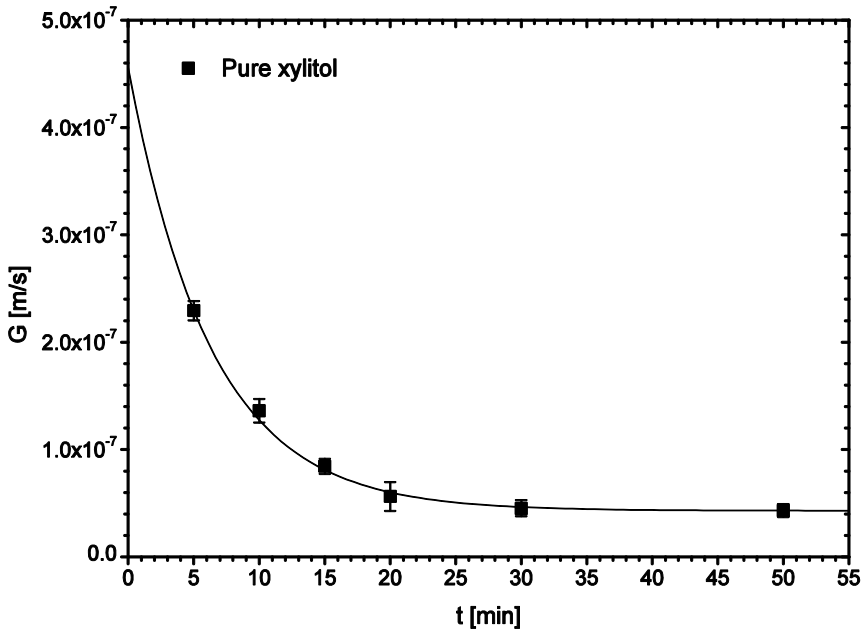


Fig. 5.2-1: Temporal decrease of crystal growth rate in a pure xylitol solution at 1 °C supersaturation.

The progress of the crystal growth rate for a supersaturation of 1 °C can be seen in Fig. 5.2-1. The crystal growth rate is rapidly dropping in the first 20 minutes of the experiment from about 4.5 • 10^{-7} m/s to 4.5 • 10^{-8} m/s. To get a reasonable crystal mass for the following analysis and to avoid the complete degradation of the supersaturation (see Chap. 6.2), the retention time for the seed crystals in the batch experiment was set to five minutes.

Based on these experimental parameters, the crystal growth rates for the three tested systems and a pure xylitol solution were determined. The results for a supersaturation of 1, 3 and 5 °C can be seen in Fig. 5.2-2.

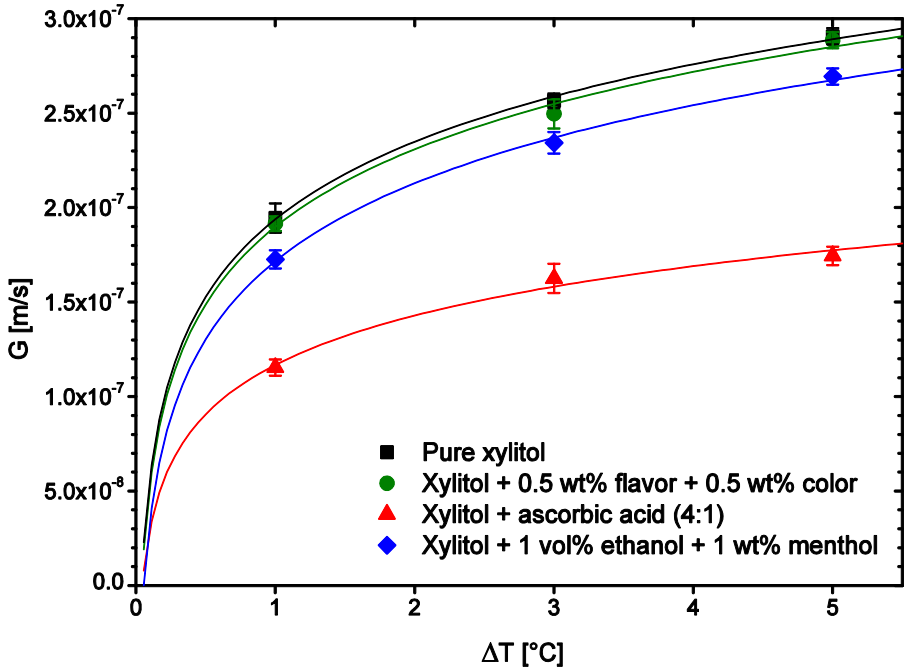


Fig. 5.2-2: Crystal growth rates of the systems depending on the supersaturation.

All analyzed crystal growth rates are increasing with increasing supersaturation. The highest growth rate could be found for the pure xylitol solution. The addition of each 0.5 wt% color and flavor is slightly lowering the crystal growth rate. But due to the standard deviations of this method, no significant difference was found.

The lowest crystal growth rate could be found for the xylitol solution with ascorbic acid. At a supersaturation of 5 °C the crystals grow with almost half of the growth rate of the pure xylitol solution. The crystal growth rate of the xylitol-ascorbic acid system is increasing with increasing supersaturation as well, but not as much as the growth rate of the pure xylitol solution. Therefore, the curve progresses with a lower slope than the

others. The crystal growth rates of the ethanolic xylitol solution with menthol is lower than the growth rates of the pure xylitol solution but higher than the growth rates of the xylitol-ascorbic acid system. However, the curve shows the same progression as the curve of pure xylitol.

Due to the apparent impact of 1 vol% ethanol on the crystal growth rates of xylitol, further experiments on the influence of different ethanol concentrations (3 and 5 vol%) have been carried out. The results can be seen in Fig. 5.2-3.

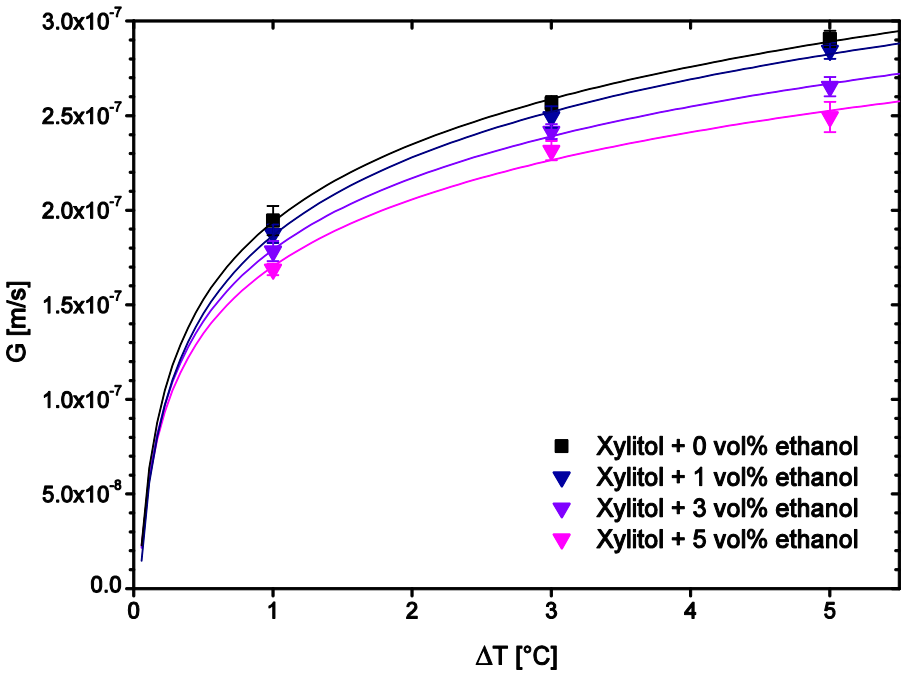


Fig. 5.2-3: Crystal growth rates of xylitol depending on the ethanol content.

All curves show the same progression, meaning that the crystal growth rates are increasing with increasing supersaturation. However, it is clearly recognizable that the crystal growth rates are decreasing with increasing ethanol concentration. The largest difference to the pure xylitol solution of about $0.4 \cdot 10^{-7}$ m/s was found for 5 vol% ethanol and 5 °C supersaturation. In general, the differences are larger at high supersaturation and smaller at low supersaturation.

5.3 Viscosity

Different viscosity measurements were carried out to determine the relation between viscosity and concentration as well as viscosity and temperature. The first results obtained at a fixed temperature of 60 °C are shown in Fig. 5.3-1 and show the concentration depending progress of the viscosity.

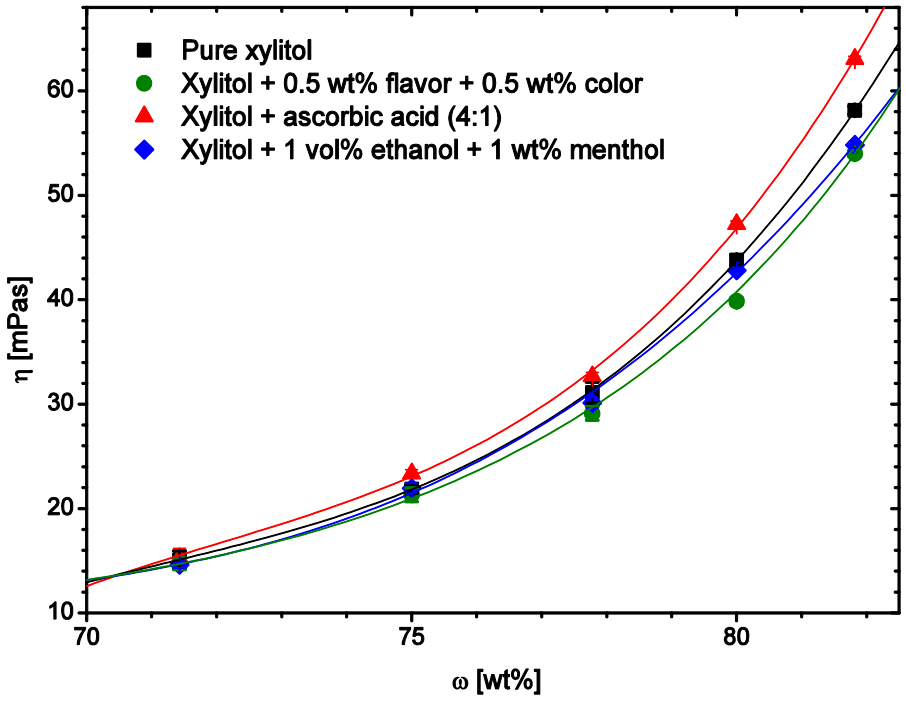


Fig. 5.3-1: Viscosities of the systems at 60 °C depending on the concentration.

It can clearly be seen that the viscosity of the three tested system is increasing with increasing concentration. At a low concentration of 71.4 wt% the viscosities are almost the same, about 15 mPas. With increasing concentration a bigger difference between the three solutions can be observed. The xylitol-ascorbic acid system shows the highest viscosity of 63.1 mPas at a concentration of 81.8 wt%. The xylitol solution has a lower viscosity under the given conditions and the colored and flavored xylitol solution as well as the ethanolic xylitol solution with menthol show the lowest viscosity of about 54.5 mPas.

Due to the temperatures during the in situ encapsulation process, the viscosity of the solutions with a concentration of 78 wt% was investigated during the cooling of the solution starting at 60 °C. The results can be seen in Fig. 5.3-2.

All the viscosity curves show the same progression during the cooling process.

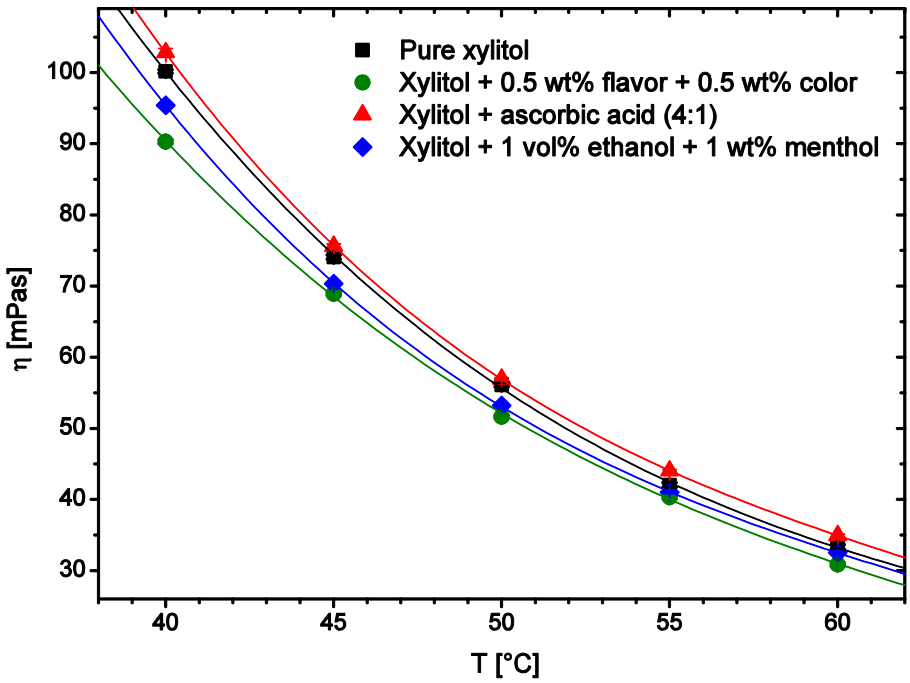


Fig. 5.3-2: Viscosities of the systems with 78 wt% depending on the temperature.

The viscosity is clearly increasing with decreasing temperature. At low temperatures the differences between the systems become clearer.

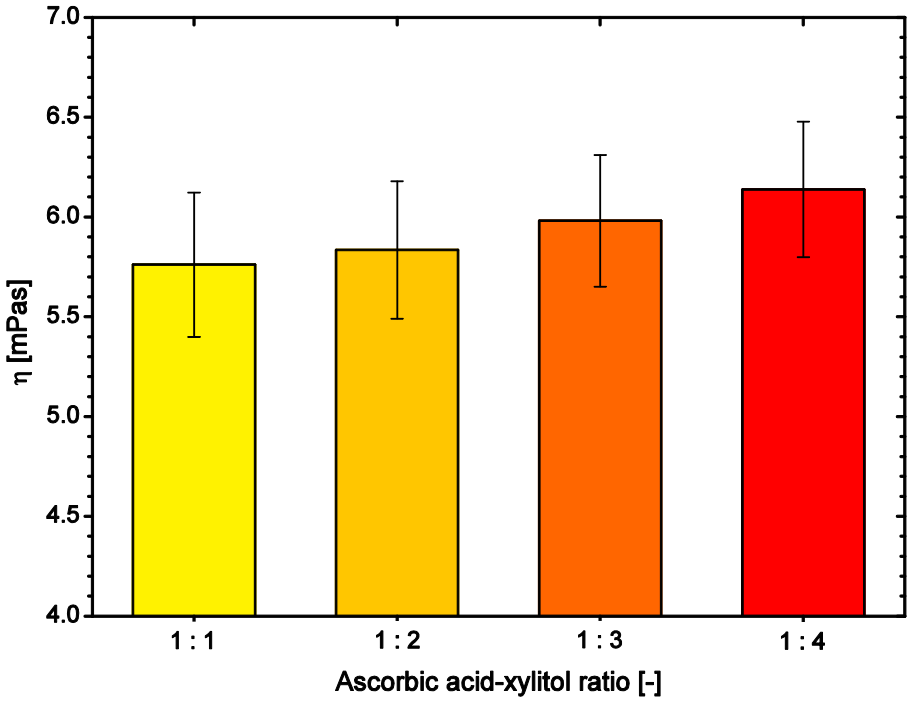


Fig. 5.3-3: Viscosity of ascorbic acid-xylitol solutions (60 wt%, 60 °C) depending on the composition.

The results of this experiment show the same order of the tested solutions, meaning that the xylitol-ascorbic acid solution still has the highest viscosity (102.8 mPas at 40 °C) and the colored and flavored xylitol solution has the lowest viscosity (90.3 mPas at 40 °C).

For the selection of the suitable composition of the xylitol solution with ascorbic acid, the influence of the composition on the viscosity was investigated. The results for a concentration of 60 wt% at 60 °C are shown in Fig. 5.3-3. It can be seen that the viscosity of the solutions is increasing with increasing xylitol content, ranging from 5.7 mPas (1:1) to 6.2 mPas (1:4). The differences between the tested solutions are rather small due to the low concentration.

5.4 Application examples

As already stated as aim of the work, the applicability of the in situ encapsulation process will be shown on three examples which are colored and flavored xylitol capsules (candy), vitamin C containing xylitol capsules (nutritional supplement) and xylitol capsules with ethanol and menthol (pre-dosed mouthwash). The production parameters as well as the properties of the final products will be presented in the following paragraphs.

5.4.1 Encapsulation parameters

The production parameters for the three different xylitol capsules can be seen in Tab. 5.4-1. It could be found that the optimal encapsulation parameters of the systems are very similar. The ideal concentration to achieve liquid filled capsules is 78 wt%. The product vessel (see Chap. 4.2.4) has to be hold at a constant temperature of 50 °C during the production. The cooling surface for the flavored capsules and the vitamin C capsules is a temperature controlled steel plate which is covered with Parafilm. The menthol capsules could not be produced by dropping the solution on a plane cooling surface but by filling it into pre-heated silicon molds with the desired shape. However, all cooling surfaces and the liquid drops after pastillation are covered with xylitol seed crystals.

Tab. 5.4-1: Production parameters for the in situ encapsulation.

System	Xylitol + 0.5 wt% flavor + 0.5 wt% color	Xylitol + ascorbic acid (4:1)	Xylitol + 1 vol% ethanol + 1 wt% menthol
Concentration	78 wt%	78 wt%	78 wt%
Temperature of the product vessel	50 °C	50 °C	50 °C
Cooling surface	Steel plate, Parafilm	Steel plate, Parafilm	Silicon molds
Temperature of the cooling surface	40 °C → 25 °C	35 °C → 25 °C → 8 °C	40 °C → 25 °C
Seeding	Xylitol	Xylitol	Xylitol, wheat starch

The initial temperature of the cooling surfaces is 40 °C for the colored and flavored capsules as well as for the menthol capsules and 35 °C for the ascorbic acid capsules. After one hour this temperature is decreased to 25 °C for all three cases. The xylitol capsules with ascorbic acid need to be cooled down further to 8 °C to achieve and optimal product. Furthermore, the menthol capsules have to be turned into a starch bed after one hour to obtain a stable crystalline shell.

5.4.2 Product properties

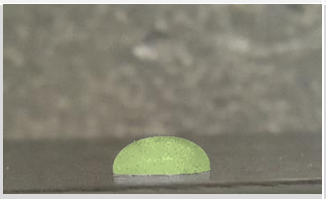
For the evaluation of the capsules, different characteristics have been investigated. The optical appearance as well as the stability and layer thickness of the crystalline shell are discussed in the following. Furthermore, the purity of the shell and the overall storage stability of the capsules are shown and evaluated.

5.4.2.1 Size and shape

The investigated capsules differ in their size, weight and shape. These properties as well as some images can be seen in Tab. 5.4-2.

The smallest produced capsules are the vitamin C capsules with a diameter of 7 mm and a weight of 70 mg. The menthol capsules are the biggest (28 mm) and also the heaviest (6 g) capsules. They weigh almost ten times as much as the vitamin C capsules.

Tab. 5.4-2: Size, weight and shape of the three different capsules.

System	Xylitol + 0.5 wt% flavor + 0.5 wt% color	Xylitol + ascorbic acid (4:1)	Xylitol + 1 vol% ethanol + 1 wt% menthol
Diameter	10 mm	7 mm	28 mm
Weight	0.10 g	0.07 g	6.00 g
h/0.5d ratio	0.70	0.83	0.95
Image			

One parameter that is listed in Tab. 5.4-2 is the h/0.5d ratio. This quotient gives as relation between the height and the radius of the capsule. If this ratio is one, the shape of the capsule is perfectly hemispheric. If the ratio is below one, the capsule have a flatter shape. The highest h/0.5d ratio of 0.95 was found for the xylitol-menthol capsules. The round shape can also be seen in the corresponding image. The colored and flavored xylitol capsules are the flattest with a h/0.5d ratio of 0.70.

5.4.2.2 Stability and layer thickness

To clarify when the capsules reach their maximum stability, measurements haven been carried out every 30 minutes after the production. The results are shown in Fig. 5.4-1.

It can be seen that the stability of the three tested capsules is increasing with time. The pure xylitol capsules reach the maximum stability of 1.2 N/cm² after about five hours. The stability of the flavored and colored xylitol capsules shows the same progression. After about five hours the maximum of 1.1 N/cm² is reached. The xylitol-menthol capsules have a lower maximum stability of 1.0 N/cm². Furthermore, this curve consists of only four points at 5.5, 6, 24 and 48 hours. It was not possible to gather stability data earlier because the capsules broke during removing them from the molds. Therefore, this curve is shown as a dotted line and should be considered as estimation due to the lack of data. Nevertheless, the trend is clear and it can be seen that this xylitol-menthol capsules reach their maximum stability later than the pure and flavored xylitol capsules.

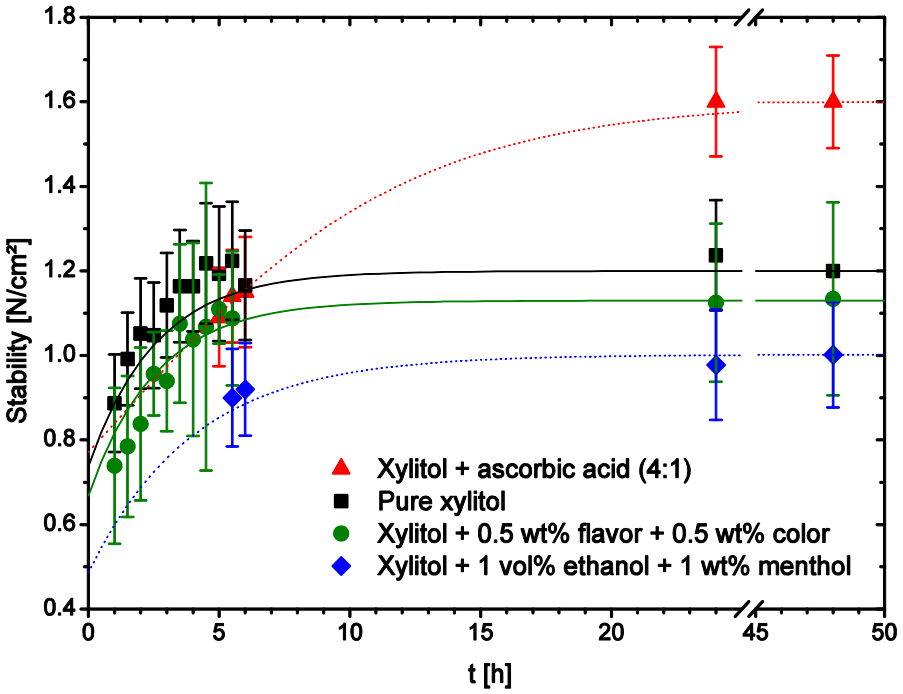


Fig. 5.4-1: Progress of the stability of the three different capsules.

The stability measurement of the ascorbic acid capsules was similar to the xylitol-menthol capsules. The first data could be gathered after five hours so that this curve consist of only a few points as well. But it can be stated that the maximum stability is reached even later than in the other cases due to the relatively high maximum stability of 1.6 N/cm² after 24 hours and the consequential progression of the curve.

Additionally to the stability, the layer thickness of the crystalline shell of the capsules was measured every 30 minutes after production. The results can be seen in Fig. 5.4-2.

In general, it can be seen that the crystal layer thickness is increasing with time, so it shows the same progression and trend as the stability. The layer thickness of the pure xylitol capsules reaches the maximum of 0.55 mm after approximately five hours, similar to the stability. The flavored and colored xylitol capsules have a slightly thinner crystalline shell with a layer thickness of 0.53 mm. This maximum is reached after five hours after the production as well. The curves for the xylitol-menthol and xylitol-ascorbic acid capsules consist of fewer points, but still more points than the stability curves. When the capsules broke, they could not be used for the stability measurements. However, the crystalline fragments of the broken capsule could be analyzed microscopically. Therefore, it was possible to obtain layer thickness data earlier then stability data.

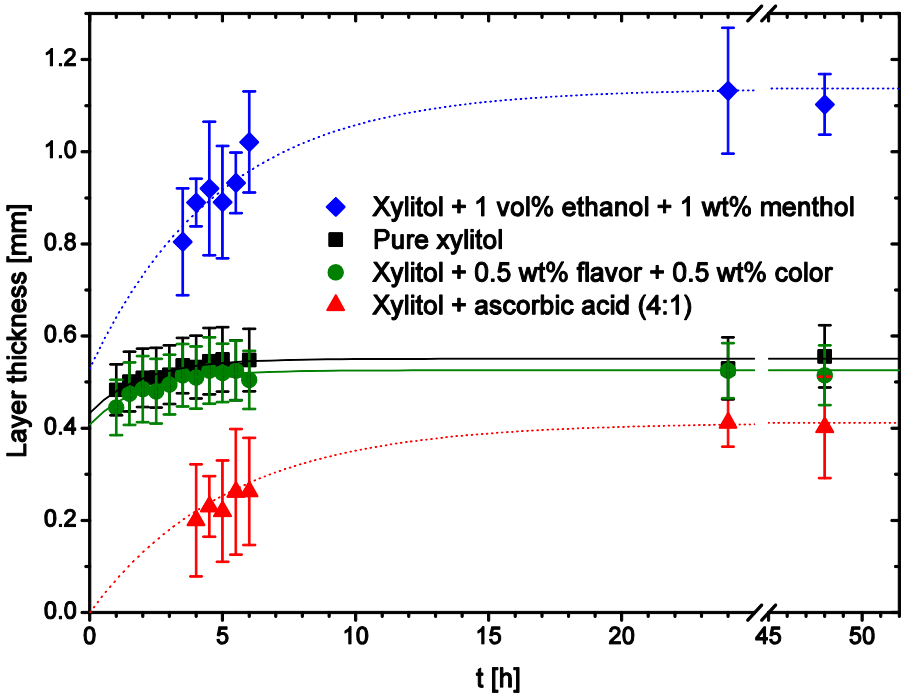


Fig. 5.4-2: Progress of the layer thickness of the three different capsules.

The highest layer thickness of 1.14 mm was found for the xylitol-menthol capsules. It can be seen from the progression of the curve that the maximum for the xylitol-menthol capsules is reached later than for the other capsules, after about 15 hours. In this case, the curve can only be seen as estimation due to the few measured points. The xylitol-ascorbic acid capsules have the thinnest crystalline shell of 0.41 mm. Similar to the xylitol-menthol capsules, the curve consists of less points and thus it can only be estimated, that the maximum is reached approximately 15 hour after production.

5.4.2.3 Purity of the shell

The purity of the capsule's shell was analyzed by means of differential scanning calorimetry (DSC). For each capsule, the pure components as well as the crystalline shell material were analyzed and the peaks were plotted in one diagram for comparison. The results for the colored and flavored xylitol capsule can be seen in Fig. 5.4-3.

The pure xylitol peak (black) has an onset temperature of 92.9 °C and a peak area of 247.2 J/g. It can clearly be seen that the peak of the flavored and colored capsule's shell (dark green) is overlapping with the pure xylitol peak. The onset temperatures are almost the same (92.8 °C) and the peak area is with 255.2 J/g slightly higher than the peak area of pure xylitol. No other peaks could be found for the crystalline shell of the

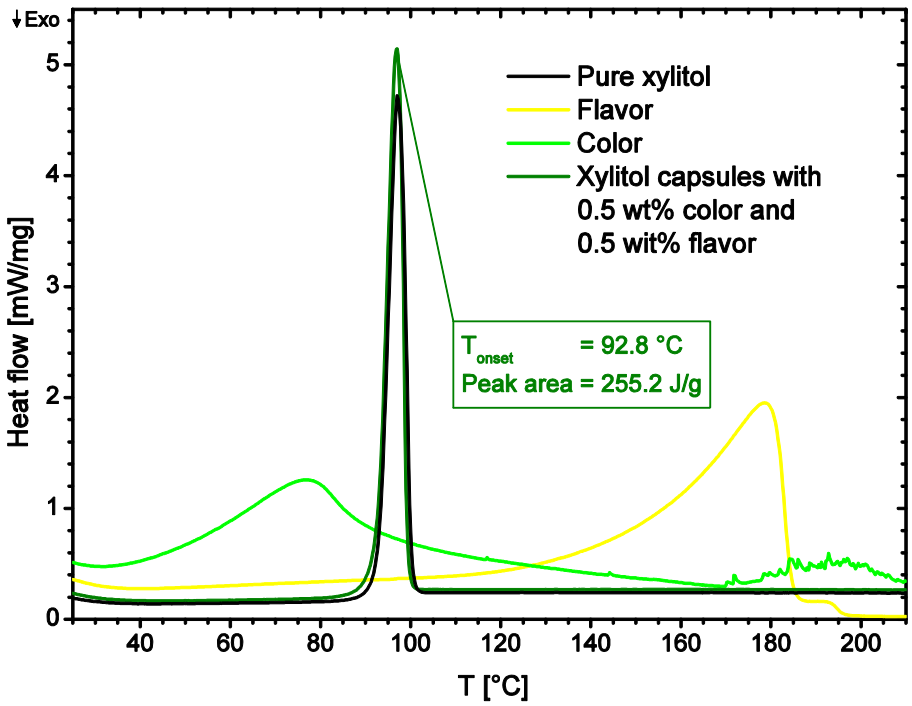


Figure 5.4-3: DSC curves of the flavored and colored capsule and its pure components.

capsule. The pure color (light green) and flavor (yellow) have each a lower and higher melting point compared to xylitol.

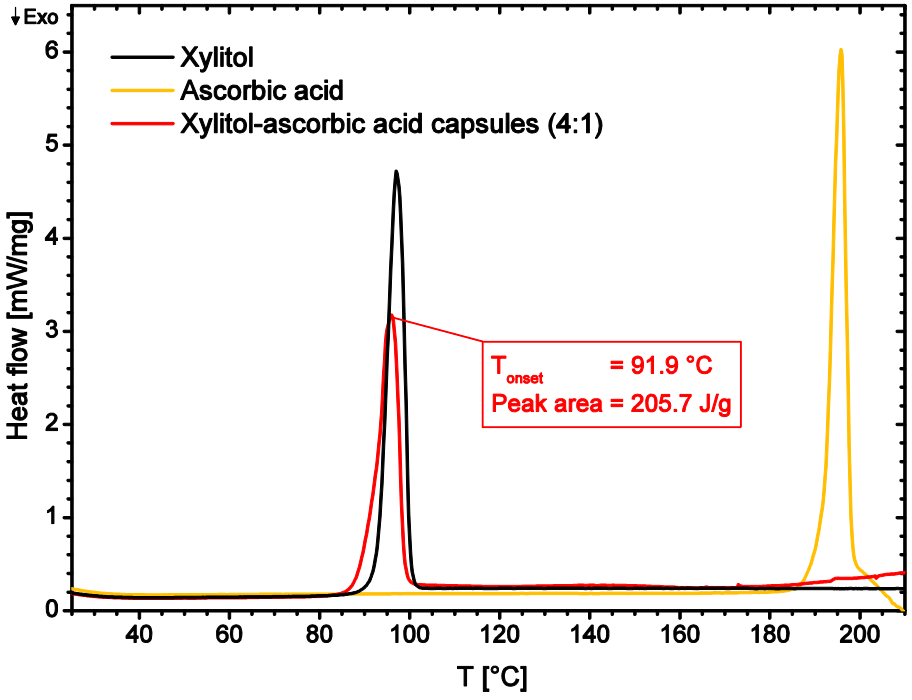


Fig. 5.4-4: DSC curves of the xylitol-ascorbic acid capsule and its pure components.

Fig. 5.4-4 shows the diffractogram of the xylitol-ascorbic acid capsules and their pure components. The melting point of the shell material (red) is 91.9 °C and thus 1 °C lower

than the melting point of pure xylitol (black). Furthermore, the peak area, meaning the enthalpy of fusion, is lower (205.7 J/g) compared to xylitol. The analysis of the capsule's shell resulted in one single peak in the diffractogram. Ascorbic acid (orange) shows one peak as well with an onset temperature of 192.1 °C.

The diffractogram for the xylitol-menthol capsules can be seen in Fig. 5.4-5. Pure L-menthol (light blue) shows the lowest melting point with an onset temperature of 42.5 °C. The analysis of pure ethanol (violet) resulted in one wide peak with an onset temperature of 78.5 °C.

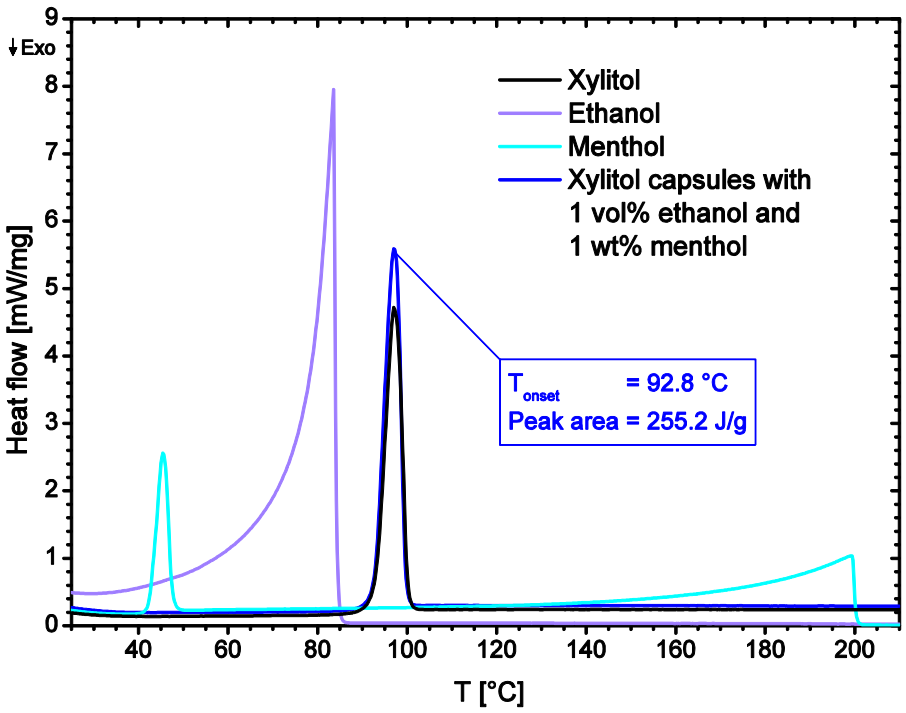


Fig. 5.4-5: DSC-curves of the xylitol-menthol capsule and its pure components.

Only one peak could be found for the crystalline shell of the xylitol-menthol capsules (dark blue) and it is overlapping with the peak of the pure xylitol (black). The capsule's shell material has a melting point of 92.8 °C and a peak area of 255.2 J/g.

5.4.2.4 Storage stability

As described in Chap. 4.2.5.3, the storage conditions were chosen to simulate extreme conditions during transport and storage. At the lowest temperature of -10 °C, the investigated capsules were too instable to be handled and analyzed. The highest chosen temperature of 60 °C caused the dissolving of the crystalline capsules. Therefore, no

stability and layer thickness could be determined for these temperatures. The same results were obtained for a humidity of 60 and 80 %. After 24 hours the capsules were dissolved and thus, no data could be gathered.

As a consequence, the layer thickness and stability of the capsules were analyzed for the storage conditions of 10, 25 and 40 °C combined with a humidity of 10 or 40 %. The results for the pure xylitol capsules can be seen in Fig. 5.4-6. The stability is shown as plain bars and the layer thickness is shown as striped bars.

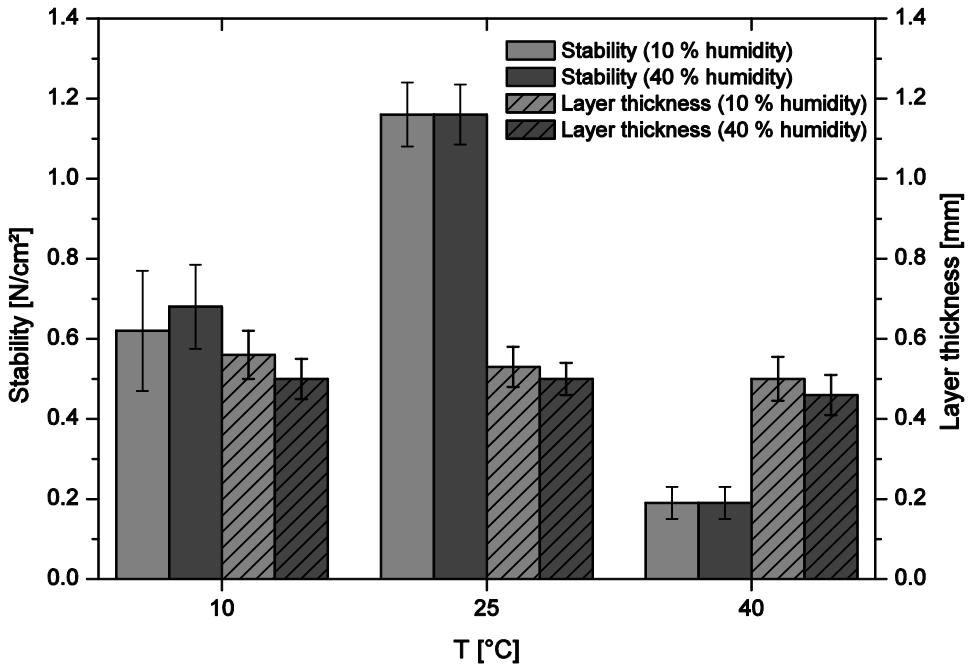


Fig. 5.4-6: Stability and layer thickness of pure xylitol capsules depending on different storage conditions.

A storage of the capsules at 25 °C and 40 % humidity represent the standard storage conditions after the production. It can be seen that a decreased humidity of 10 % has no significant influence on stability and layer thickness. In general it is recognizable that the layer thickness stays approximately the same independent of the chosen storage condition. But the stability is influenced by the temperature and humidity. Storing the capsules at 40 °C leads to the lowest stability of 0.19 N/cm². Decreasing the temperature to 10 °C is decreasing the stability of the capsules as well (to about 0.65 N/cm²), but not as much as for 40 °C.

The results for the colored and flavored capsules are similar to the results of the pure xylitol capsules and can be seen in Fig. 5.4-7.

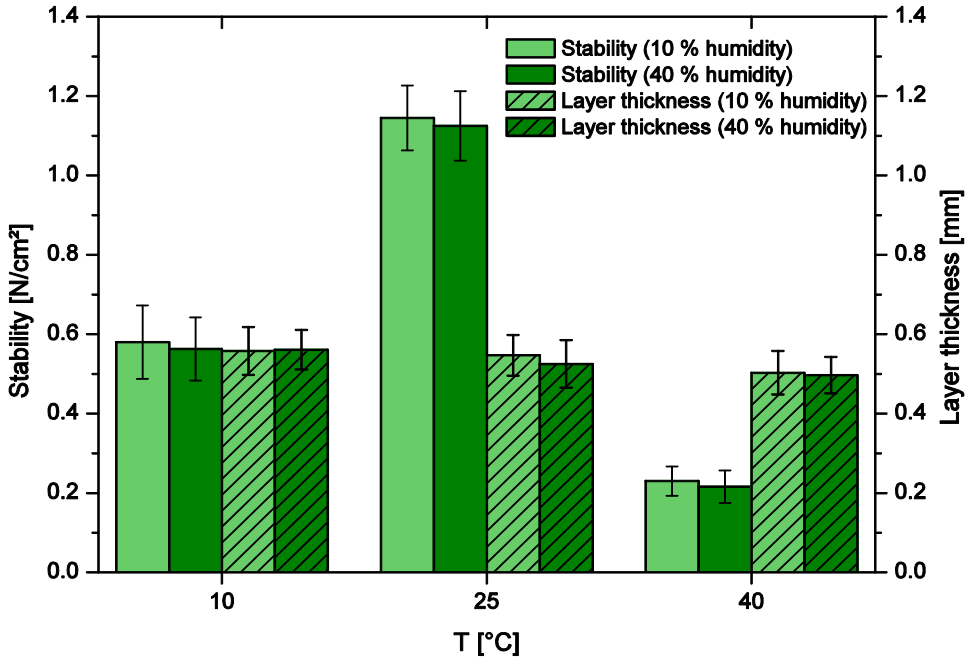


Fig. 5.4-7: Stability and layer thickness of flavored and colored xylitol capsules depending on different storage conditions.

The layer thickness of the crystalline shell is not significantly affected by temperature and humidity and is slightly varying about 0.53 mm.

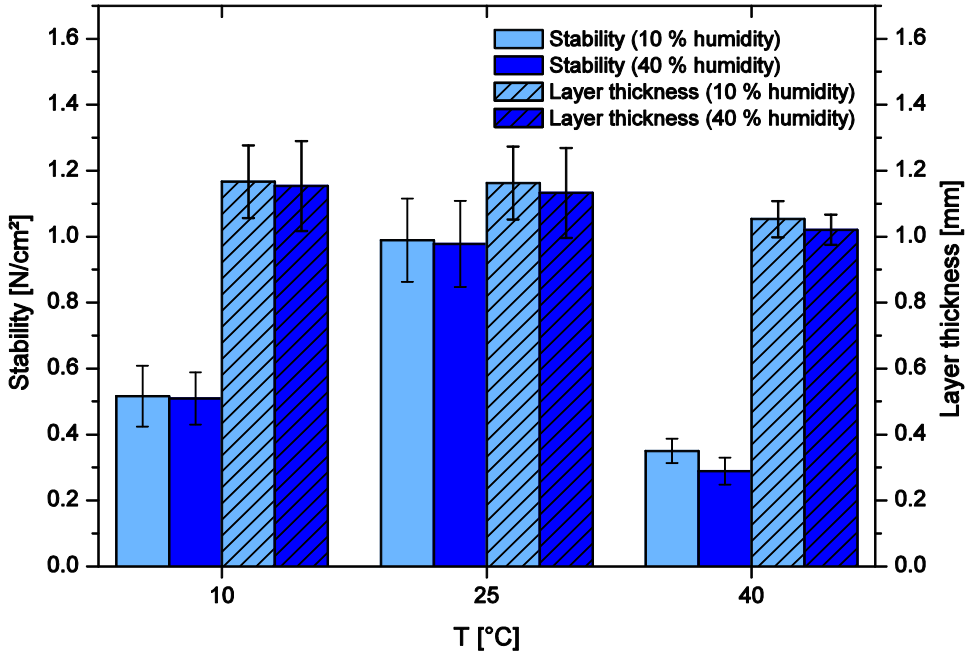


Fig. 5.4-8: Stability and layer thickness of xylitol-menthol capsules depending on different storage conditions.

The stability is not influenced by changing the humidity as well. The highest stability was found at 25 °C (1.12 N/cm²) and the lowest stability of 0.22 N/cm² was reached after storing the capsules at 40 °C. A storage of the products at 10 °C leads to a stability of 0.57 N/cm².

The stability and layer thickness of the xylitol-menthol capsules can be seen in Fig. 5.4-8. These results show a similar trend as the previously shown data. The layer thickness of the crystalline shell is not influenced by temperature or humidity and the stability is not affected by the humidity as well. Storing the capsules at 25 °C leads to the highest stability of 0.98 N/cm² and a storage at 10 °C is decreasing the stability to 0.51 N/cm². The lowest stability of 0.32 N/cm² was found for the highest temperature of 40 °C.

The layer thickness and stability data of xylitol-ascorbic acid capsules under different storage conditions are shown in Fig. 5.4-9.

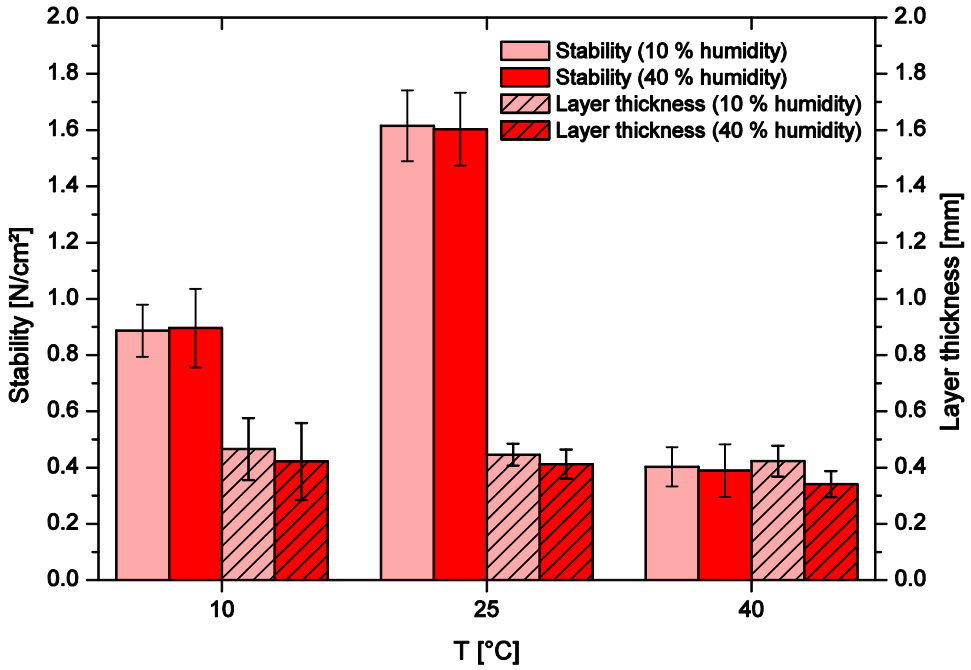


Fig. 5.4-9: Stability and layer thickness of xylitol-ascorbic acid capsules depending on different storage conditions.

It clearly can be seen that layer thickness and stability show the same trend as the other application examples. The thickness of the crystalline layer is not affected by temperature and humidity and is slightly varying about 0.44 mm. Storing the capsules at the standard conditions of 40 °C and 40 % humidity leads to the highest stability of

1.61 N/cm². Decreasing the humidity has no apparent influence on the stability. A decrease in temperature to 10 °C results in a decrease of the stability to 0.89 N/cm². The highest investigated temperature of 40 °C leads to the most instable capsules with a stability of 0.40 N/cm².

6. Discussion

6.1 Metastable zone

As previously described in Chap. 4.2-1, the solubility was determined gravimetrically and the nucleation points were gathered by means of an ultrasonic probe. To ensure the comparability of these data, the solubility of a pure xylitol solution was determined by ultrasound measurement and was compared to the gravimetric results. The solubility curves are shown in Fig. 6.1-1.

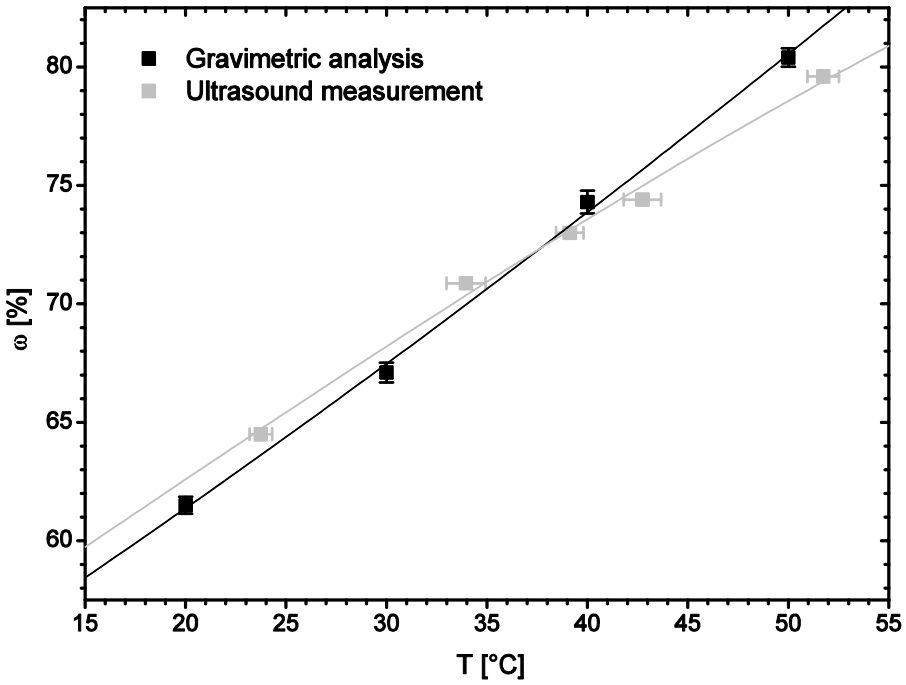


Fig. 6.1-1: Solubility data of a pure xylitol solution gathered by two different methods.

In general, it can be seen that the solubility of xylitol in water is increasing with increasing temperature. The solubility curves obtained by the two different methods differ slightly from each other. At about 37 °C and 72 wt% both curves have a point of intersection. Below and above this point the difference in solubility temperature is up to about 2 °C. Considering this rather small variation and the standard deviations of the methods, the data of gravimetric and ultrasound analysis are comparable and can be plotted in one diagram (see Chap. 5.1).

For the discussion and comparison of the metastable zone widths of the tested systems, the solubility and nucleation points at a concentration of 60 wt% are plotted in Fig. 6.1-2.

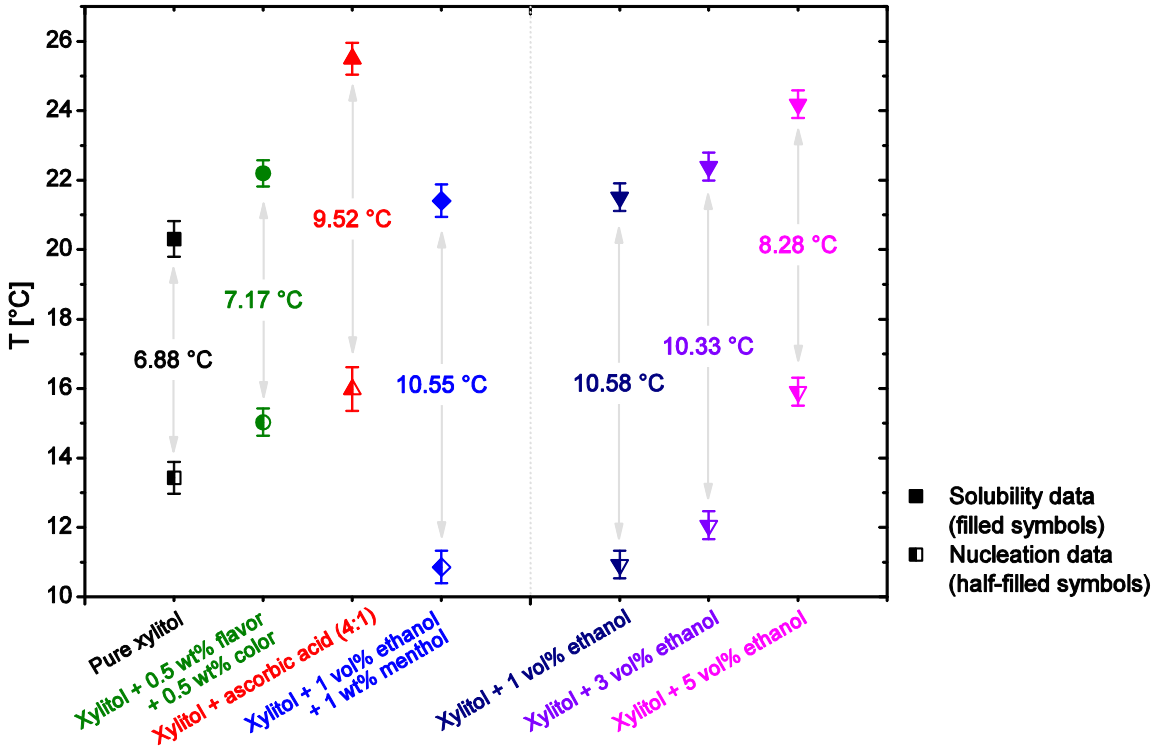


Fig. 6.1-2: Metastable zone widths of the tested solutions at a concentration of 60 wt%.

The metastable zone of a pure xylitol solution at 60 wt% is 6.88 °C wide. The addition of each 0.5 wt% color and flavor is widening the metastable zone slightly to 7.17 °C. But including the standard deviation of the method, no significant kinetic changes were found. Referring to Ulrich et al. [Ulr04], it can clearly be differentiated if an added substance acts as additive or third component. An additive is added in small amounts and does not have a significant influence on the thermodynamics of the system, whereas the kinetics can be affected. A third component or co-solvent changes the thermodynamics as well as the kinetics of the system.

Looking at the solubility points of the colored and flavored xylitol solution, it can be seen that the solubility temperature at a concentration of 60 wt% is increasing, compared to the pure xylitol solution, from 20.3 °C to 22.2 °C. The decreased solubility is caused by a lower solubility of xylitol in the pure flavor and color. Including the standard deviations of this measurement, the difference in solubility is about 1 °C. This rather small changes in solubility and the fact, that only 0.5 wt% of color and flavor were

added to the solution, lead to the conclusion that the used food coloring and flavoring act as additives.

The solubility temperature of the xylitol-ascorbic acid solution is increased significantly compared to the pure xylitol solution. Furthermore, the metastable zone is clearly larger (9.52 °C) than the metastable zone of the pure xylitol solution. Due to these thermodynamic and kinetic changes, ascorbic acid acts as third component in the system. Besides, the amount of ascorbic acid alone (20 wt% of the mixture) is reason enough to consider ascorbic acid rather as a third component than as an additive.

The addition of 1 vol% ethanol and 1 wt% menthol to a pure xylitol solution has no significant influence on the solubility. However, the metastable zone width is clearly increased from 6.88 °C to 10.55 °C and thus, the kinetics have changed. Referring to these information, ethanol as well as menthol can be seen as additives. Comparing the solubility temperatures of the xylitol solution containing 1 vol% ethanol and the solution containing each 1 vol% ethanol and menthol, no difference can be seen. That means that the addition of menthol has no influence on neither the thermodynamics nor the kinetics of the solution. Thus, menthol definitely acts as additive. But looking at the different testes ethanol contents of 1, 3 and 5 vol%, ethanol in general cannot be considered as additive.

The addition of bigger amounts of ethanol has an apparent influence on the solubility of xylitol. The highest applied ethanol amount of 5 vol% is shifting the solubility of xylitol about 3.9 °C to higher temperatures. This is caused by the low solubility of xylitol in organic solvents, which was previously described in the literature by Hao et al. [Hao06] and Wang et al. [Wan07]. Furthermore, Wang et al. [Wan13] could show that the solubility of xylitol in water is decreasing with increasing ethanol content, whereas only relatively high ethanol concentration were investigated.

The experimental results presented in Fig. 6.1-2 show, that the addition of 1 and 3 vol% ethanol don’t cause a significant change of the solubility. But it can be seen that the addition of 5 vol% ethanol is lowering the solubility of xylitol in water. It was proven that adding ethanol amounts bigger than 5 vol% changes the solubility of xylitol in water whereas smaller amounts don’t show a thermodynamic effect. Therefore, ethanol contents over 5 vol% act as third component or co-solvent while lower ethanol contents can be considered as additives.

However, it is clearly recognizable that the addition of different amounts of ethanol has different effects on the nucleation points and thus on the width of the metastable zone. Overall it can be seen in Fig. 5.1-2 that the metastable zone becomes smaller with increasing temperature and concentration, independent of the ethanol content. By adding ethanol the metastable zone width increases. Omar et al. [Oma04] have shown that there is a strong correlation between solvent effect on the solubility and the metastable zone width. The lower the solubility in a solvent the wider is the metastable zone due to the increased energy that is necessary to initiate the nucleation.

Though the addition of ethanol is decreasing the solubility, the metastable zone is enlarged for all the tested ethanol amounts. However, the widening of the metastable zone itself is depending on the ethanol concentration. It was found that the lowest used ethanol amount of 1 vol% is enlarging the metastable zone to 10.58 °C. As can be seen in Fig. 6.1-2, this represents a local maximum of the metastable zone widths as function of the ethanol content.

The widening of the metastable zone can be explained by different effects in the solid and liquid phase. Regarding the solid phase, ethanol inhibits the nucleation. The dissolved ethanol molecules adsorb to the clusters from which the nuclei (solid particles) will form. This will result in an increase of the metastable zone width (hence a suppression of nucleation).

Regarding the liquid phase, two different effects can be described. On the one hand, the structure of the solution and the interaction between the molecules change by adding ethanol [Tit02]. On the other hand, a decrease of the viscosity leads to faster diffusion processes and reduces the metastable zone width. The addition of ethanol is lowering the viscosity of the saturated solutions. Therefore, the higher the ethanol content, the lower the viscosity and the lower the metastable zone width.

The effect in the solid phase (increase of metastable zone width) and the effects in the liquid phase (decrease of metastable zone width) act contrary. The superposition of these opposing phenomena leads to a minimum effect at low ethanol concentrations and results in a local maximum of the metastable zone width at an ethanol concentration of 1 vol%. The addition of ethanol increases the metastable zone width due to the inhibited nucleation. However, the interfering effects in the liquid phase have obviously

more impact on the metastable zone. Thus, an increase of the ethanol content results overall in a decrease of the metastable zone width [Har16b].

Summarized, it could be shown that the addition of the investigated amounts of ascorbic acid as well as 5 vol% ethanol to a pure xylitol solution is changing the solubility and thus, the thermodynamic properties of the solution. Therefore, these substances have to be seen as third component or co-solvent, in case of ethanol. The kinetics, meaning the nucleation point and hence the metastable zone width, is affected by the addition of ascorbic acid, 1 wt% menthol with 1 vol% ethanol and every investigated amount of ethanol. In all cases, the metastable zone width is increased. The local maximum of the metastable zone width for the addition of 1 vol% ethanol is caused by the superposition of effects in the solid and liquid phase during nucleation.

6.2 Crystal growth rate

As can be seen in Fig. 5.2-1, the crystal growth rate is rapidly dropping in the first 20 minutes of the experiment due to the degradation of the supersaturation. At the beginning of the experiment, when the supersaturation is the highest, the crystal grow the fastest. The concentration of the solution will decrease due to the crystals growing which leads to a decrease of supersaturation. Thus, the driving force for the crystal growth is lower and the crystal growth rate decreases. Therefore, the retention time for the seed crystals in the batch experiment was set to five minutes to avoid the complete degradation of the supersaturation and to get a reasonable crystal mass for the following analysis.

A comparison of the crystal growth rates to literature data is difficult due to only few crystal growth studies on xylitol. Martínez et al. [Mar08] have investigated the crystal growth rates but under completely different conditions. The crystals were grown at a subcooling of about 10 °C for on average 100 minutes and less seed crystals were used. Furthermore, the growth rates were calculated from the crystal size and crystal size distribution. However, comparing the experimental result for 1 °C subcooling and 50 minutes residence time (Fig. 5.2-1, $4.5 \cdot 10^{-8}$ m/s) and the growth rates gathered by Martínez et al. ($2.4 \cdot 10^{-8}$ m/s [Mar08]) it can be seen that the growth rates are of the same order of magnitude.

Fig. 5.2-2 shows the crystal growth rates plotted against the subcooling. It can be seen that in general the crystal growth rates of xylitol are increasing with increasing supersaturation, as expected. A higher degree of subcooling results in a higher supersaturation and thus in a higher driving force. Due to the increased driving force, the crystals in the different tested systems grow faster with an increased degree of subcooling.

For better comparison and discussion, the crystal growth rates of the systems and a pure xylitol solution with a supersaturation of 1 °C and 5 minutes residence time are plotted in Fig. 6.2-1.

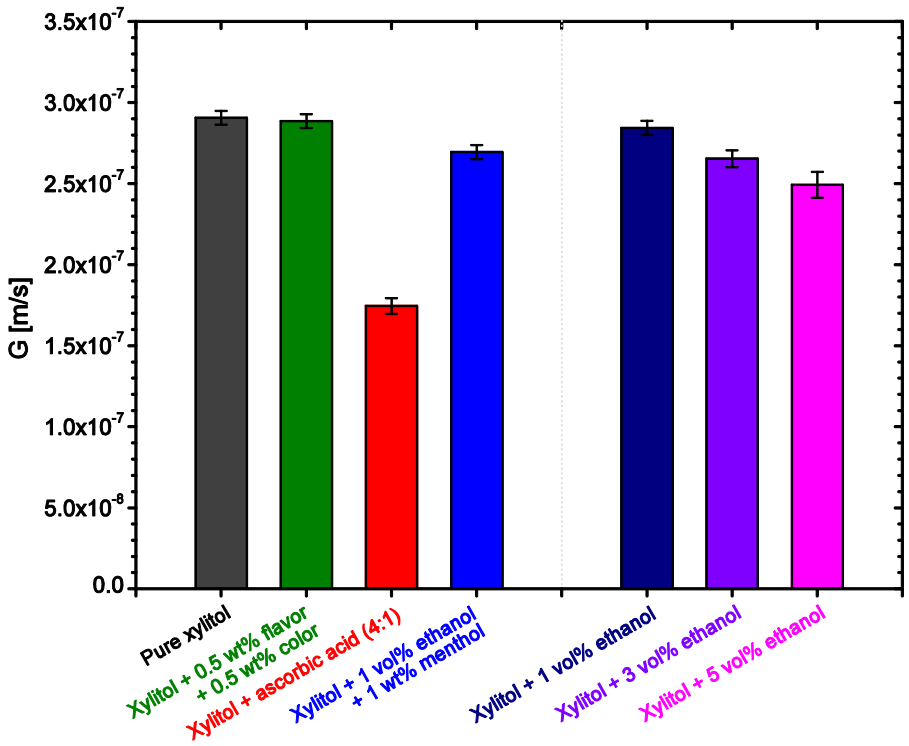


Fig. 6.2-1: Crystal growth rates of xylitol for 1 °C supersaturation and 5 minutes in the tested solutions.

It can clearly be seen that the addition of each 0.5 wt% flavor and color has no influence on the crystal growth rates of xylitol. This proves the statement that the used color and flavor act as additives. Additives could cause changes in the kinetics of the system but these small amounts of flavor and color neither affect the thermodynamics nor the kinetics.

For the xylitol-ascorbic acid system, a significant decrease of the crystal growth rates was determined. The high ascorbic acid content, 20 wt% of the mixture, has an apparent effect on the kinetic properties of the system. Additionally to this high amounts and

the already shown thermodynamic effects on the solubility, it can be confirmed that ascorbic acid acts as a third component in this system.

The crystal growth involves different steps like the mass transfer of the dissolved molecules from the solution to the crystal surface and the integration into the growth site [Gou09]. One possible explanation for the decreased growth rate is a depression of the growth of certain crystal faces. The growth of xylitol crystals in this ascorbic acid containing solution was analyzed microscopically as well, but no apparent change in the crystal habit and shape could be observed. Thus, it can be assumed that the diffusion process of the molecules to the crystal surface is inhibited and results in a lower crystal growth rate.

As it is shown in Fig. 6.2-1, the addition of 1 vol% ethanol to a pure xylitol solution is slightly lowering the crystal growth rate. But due to the standard deviations of the results, no significant difference to the growth rate of a pure solution could be found. But looking at the encapsulation solution containing 1 vol% ethanol as well as 1 wt% menthol, it is clearly recognizable that the crystal growth rate is decreased. That means that menthol is decreasing the crystal growth rate and affects the kinetics of the system. This result proves the statement that menthol has to be seen as additive in this solution (see Chap. 6.1).

But if the ethanol content is increasing, a noticeable decrease of the crystal growth was observed. Hao et al. [Hao06] could show that the addition of the solvent methanol inhibits the crystal growth of xylitol. But the lowest investigated methanol content was 33.3 vol%. The results shown in Fig. 6.2-1 confirm that the crystal growth is inhibited by a solvent. It could be shown that ethanol is decreasing the growth rates and that even small amounts (< 3 vol%) cause this phenomenon. This kinetic effect cannot be observed for ethanol contents lower than 3 vol%. The kinetic changes also confirm that ethanol can act as additive or co-solvent, depending on the used concentration.

Similar to the ascorbic acid system, the growth of the xylitol crystals was analyzed microscopically in addition to the batch experiment but no changes in the crystal morphology was found. Thus, the crystal growth rates are decreasing due to a inhibition of the diffusion process of the molecules to the crystal surface [Gou09].

Summarized, the conclusions drawn from the results of the metastable zone could be confirmed. Kinetic effects due to a decreased crystal growth rate were found for the

solutions containing ascorbic acid, 1 wt% menthol and 1 vol% ethanol as well as 3 and 5 vol% ethanol. Since no changes in the crystal morphology could be found, the depression of the crystal growth rate is a result of inhibited diffusion processes of the molecules to the crystal surface.

6.3 Viscosity

As can be seen in Figs. 5.3-1 and 5.3-2, the viscosity of the tested solutions is increasing with increasing concentration and decreasing temperature. If the temperature is decreased the Brownian motion decreases which results in a lower diffusivity and thus a higher viscosity [Ein05, Job11].

The viscosities of a pure xylitol solution as well as the three tested systems at a constant temperature of 40 °C and a concentration of 78 wt% can be seen in Fig. 6.3-1.

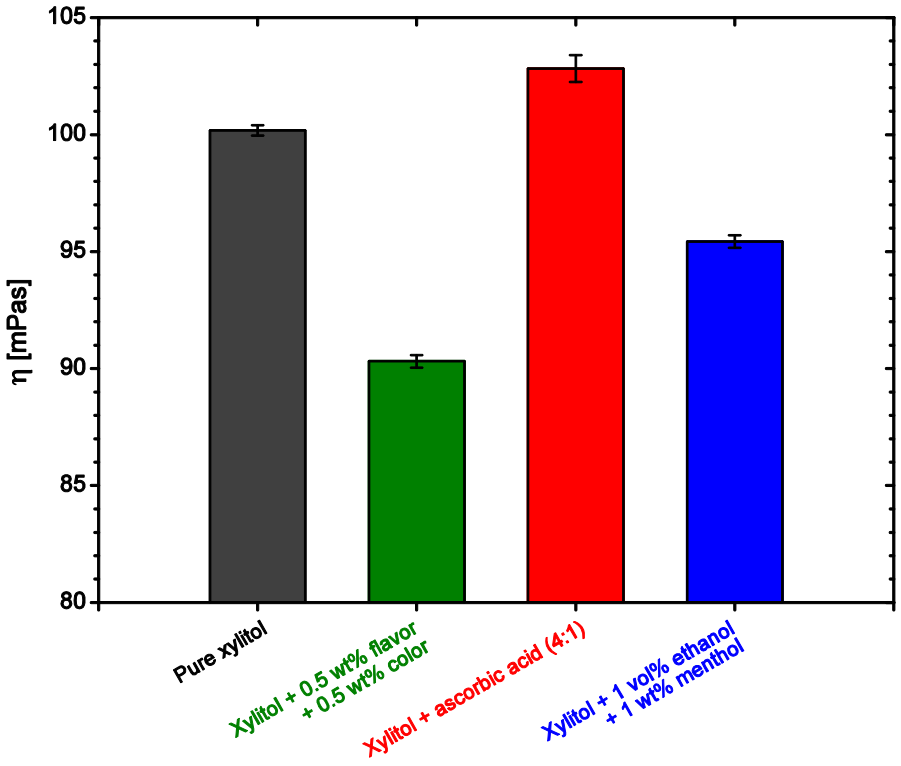


Fig. 6.3-1: Viscosity of the tested solutions at 78 wt% and 40 °C.

The viscosity of a pure xylitol solution under the given conditions is 100 mPas. The addition of each 0.5 wt% color and flavor is lowering the viscosity remarkably to

90 mPas. This change has its origin in the low viscosity of the added substances. However, a lower viscosity would result in a smaller metastable zone because the diffusivity is higher and the molecules can move easier so that the nucleation would occur earlier compared to a higher viscous solution. But, as can be seen in Fig 6.1-2, the metastable zone width is not significantly affect by the addition of color and flavor. This leads to the conclusion that the applied color and flavor are inhibiting the nucleation. But due to the superposition of these two effects (low viscosity and inhibited nucleation), no apparent effect could be observed.

The same phenomenon can be found for the crystal growth rates. Regarding the low viscosity of the solution, a higher crystal growth rate would be expected due to the increased diffusivity. But, similar to the nucleation, no significant difference could be observed. This leads to the same conclusion, that the added amount of color and flavor is inhibiting the crystal growth. However, in superposition with the low viscosity, this effect is not noticeable. Nevertheless, these kinetic effects confirm that the used color and flavor act as additives in this system.

The xylitol solution containing 1 vol% ethanol and 1 wt% menthol has a viscosity of 95 mPas, which is lower than the viscosity of a pure xylitol solution. As already discussed, the decreased viscosity results in a higher diffusivity and thus in a wider metastable zone, which can be seen in Fig. 6.1-2. Due to the lower viscosity, a higher crystal growth rate would be expected. But the crystal growth rates are even slightly lower compared to a pure xylitol solution. This effect is caused, similar to the colored and flavored xylitol solution, by the superposition of the inhibited crystal growth and the low viscosity. But in this case, the influence of the suppression of the crystal growth is bigger than the effect of the decreased viscosity, which leads to an overall lower crystal growth rate.

The highest viscosity of 103 mPas was measured for the xylitol-ascorbic acid solution. This increased viscosity leads to slower diffusion processes and thus to a wider metastable zone and a slower crystal growth (Fig. 6.1-2). Fig. 6.3-1 shows the result for a solution consisting of 20 wt% ascorbic acid and 80 wt% xylitol. As can be seen in Fig. 5.3-3, the viscosity is depending on the composition of the solution. With increasing xylitol amount, the viscosity is increasing as well. This is the main reason, why the ratio 4:1 (xylitol : ascorbic acid) was chosen. Fig. 5.3-3 shows the results for solutions with a relatively low concentration of 60 wt% at a relatively high temperature of 60 °C.

Unfortunately, the analysis of higher concentrated solutions was not possible due to the low solubility of ascorbic acid and the corresponding high temperatures that would have been necessary to carry out the measurement. But the differences between xylitol-ascorbic acid solutions with a ratio 4:1 and 3:1 was clearly recognizable during the production of the capsules due to the higher concentration of the solutions. A higher viscosity of the solution results in capsules with a more hemispheric shape and thus a better product [Kim03]. This aspect and the influence of the production parameters are discussed in the following paragraph.

Summarized, the determined viscosities revealed some kinetic effects for the xylitol solutions containing flavor and color as well as ethanol and menthol. It could be shown that the added substances are inhibiting the nucleation and crystal growth but due to the superposition with the lowered viscosity, this effect could not be seen from the phase diagram or the determined crystal growth rates. Regarding the ascorbic acid containing solution, the viscosity confirms the changes of crystal growth rate and nucleation points.

6.4 Application examples

The experimental results from the production of the three different xylitol capsules, including manufacturing parameters and product properties, will be discussed in the following.

6.4.1 Encapsulation parameters

The optimal encapsulation parameters for the three different capsules are presented in Tab. 5.4-1. The chosen conditions are explained more detailed in the following and the progress of the concentration during the production of pure xylitol capsules can be seen in Fig 6.4-1.

The required encapsulation solutions have to be prepared above the saturation temperature, so that all the components dissolve in the solvent. In the case of the pure xylitol capsules, xylitol was dissolved in water at 60 °C (1). Before the pastillation, the solution has to be cooled down to the temperature of the product vessel (50 °C) to reach a saturated or supersaturated state (2). The solution is then divided into drops

that are deposited on the cooling surface which was prior covered with Parafilm and xylitol seed crystals and tempered to 40 °C (3). When the supersaturated drops get in contact with the xylitol seed crystals from the bottom and top and they are cooled down by the cooling surface, the crystallization is initiated immediately and the concentration will drop (4). The application of seed crystals from both sides is essential to provide sufficient nuclei on the surface of the drops. The nuclei then grow to a uniform crystalline shell that encloses the liquid core [Ulr94]. The capsule's shell will grow until the supersaturation in the liquid core reduces and reaches the saturation point at the given storage temperature of 25 °C (5).

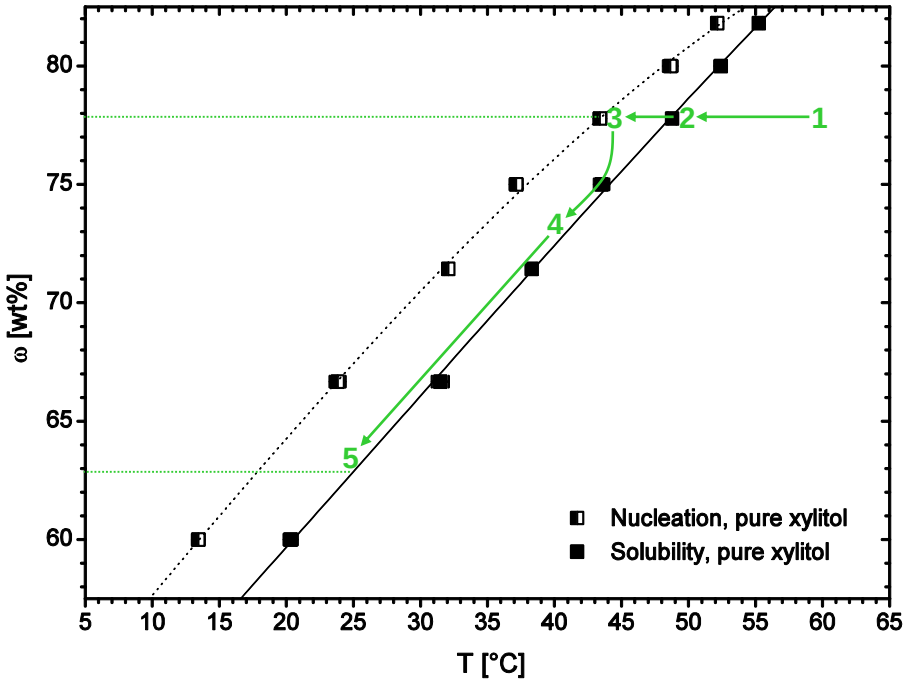


Fig. 6.4-1: Progress of the concentration during the encapsulation process.

The temperatures of the cooling surface and storage play a determining part in the quality of the capsules including shell defects. If the temperature is too low, the crystallization would be too fast which results in big crystals in the shell and thus a low stability. Additionally, the liquid core would cool down very fast as well which results in a decrease of the volume. Due to the density difference between solid shell and liquid core, this depression will lead to hollows and holes in the crystalline shell (see Chap. 2.1.5) [Ulr94]. Furthermore, the bottom of the capsules would be too thick because of the direct contact to the cooling surface. The saturation point would be reached so fast that the top part of the capsule could not be formed properly. To

achieve a stable shell, the xylitol has to crystallize slowly so that top and bottom part of the crystalline shell have a similar layer thickness and a stable crystalline structure can be obtained.

Such stable capsules could be produced with a cooled surface tempered to 40 °C for pure xylitol, xylitol-menthol as well as colored and flavored xylitol capsules and 35 °C for the vitamin C capsules. A higher temperature was not feasible for the ascorbic acid system because the crystallization takes too long due to the low crystal growth rate. After one hour, the temperature is decreased to 25 °C at which the flavored and colored as well as the xylitol-menthol capsules are stored until the supersaturation in the liquid core is degraded and the equilibrium is reached.

For the xylitol-ascorbic acid capsules, an additional cooling step was required to obtain stable products. After one hour at 25 °C, the temperature was decreased further to 8 °C. This is a necessary step to expedite the crystallization time of these capsules. Due to the decreased growth rate (compared to pure xylitol), the capsules would take too much time to crystallize if they were stored at 25 °C. This way, after one hour at 8 °C, the capsules also reached the equilibrium in the liquid core and could be used for the further analysis of the product properties much earlier.

Another exception in the manufacturing process is the shaping of the xylitol-menthol capsules, which are the biggest produced capsules. After filling the solution into the pre-treated silicon molds and one hour storage at 25 °C, they had to be turned into a wheat starch bed. At this point of the production, the capsules already had a thin crystalline shell. The capsules in the molds have to be turned to achieve a uniform layer thickness. Due to the diffusion of the molecules according to gravity, the bottom crystal layer became much thicker. By turning the molds, the top part could grow thicker which results in an overall uniform layer thickness and thus a better stability. A wheat starch bed was chosen regarding to already established process for manufacturing liquid filled candies [Cap90]. On the one hand, the starch bed could collect the liquid, if the capsules broke during turning. On the other hand, wheat starch acts as seed crystals and benefits the crystallization of the shell and thus the removal of potential defects in the capsule’s shell.

6.4.2 Product properties

For the evaluation of the capsules different product properties were analyzed. Before the application of in situ encapsulation, the intended properties of the capsules have to be defined. The major product characteristics are size, shape, stability, layer thickness and purity of the crystalline shell as well as the storage stability.

6.4.2.1 Size and shape

As can be seen in Tab. 5.4-2, the h/0.5d ratio was introduced to evaluate the hemispheric shape of the capsules. At an h/0.5d ratio of 1, the capsules would be perfectly hemispheric. To obtain nicely shaped products, the cooling surface was covered with Parafilm, which is an elastic paraffin-polyolefin-foil with a rough surface. The rough surface causes less contact of the liquid drop to the cooling surface. Hence, the contact angle between drop and surface is increased and the capsules become more hemispheric [Bic99, Dub14, Kim03].

The optical appearance and shape of a drop is influenced by different factors like the collision with the cooling surface, diameter, density, viscosity, surface tension, temperature and contact angle [Ber99]. The surface tension and gravity are the main factors that influence the shape of a liquid drop. Gravity is forcing the liquid to spread on the surface and the surface tension is counteracting and is keeping the drop in shape. Low viscous drops will spread more than high viscous drops. Bigger drops with a larger diameter will spread more because the higher mass is easier affected by gravity.

Looking at the capsules, the solidification process of the drop has a major impact on the capsule's shape. When the supersaturated drop hits the cooled surface and gets in contact with the seed crystals, the crystallization is initiated and a thin crystalline shell will be formed. If the crystallization of the shell is faster than the deformation of the liquid drop due to gravity, the capsule will have a more hemispheric shape. If the crystallization is too slow, the drop will spread on the surface before the first crystal layer could grow.

The smallest xylitol-ascorbic acid capsules have the most hemispheric shape of the capsules that were produced by dropping the solution on a flat surface. As explained above, their shape is caused by the relatively high viscosity and the small diameter. The flavored and colored xylitol capsules are bigger and the solution is less viscous

resulting in the flattest produced capsules with an h/0.5d ratio of 0.7. Contrary to these results, the xylitol-menthol capsules have the most hemispheric shape (h/0.5d=0.95), even though the solution has a lower viscosity. This is caused by the production step of filling the solution into pre-treated silicon molds. Due to the low viscosity of the solution and the large diameter of 28 mm, it was not possible to obtain nicely shaped capsules only by dropping the solution on a flat surface. Filling the solution into molds and letting the capsules crystallize in these molds results in almost hemispheric capsules and shows that the shape can vary by using different molds.

6.4.2.2 Stability and layer thickness

As can be seen in Figs. 5.4-1 and 5.4-2, the capsules were analyzed every 30 minutes after production to determine the progress of stability and layer thickness. Both parameters are increasing over time for all the tested systems. After the production of the capsules, when the liquid and supersaturated drops get in contact with the cooling surface which is covered by seed crystals, the crystallization of the shell will start immediately. A crystal layer will be formed and the layer thickness and thus the stability of the capsules will increase. The crystalline shell of the capsules will then continue to grow until the supersaturation in the liquid core is degraded and the thermodynamic equilibrium is reached. In this state, the capsules will remain with their maximum layer thickness and stability.

The pure xylitol capsules as well as the colored and flavored capsules reach their maximum stability and layer thickness the fastest, after approximately four hours. This can be explained by the crystal growth rates of the systems. The pure xylitol solution has the highest crystal growth rate compared to the other solutions. The colored and flavored xylitol system shows the same crystal growth, which results in the same progress of stability and layer thickness of the capsules. Additionally to the crystal growth rates, the viscosities of the solutions are one reason for the different crystallization times. As already discussed in Chap. 6.3 and shown in Fig. 6.3-1, the viscosity of the colored and flavored xylitol solution is the lowest of all the tested systems. This would lead to the assumption that the crystal growth would be lower. But due to the superposition of these two effect, no difference in crystal growth rate can be found. Thus, the capsules take the same time to reach their maximum stability compared to the pure xylitol capsules.

The xylitol-menthol capsules reach their thermodynamic equilibrium later, even though only few data could be gathered due to the breaking of the capsules while removing them from the molds. But the trend of layer thickness and stability can clearly be seen and can be explained by the decreased crystal growth rate. The xylitol crystals in this system grow slower and thus, the degradation of the supersaturation in the liquid core of the capsules takes more time and the equilibrium is reached later. Regarding the viscosity, the effect of the decreased crystal growth rate is superimposing the decreased viscosity. Therefore, the crystalline shell grows slower, the supersaturation in the liquid core is degraded slower as well and thus the maximum stability is reached later.

The xylitol-ascorbic acid capsules takes the longest time to reach their equilibrium. The crystal growth rate is the lowest of the tested systems which leads to a slower increase of layer thickness and stability. Therefore, the thermodynamic equilibrium as well as the maximum of layer thickness and stability is reached later compared to the other tested systems. The reasons for the xylitol-ascorbic acid capsules reaching the thermodynamic equilibrium last are on the one hand the highest viscosity and on the other hand the lowest crystal growth rate of the tested systems.

Fig. 6.4-2 shows the maximum layer thickness and stability of the analyzed capsules after 24 hours storage at 25 °C. The data are plotted with increasing diameter of the capsules, beginning with xylitol-ascorbic acid, pure xylitol, flavored and colored xylitol and xylitol-menthol capsules from left to right. It can be seen that there is a relation between the investigated parameters and the capsule's size. The layer thickness is increasing with increasing diameter. This would lead to the assumption, that the capsules become more stable with increasing size. But it can clearly be seen that the stability is decreasing with increasing diameter.

Additionally to the layer thickness and stability, the crushing force is plotted. The crushing force is the pressure that need to be applied to break the capsules (see Chap. 4.2.5.2). Fig. 6.4-2 shows the same trend for layer thickness and crushing force, with increasing capsule size the crushing force is increasing as well. This is caused by the thicker crystalline shell. If the capsule's shell is thicker, more pressure has to be applied before the capsules break. In contrast, the stability is decreasing because it is related to the capsule's area (see Chap. 4.2.5.2). The increase of layer thickness and

crushing force cannot compensate the size increase. This results in an overall decreased stability.

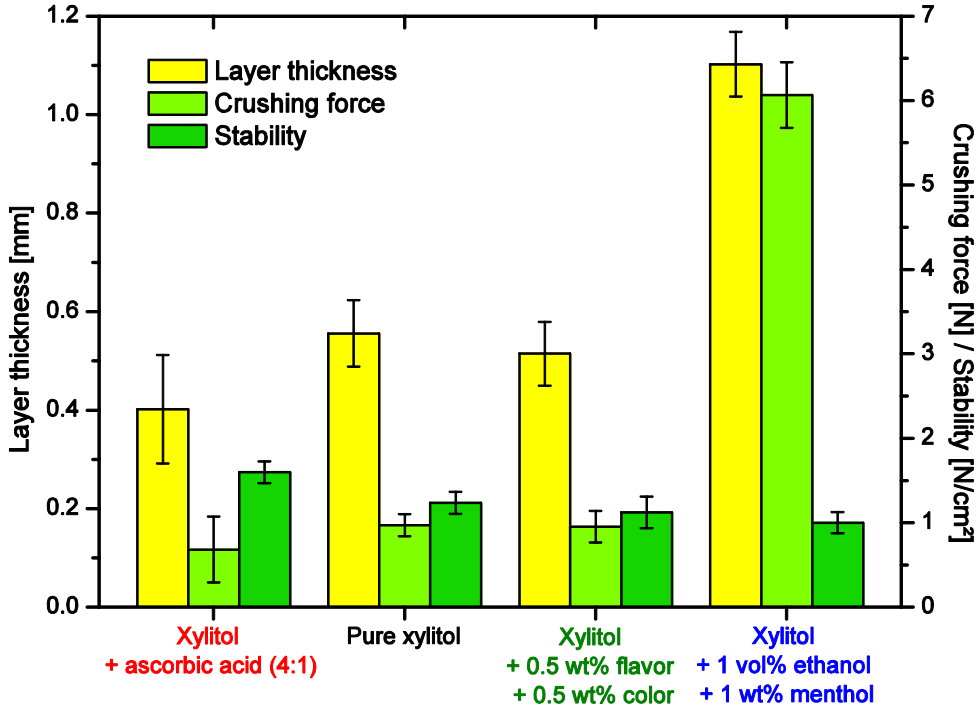


Fig. 6.4-2: Comparison of layer thickness, crushing force and stability of the capsules.

To explain why the xylitol-ascorbic acid capsules are most stable and the xylitol-menthol capsules are the most instable ones, the mass and volume of the capsule's shell are helpful criteria. The calculation of the volume of the capsule ($V_{capsule}$) is based on the equation for the volume of a flattened rotational ellipsoid (Eq. 6-1) due to their not perfectly hemispheric shape [Göh99].

$$V_{capsule} = \frac{4}{3} \cdot \pi r^2 h \cdot \frac{1}{2} \qquad \text{(Eq. 6-1)}$$

Eq. 6-1 includes the radius (r) as well as the height (h) of the capsules. Because the capsules are not completely round ellipsoids and have a flat bottom, the factor ½ was added to the equation to obtain the ellipsoid section. The volume of the liquid core (V_{core}) can be calculated similar to the volume of the capsule (Eq. 6-2). Only the radius and height have to be corrected due to the grown crystalline shell and the resulting decreased volume compared to the whole capsule.

$$V_{core} = \frac{4}{3} \cdot \pi (r - h_{shell})^2 \cdot (h - 2h_{shell}) \cdot \frac{1}{2} \qquad \text{(Eq. 6-2)}$$

$$V_{shell} = V_{capsule} - V_{core} \quad \text{(Eq. 6-3)}$$

Therefore, the radius has to be reduced by the layer thickness (h_{shell}) and the height has to be reduced by twice the layer thickness, because the crystalline layer can be found on top and bottom of the capsule. The radius is only affected on the outside of the capsule. After this, the volume of the crystalline shell (V_{shell}) can easily be calculated by subtracting the volume of the core from the volume of the whole capsule (Eq. 6-3). The results for the tested systems can be seen in Tab. 6.4-1.

Tab. 6.4-1: Volumes of the produced capsules.

	Xylitol capsule + ascorbic acid (4:1)	Pure xylitol capsule	Xylitol capsule + 0.5 wt% color + 0.5 wt% flavor	Xylitol capsule + 1 vol% ethanol + 1 wt% menthol
r [mm]	3.500	5.000	5.000	14.000
h [mm]	2.900	3.500	3.500	13.300
h_{shell} [mm]	0.412	0.530	0.525	1.133
$V_{capsule}$ [cm³]	0.074	0.183	0.183	5.460
V_{core} [cm³]	0.041	0.102	0.103	3.827
V_{shell} [cm³]	0.033	0.081	0.081	1.633
V_{shell}/V_{core} [-]	**0.795**	**0.795**	**0.783**	**0.427**

It can be seen that the volume of the capsules is increasing with increasing diameter, as expected. The volume of the liquid core and crystalline shell are increasing with increasing capsule's size as well. But the ratios between the volume of the shell and the volume of the liquid core (V_{shell}/V_{core}) show the opposite trend, they are decreasing with increasing diameter. That means that even if the absolute layer thickness of the crystalline shell is increasing with increasing capsule's size, the proportional amount of crystalline shell material is decreasing. In other words, the capsules with a bigger liquid core have a proportional thinner crystalline shell which results in a lower stability. This is exactly what could be observed for the produced capsules and what is shown in Fig. 6.4-2.

Besides the volume, the mass of the crystalline shell is proving that the stability is decreasing with increasing capsule's size. The mass of the shell material (m_{shell}) can be calculated with the following equation (Eq. 6-4).

$$m_{shell} = \frac{0.78 \cdot m_{capsule} \cdot \Delta\omega}{100\ \%} \qquad \text{(Eq. 6-4)}$$

The amount of xylitol that crystallizes as the capsule's shell ($\Delta\omega$) can be taken from the phase diagram of the systems (Fig. 5.1-1). By knowing the production conditions (78 wt%) and the storage temperature (25 °C), it can easily be read how much xylitol will be dissolved in the liquid core during storage. Thus, the difference between initial concentration and concentration in the liquid core at 25 °C is the amount of xylitol that crystallizes as shell. The factor 0.78 was added to get the amount of xylitol in the capsule, excluding the amount of water. Due to the different solubility of the systems at storage temperature, the xylitol mass in the crystalline shell varies. The results are shown in Tab. 6.4-2.

Tab. 6.4-2: Mass of the crystalline shell of the produced capsules.

	Xylitol capsule + ascorbic acid (4:1)	Pure xylitol capsule	Xylitol capsule + 0.5 wt% color + 0.5 wt% flavor	Xylitol capsule + 1 vol% ethanol + 1 wt% menthol
$m_{capsule}$ [g]	0.070	0.100	0.100	6.000
ω [wt%]	59.550	62.880	61.710	62.220
Δω [wt%]	18.450	15.120	16.290	15.780
m_{shell} [g]	**0.010**	**0.012**	**0.013**	**0.739**

It can be seen that the concentration in the liquid core, and thus the difference between initial and storage concentration, has no apparent relation with the size of the capsules. But looking at the calculated mass of the xylitol in the crystalline shell, it is clearly recognizable that the mass of the shell is increasing with increasing diameter and also with increasing layer thickness. That causes the increase of the crushing force which is plotted in Fig. 6.4-2.

Unfortunately, it is difficult to compare the stability of the investigated liquid filled capsules with other products because there are no products similar to the capsules produced by in situ encapsulation. Either the shells consist of a non-crystalline material or

the shape is different, which leads to incomparable results of the stability measurement. Nevertheless, the presented method is suitable to evaluate and compare the properties of the capsules with each other and it can be said that the lowest stability of about 1 N/cm² for the xylitol-menthol capsules is still high enough to ensure a safe handling and further processing.

6.4.2.3 Purity of the shell

The diffractograms of the crystalline shell of the produced capsules presented in Chap. 5.4.2.3 show only one peak at approximately the melting temperature of pure xylitol. If the capsule's shell would contain major impurities, another or even several other peaks close to the peaks of the pure components would appear. The absence of these peaks leads to the conclusion that the crystalline shells of the capsules are relatively pure, meaning they do not contain inclusions of the other used components.

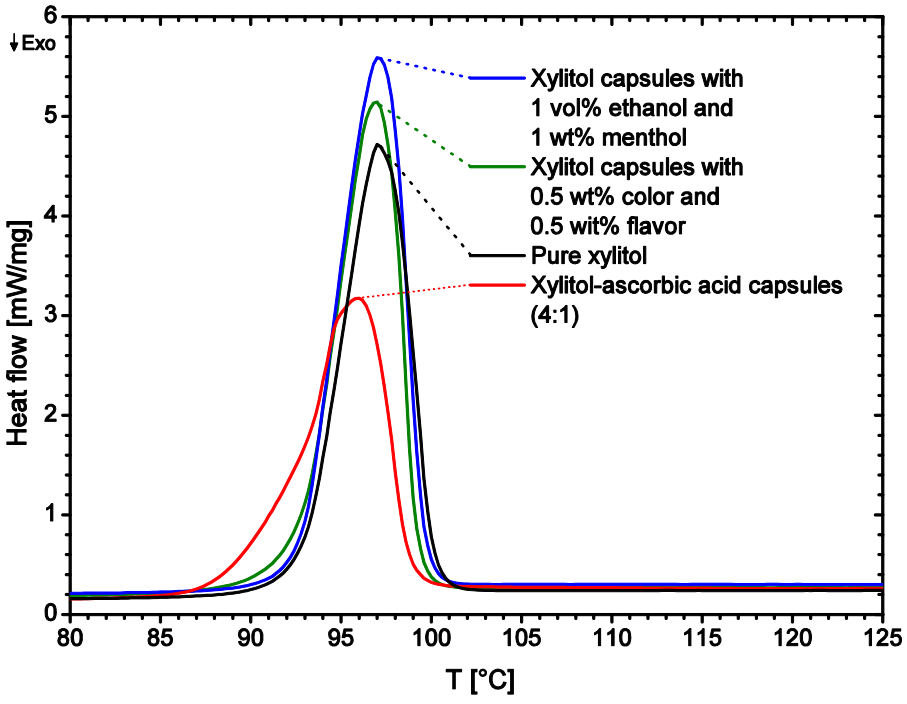


Fig. 6.4-3: DSC peaks of pure xylitol and the capsule's crystalline shell.

The onset temperature as well as the height and thus also the area of the peak can be used to estimate the purity of the investigated material. If the peak height and area are different and the onset temperature is lower, the substance includes impurities [Pla69]. The peaks of the capsule's shell material as well as pure xylitol are plotted for comparison in Fig. 6.4-3.

It can be seen that the peak of the shell of the xylitol-ascorbic acid capsules shows the biggest deviation from the pure xylitol peak, regarding peak height, area and onset temperature. To quantify these differences, Plato and Glasgow [Pla69] developed a method for the determination of the purity of organic compounds based on DSC data. It is based on the relation between the heat of fusion (H_f) and onset temperature (T_o) of the analyzed material and the difference between the onset temperature of the investigated sample and the pure material (ΔT) (Eq. 6-5).

$$Impurity\ [mol\%] = 100 \cdot \frac{H_f}{RT_o^2} \cdot \Delta T \qquad \text{(Eq. 6-5)}$$

The resulting impurities for the crystalline shell material of the produced capsules as well as the other parameters are shown in Tab. 6.4-3.

Tab. 6.4-3: Data and results for the calculation of the impurity of the capsule's shell.

	Pure xylitol	Xylitol capsule + 0.5 wt% color + 0.5 wt% flavor	Xylitol capsule + ascorbic acid (4:1)	Xylitol capsule + 1 vol% ethanol + 1 wt% menthol
T_o [K]	366.05	365.95	365.05	365.95
ΔT [K]	0.00	0.10	1.00	0.10
Peakarea [J/g]	247.20	254.20	205.80	278.70
H_f [J/mol]	37611.48	38676.53	31312.47	42404.21
Impurity [mol%]	0.00	0.35	2.81	0.38

It can be seen that the biggest temperature difference of 1 °C can be found for the xylitol-ascorbic acid capsules. The onset temperatures of the flavored and colored xylitol capsule as well as of the xylitol-menthol capsule only differ by 0.1 °C. This already indicates, that the ascorbic acid containing capsules have the most impurities. Including the peak area, meaning the heat of fusion, the impurity can be calculated and shows the same results. The xylitol-ascorbic acid capsules have the highest impurities in the shell of 2.81 mol%. The flavored and colored xylitol capsules and the xylitol-menthol capsules have clearly lower impurities of 0.35 and 0.38 mol%, respectively.

The reasons for the impurities can be found in the production conditions. For the crystallization of the xylitol-ascorbic acid capsules, an additional cooling step was necessary to get a stable product in a reasonable time. This cooling step to 8 °C (see Chap. 5.4-1) was needed due to the low crystal growth rate. Therefore, the capsules were forced to crystallize faster which led to more inclusions and thus to a higher impurity. The high viscosity of the system is additionally supporting the formation of inclusions due to slower diffusion processes in the liquid core of the capsules.

Compared to this system, the colored and flavored xylitol capsules and the xylitol-menthol capsules have both a higher crystal growth rate. That means no additional cooling step was necessary and thus less impurities were included in the crystalline shell. Furthermore, the viscosity is lower compared to the xylitol-ascorbic acid system which also reduces the inclusion of impurities.

Overall it can be said, that the impurities in the capsule's shell are relatively small. Two of the capsules have less than 1 mol% impurities in their crystalline shell. Even the highest impurities of 2.81 mol% do not affect the properties and quality of the product. That proves that the in situ encapsulation process is a suitable method for the encapsulation of liquids in a pure shell material, if the process parameters, including the crystallization speed and time, are controlled properly.

6.4.2.4 Storage stability

When the produced capsules reach their maximum layer thickness and stability, they are always in a state of thermodynamic equilibrium between liquid core and crystalline shell. Thus, the temperature and humidity during storage have a crucial influence on the storage stability.

As already mentioned in Chap. 5.4.2.4, several of the intended storage conditions could not be analyzed. Storing the capsules at a temperature of -10 °C lead to very instable products. In fact, the stability was not sufficient to handle the capsules during the analysis. This is caused by the strong subcooling of the capsules. When the products were stored at this low temperature, the liquid core of the capsules is again supersaturated and the containing xylitol will start to crystallize. This will lead to a growth of the capsule's shell, but it could also induce spontaneous nucleation in the liquid core. If nucleation occurs, the xylitol will randomly crystallize and these crystals would

attach to the crystalline shell. This results in a more loose connection of the crystals in the shell and thus in a low stability. Furthermore, the analysis itself was carried out at room temperature. That means, that the temperature of the capsules was increased to 25 °C before analysis. Even though the capsules were not stored at this temperature for a long time, it was enough time to heat them up again. This caused the xylitol crystals to dissolve again so that the already instable shell became even more instable. If no spontaneous nucleation took place, the crystalline shell would simply grow thicker which should result in a more stable product. But as already mentioned, the temperature increase before and during the analysis leads to the partly dissolution of the capsules and thus the decrease of stability.

The products stored at a high humidity of 60 and 80 % could not be analyzed because the capsules were completely liquid after the storage. Due to the conditions, independent of the temperature, the crystalline shell of the capsules easily dissolved in the atmospheric humidity so that only liquid drops could be found.

As can be seen in Figs. 5.4.6 to 5.4.9, the layer thickness of the crystalline shell of the capsules is not affected by temperature and humidity in a range of 10 to 40 °C and 10 to 40 %. This is caused by the temperature during the analysis, as already stated above. At low temperatures (10 °C), the shell of the capsules should grow thicker which should result in a higher stability. But due to the higher temperature during analysis (compared to storage temperature), the crystalline shell is partly dissolving which leads to a capsule with almost the same layer thickness compared to capsules stored at room temperature. As a result, the stability of the product is significantly decreased.

Basically the same phenomenon occurs with the capsules stored at 40 °C, just the other way around. During storage at high temperatures, the crystalline shell is partly dissolving so that the layer thickness is decreasing and more xylitol is dissolved in the liquid core. But during analysis at 25 °C, some of the xylitol in the core is crystallizing as the shell again. Due to the previous dissolution of some parts of the shell, the crystalline structure is different. This results in capsules with the lowest stability, even though the thickness of the crystalline shell remains the same for all the tested storage conditions.

6.5 Summary of the parameters and product properties

In general, the production conditions are determining the quality and properties of the products. It was found that the application of Parafilm as cover for the cooling surface was necessary to obtain nicely shaped drops. Due to the rough surface of Parafilm and the resulting lower contact angle, the shape of the capsules could be improved. Furthermore, the application of seed crystals is essential to get a uniform crystalline shell and a balanced ratio between top and bottom layer thickness, which results in a higher stability. Due to the thermodynamic equilibrium between liquid core and crystalline shell, all produced capsules are relatively sensitive to drastic changes of the storage conditions. This problem might be solved by using suitable packaging.

The **xylitol-ascorbic acid solution** contains 20 wt% ascorbic acid and shows the lowest solubility of all tested systems. The metastable zone is enlarged compared to a pure xylitol solution. These thermodynamic and kinetic effects and the high amount of ascorbic acid lead to the conclusion, that ascorbic acid acts rather as a third component than as an additive. The viscosity of the system is the highest measured viscosity and results in a significantly decreased crystal growth rate, compared to a pure xylitol solution.

The produced xylitol-ascorbic acid capsules are the smallest ones and have the roundest shape, compared to the other capsules produced by dropping the solution on a cooling surface. Due to their mass and surface tension, they keep the most hemispheric shape. The ratio between crystalline shell and liquid core is the highest which leads to the highest stability. Furthermore, it means that only a small volume of liquid can be encapsulated. The time until the capsules reach their maximum stability is the relatively long due to the high viscosity and low crystal growth rate. These two parameters as well as the production conditions are also the reason for the (compared to the other capsules) high impurities in the crystalline shell. Due to the additional cooling step, the crystalline shell is forced to grow faster than the other capsules. In combination with the high viscosity, this leads to more inclusions and thus more impurities.

The **colored and flavored xylitol solution** has almost the same solubility but a wider metastable zone width compared to a pure xylitol solution. Since no thermodynamic changes could be found, the added flavor and color act as additive. This is proven by the different kinetic effects. The viscosity of the system is the lowest one and would

lead to the assumption that the crystal growth is faster than the growth in a pure xylitol solution. But due to the determined growth rate, which is almost equal to the pure xylitol solution, an inhibition of the crystal growth was found.

The produced colored and flavored xylitol capsules are medium sized and not perfectly hemispherical shaped. Due to their low height, they have a shape of an ellipsoid. The layer thickness of the capsules is higher compared to the xylitol-ascorbic acid capsules. The ratio between crystalline shell and liquid core is lower which leads to a lower stability and shows that a bigger volume of liquid can be encapsulated. The crystallization time of the capsules is the fastest due to the highest crystal growth rate and the lowest viscosity. The viscosity and growth rate are also the reasons for the low amount of impurities that were determined by DSC.

The **xylitol solution containing 1 vol% ethanol and 1 wt% menthol** has almost the same solubility as a pure xylitol solution but a significantly wider metastable zone. Due to no apparent thermodynamic effects, these amounts of ethanol and menthol have to be seen as additives. But higher amounts of ethanol result in a lower solubility and thus, act as co-solvent. The viscosity is decreased by the addition of ethanol and menthol which leads to a decrease of the crystal growth rate.

The xylitol-menthol capsules are the only capsules that were produced by filling the solution into molds because no nicely shaped capsules could be achieved by dropping the solution on a flat surface. Therefore, it was possible to produce much bigger capsules and the application of molds makes it possible to vary in shape and size. The produced capsules have an almost perfectly hemispheric shape and the highest measured layer thickness. The low ratio between crystalline shell and liquid core explains the low stability and shows, that a big volume of liquid can be encapsulated. The capsules need more time to reach their maximum stability compared to the colored and flavored capsules. This is caused by the low crystal growth rate. But the purity of the crystalline shell benefits from the low viscosity and growth rate due to the formation of less inclusions.

6.6 General guideline for the application of in situ encapsulation

The investigation of the three application examples and the analysis of the mentioned process parameters and product properties help to derive a general guideline for the application of in situ encapsulation. The different criteria that need to be fulfilled are schematically shown in Fig. 6.6-1.

After the **definition of the product properties**, two different aspects of the production have to be considered. On the one hand, the used materials and solvents have to be investigated. On the other hand, the process and its parameters have to be defined and optimized.

The used shell and core **materials** should fulfill the requirements of the desired application, meaning that e.g. an edible product should consist of non-toxic materials. Furthermore, both substances have to be soluble in the same solvent, to ensure a homogeneous solution for the production of the capsules. Regarding the materials, three main points need to be analyzed.

The most important information for the production of the capsules can be obtained from the phase diagram. The solubility and metastable zone width of the used materials, including additives and solvents, have to be determined. It could be shown that already small amounts of different additives can change the properties of a solution significantly. The knowledge about the solubility is important to find the suitable temperatures for the preparation of the used solution. The metastable zone is of great importance because it determines the working area of the system. The crystallization can only be initiated within the metastable zone. Therefore, it is essential to know how far the solution can be cooled down before nucleation occurs. Thus, the operating range for the production is mainly restricted by the solubility and nucleation curve. The concentration of the solution is another important parameter that has to be adjusted. The concentration has to be chosen high enough to ensure the capsules to form a stable crystalline shell. But a too high concentration would result in a product with a very thick shell and thus, only a small volume of liquid. The optimal balance between the desired product properties and the quality of the product has to be found.

The second important parameter, which is mainly affecting the production time, is the crystal growth rate of the used materials. It is desirable to find a system with a high crystal growth rate to shorten the process time and thus the production costs.

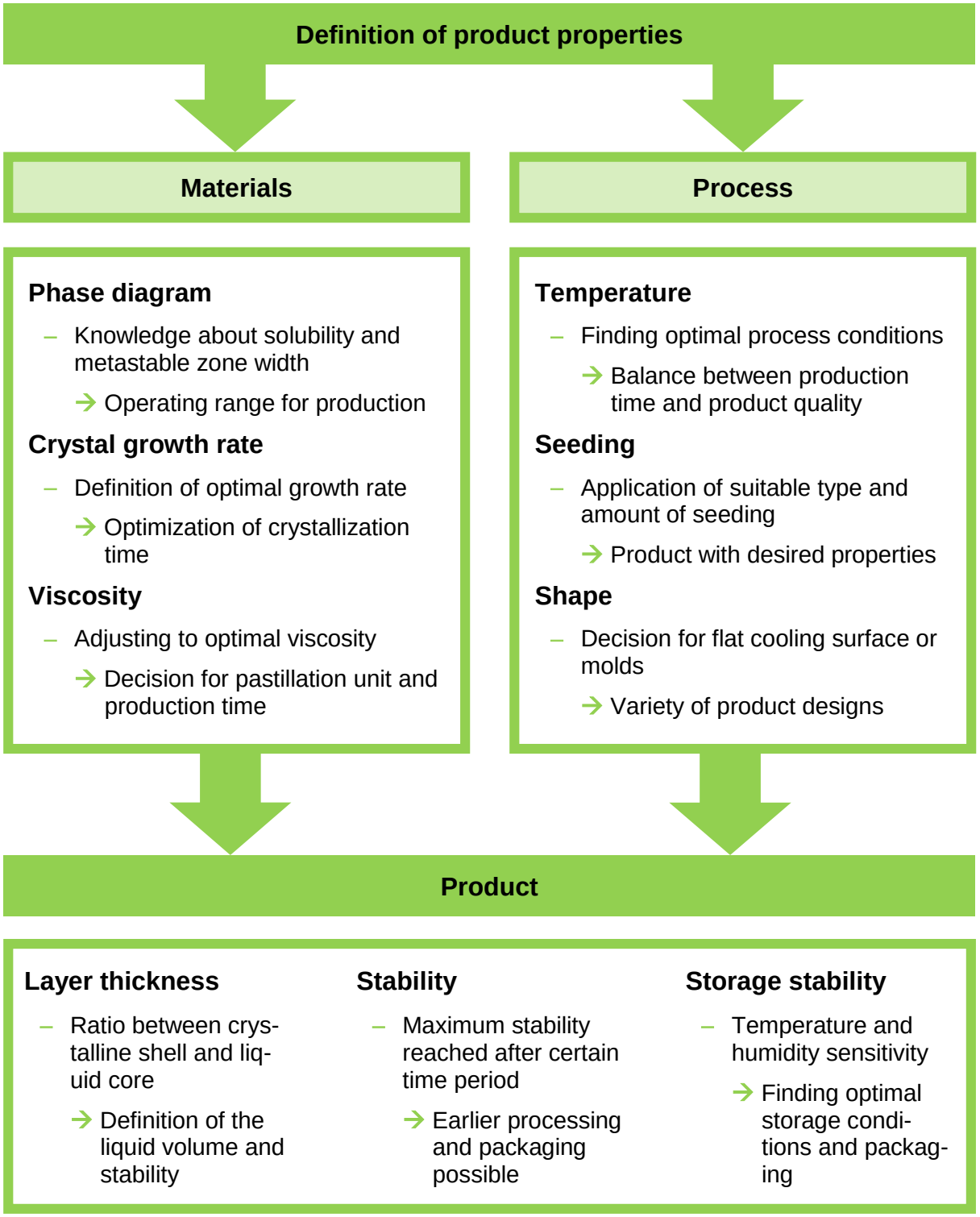


Fig. 6.6-1: Schematic guideline for the application of in situ encapsulation.

A high growth rate causes the liquid drops to crystallize faster. Furthermore, the capsules reach their equilibrium and the related maximum stability faster due to the faster degradation of the supersaturation in the liquid core. But high crystal growth rates will also result in relatively big crystal in the shell which will form a more instable shell compared to small slowly grown crystals. The optimal balance between the maximum stability of the capsules and the required production time has to be found.

Besides these two parameters, it could be shown that the viscosity has a big influence on the shape of the capsules, meaning that a higher viscosity leads to more roundly shaped products. But if the solution is highly viscous, the diffusion processes are slowed down. Therefore, the crystallization of the capsules takes more time and the production time and cost are increased. Besides the influence on the products, the viscosity decides which pastillation unit has to be used, because the different types of pastillation units with each different working ranges are defined by the viscosity of the used solution.

After considering the properties of the materials, the production **process** itself is defined by the three criteria shown in Fig. 6.6-1. Finding the optimal temperatures is essential to obtain products of high quality within a short manufacturing time. First, the temperature of the product vessel and thus of the used solution has to be optimized. The solution has to be saturated or even supersaturated, so that the crystallization will start immediately after the pastillation step. The temperature of the cooling surface has to be adjusted so that the capsules crystallize fast enough to enable further processing like packaging or storage. If the cooling surface is too cold, the crystalline shell would grow too fast which results in big crystals, a big difference between top and bottom of the crystalline layers and thus an instable product. As a last step, the capsules have to be stored under defined conditions. Due to the thermodynamic equilibrium between liquid core and crystalline shell, the capsules are relatively sensitive to large variation of temperature and humidity. But the sensitivity again is defined by the used materials.

The application of seeding during the pastillation process is essential to obtain products with a uniform shell. Furthermore, the seed crystals covering the cooling surface will initiate the crystallization of the capsules and thus, ensure the capsules to have the same starting point and crystallization time. The seeding applied on top of the liquid drops is necessary to achieve a balanced ratio between the layer thicknesses of the top and bottom of the crystalline shell. Thereby, products with a maximum stability can

be obtained. The application of seeding has to be optimized regarding the necessary amount of seed crystals and the actual material. For the tested application examples, the encapsulation material itself applied as seeding led to the best results.

The pastillation process is defining the shape of the capsules. By dropping the solution on flat cooling surfaces or a flat conveyer belt, the shape of the capsules will be more or less hemispheric. The roundness of the products is mainly affected by the viscosity of the solution, the size of the drops and the equilibrium between gravity and surface tension. But, especially for big capsules, the shape will be a little bit flatter than a hemisphere. If a hemispheric shape is desired or if the product should have a completely different shape, the used solution can easily be filled in pre-treated molds. That does not mean that these capsules cannot be produced continuously, the conveyer belt can include molds so that solution can be filled in the molds by the pastillation unit.

After adjusting and optimizing the system and process parameters, the resulting **products** have to be analyzed regarding their layer thickness, stability and storage stability. As already mentioned, the layer thickness of the crystalline shell has a big influence on the product's quality. On the one hand, the volume of the encapsulated liquid is depending on the layer thickness of the shell. If the crystalline shell is thicker, the liquid core is smaller. But a thicker shell will result in a higher stability. Therefore, these two aspects have to be balanced referring to the desired product properties. On the other hand, the ratio of top and bottom of the crystalline shell is important for the stability. If either top or bottom shell is thicker or thinner than the other, this will lead to a decreased stability, because the capsule will automatically have a weak point where they tend to break.

The already discussed stability is the best parameter to evaluate the capsule's quality. Of course, the product should have a stability as high as possible, but it is important to ensure that the other product properties do not suffer. A high stability can be reached by increasing the layer thickness of the capsules, but this could lead to a decreasing liquid core which might not be desirable. Furthermore, the time the capsules take to reach that stability is of great importance. If the crystallization time is too long, the capsules cannot be processed further. It is more meaningful to find the minimum stability that is necessary to handle and package the capsules. The thermodynamic equilibrium between core and shell can easily be reached later during storage and

transport. In this way, the products will have their maximum stability when they get to the customer.

Therefore, the storage stability and sensitivity to varying temperatures and humidity have to be known. An increase of the storage temperature would lead to a partially dissolution of the crystalline shell according to the phase diagram of the system due to the thermodynamic equilibrium. Decreasing the storage temperature would result in thicker crystalline shells or even a completely crystallized capsule. In both cases, the stability will be decreased significantly. The same case is for varying the humidity. A lower humidity would not affect the stability of the products. But very humid environmental conditions will cause the crystalline shell to dissolve in the atmospheric moisture. The robustness of the products against temperature and humidity changes depends strongly on the used materials and their phase diagram. A solubility curve with a flat slope would be ideal referring to the storage conditions. It means, that changes in the temperature would not affect the concentration significantly and the crystalline shell would remain almost the same. But the encapsulation process itself requires a steep slope, because the capsules are produced by cooling crystallization. The changes of the concentration during the cooling process defines the layer thickness and thus stability of the capsules. Due to these two contradictory requirements, a balance between stability of the capsules and sensitivity to temperature and humidity changes has to be found. A storage under constant conditions would be ideal, but probably not easy to realize. But the choice of a suitable packaging can overcome this issue.

If all the mentioned parameters are optimized and a balance between the desired product properties, the used materials and the process conditions can be found, a product of high quality can be produced. A detailed decision tree for finding the optimized production conditions can be seen in Fig. 6.6-2. In general, for the optimization and application of in situ encapsulation, the properties of the used materials including solvents and additives, have to be analyzed as a first step. With these results and the given starting conditions the first capsules can be produced. By evaluating these capsules and varying the process parameters, the optimum for the products and process can be found.

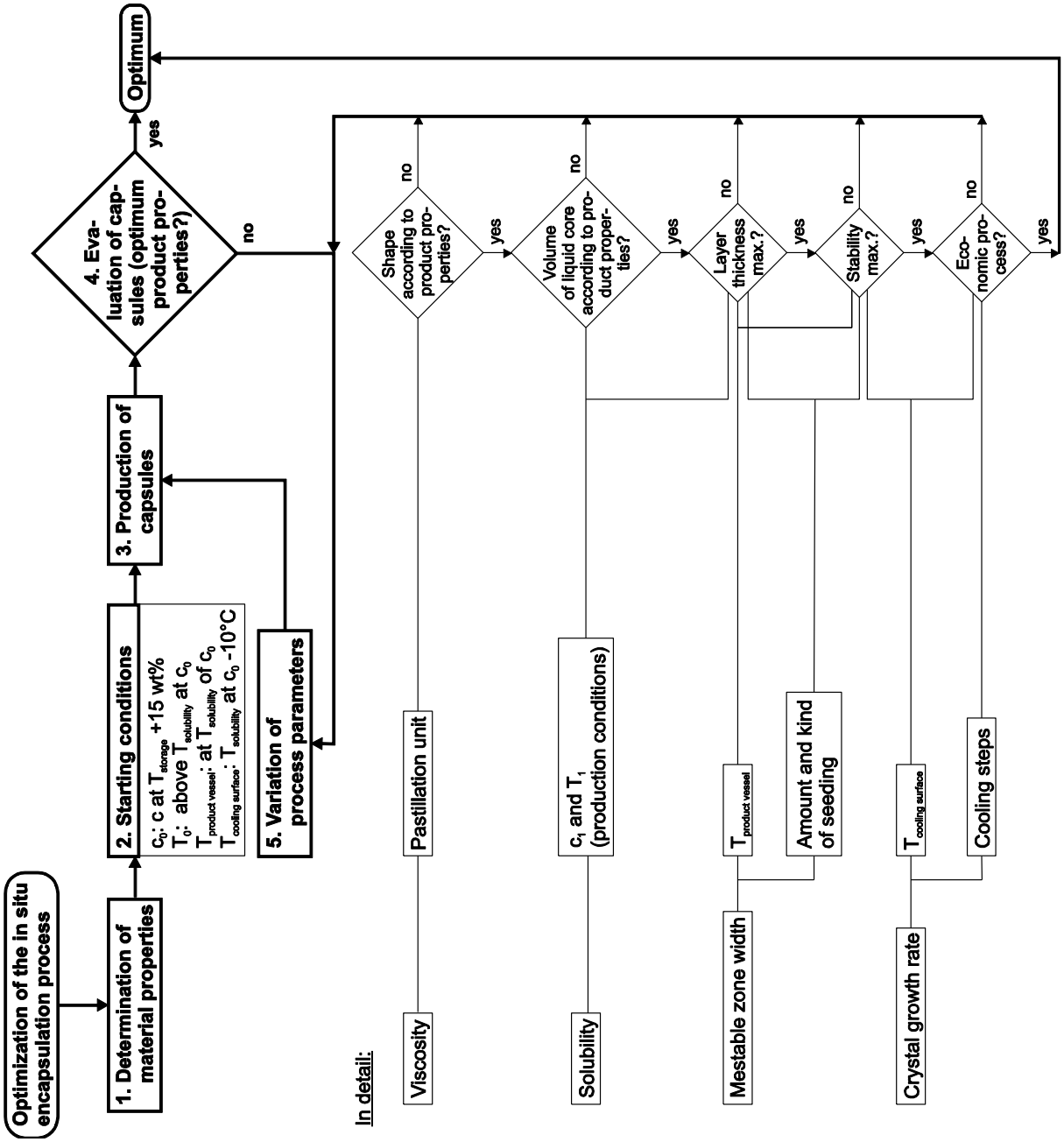


Fig. 6.6-2: Decision tree for the application of in situ encapsulation.

In detail, the viscosity is a critical factor for the decision for the suitable pastillation unit and thus for the shape of the products. If the desired shape and size cannot be obtained by changing the pastillation unit and dropping the solution onto a flat conveyer belt, the cooling surface has to be modified. It could be shown, that the encapsulation process can also be carried out by filling the solution into pre-treated molds.

The solubility of the used materials is a crucial parameter and has to be analyzed at the beginning. The solubility at the later storage temperature (often room temperature) can be used as starting point. The experiments have shown, that the concentration of the used solution should be at least 15 wt% higher than the equilibrium concentration at storage conditions. This way, the production concentration of the solution and also the temperature for the preparation of the solution, which is above the solubility temperature, can be found. The concentration is mainly affecting two product properties, the volume of the encapsulated liquid and the layer thickness of the crystalline shell. Both parameters have to be balanced referring to the desired product properties. If the wanted volume of liquid is achieved and the corresponding layer thickness is maximized, this aspect is optimized and will result in an ideal product. If these requirements are not fulfilled, the concentration has to be adjusted until the desired product properties are achieved.

Besides the solubility, the knowledge about the nucleation curve of the used materials gives important information about the process. Knowing the nucleation points, especially at the production concentration, reveals the metastable zone width which represents the working area of the process. These information are important because the solution has to be in a saturated or even supersaturated state during the production. Therefore, the temperature of the solution and thus of the product vessel can be found. Furthermore, the metastable zone determines the temperature range in which the seed crystals should be applied to initiate the crystallization of the capsules. Both process parameters are directly influencing the layer thickness and stability of the products. If the maximum stability of the capsules is reached, the optimal production condition were found. If the products are not stable enough, the temperature of the product vessel and the type and amount of seeding material have to be adjusted.

The third important property of the used materials is the crystal growth rate which is mainly affecting the temperature of the cooling surface and the number of cooling steps during the production. Thus, also the production time is affected by the crystal growth

rate. It is desirable to choose materials with a high crystal growth rate to keep the production time short and economic. For substances with a high crystal growth rate, the temperature of the cooling surface should not be too low, because as already mentioned, too fast growing crystals lead to instable capsules. As starting condition, it is recommended to set the cooling surface to a temperature about 10 °C below the temperature of the product vessel. After about 30 minutes, the temperature can be set to storage temperature so that the crystalline shell can grow and the maximum stability can be reached. If these conditions lead to an instable product, the temperature of the cooling surface as well as the number of cooling steps has to be varied until the maximum stability and thus the optimum conditions are found. The adjustment of the cooling steps should always happen with regard to the production time, to keep the process economic.

The in situ encapsulation of liquids can be applied to new substances if all the mentioned parameters are adjusted properly, referring to the decision tree shown in Fig. 6.6-2. By optimizing the product properties, like shape, volume of the encapsulated liquid, layer thickness of the crystalline shell and stability, a product of reproducible quality can be obtained in an effective and economic way.

7. Outlook

The feasibility of the in situ encapsulation process was shown by three case studies of liquid-filled xylitol capsules and a general guideline as well as a detailed decision tree for the application of such a process was derived. Due to the similarity of the three tested systems, it would be of great interest to gather more data by using other substances. The production of liquid-filled capsules consisting of other materials and having another shape would confirm the feasibility of the developed decision tree and the whole encapsulation process itself.

Furthermore, the shown experiments were carried out in lab scale and discontinuously. The next step for the scaled up application of in situ encapsulation is the production of liquid-filled capsules in industrial scale. The continuous production of the capsules will show if the determined parameters can be applied in a larger scale too and if the general guideline and decision tree are still applicable in their present forms.

Closely connected to the up-scaling of the production is the development of a suitable packaging technique. The packaging has to match the product properties as well as the intended purpose. For example, a pharmaceutically applied capsule could be packed in blister packaging whereas a potential candy could be packed in bags or boxes. Furthermore, the packaging of the capsules could already happen before the products reach their maximum stability. Therefore, the production time can be shortened and the products will have reached their maximum stability and final properties, when they arrive at the customer’s place. The application of suitable packaging can also help to overcome the sensitivity of the used materials against temperature and especially moisture.

8. Summary

The encapsulation of liquids is a common approach for sensitive materials, like volatile liquids or active pharmaceutical ingredients and improves the quality of diverse products. The established encapsulation techniques involve limited particle sizes, a big loss of material and thus high processing costs. The in situ encapsulation represents, due to its few process steps, an effective, low energy consuming and economic alternative. It combines the well-known techniques of pastillation and crystallization to a new encapsulation process which results in crystalline products with a liquid core.

Before the in situ encapsulation can be applied to a system, the used materials have to be analyzed regarding their thermodynamic and kinetic properties. Three xylitol containing solutions were chosen to demonstrate the proof of concept and the effects of the different components in the solutions.

The colored and flavored xylitol solution can be used to produce liquid-filled candies. It could be shown that the addition of each 1 wt% color and flavor do not cause a significant change of the solubility and nucleation, compared to a pure xylitol solution. Thus, the metastable zone width is not affected too. The viscosity is decreased whereas the crystal growth rate is not changed. This leads to the conclusion that the crystal growth and nucleation is inhibited. The superposition with the decreased viscosity leads to no visible changes of the growth rate. These kinetic effects show that the added color and flavor have to be seen as additives.

The xylitol-ascorbic acid solution can be used to produce small capsules which can be applied as vitamin C supplement. It could be shown that the addition of 20 wt% ascorbic acid is lowering the solubility and increasing the metastable zone width of xylitol. The crystal growth rate is decreased as well, which can be explained by the increased viscosity. Due to these thermodynamic effects, ascorbic acid acts as a third component in this solution.

The xylitol solution containing ethanol and menthol can be used to produce big capsules representing pre-dosed mouthwash. The solubility of xylitol is not changed by adding 1 vol% ethanol and 1 wt% menthol, compared to a pure xylitol solution. The investigation of different ethanol amounts has shown that this thermodynamic effect is

caused by the added ethanol. Menthol itself does not influence the solubility. The addition of ethanol is also widening the metastable zone, whereby a maximum could be found for the addition of 1 vol% ethanol. The decreased viscosity is superimposing with the inhibited crystal growth rate, which leads to an overall decreased growth rate and different metastable zone widths. Furthermore, it could be shown that the added menthol as well as ethanol in different concentrations are lowering the crystal growth rate. Therefore, it can be said that menthol and up to 3 vol% ethanol act as additives. Higher ethanol contents have to be seen as co-solvent.

Based on these properties, the optimal production conditions could be found. Due to the similar properties of the solutions, the optimal process parameters are very similar as well. In general, the cooling surface should be very rough for an optimal shape of the capsules. The application of seed crystals was found to be essential to achieve a stable product with a uniform crystalline shell. The xylitol-menthol capsules were produced by filling the liquid into molds because the viscosity was to low and the size too big to obtain nicely shaped products by dropping the solution onto a flat surface. They also had to be turned into a starch bed to achieve an optimal capsule. The xylitol-ascorbic acid capsules had to run through a third cooling step to accelerate the crystallization and shorten the process time.

The produced capsules were evaluated regarding their stability, purity and layer thickness of the crystalline shell. It could be shown that the ratio between crystalline shell and liquid core is important for the stability. The higher this ratio, the more stable the capsules. The crystalline shell was found to be relatively pure, depending on the crystallization speed. The shell of faster crystallizing capsules include more impurities than the shell of slower grown ones. The storage stability of the products is still an issue. Due to the thermodynamic equilibrium between liquid core and crystalline shell, the capsules are relatively sensitive to temperature and humidity changes. A suitable packaging could help to overcome this issue. This should be embedded in the up-scaled manufacturing process, which should be developed and optimized in the future.

Concluding can be said that the **proof of concept** was given by showing the feasibility of the in situ encapsulation process for three different examples. The analysis of the used materials and produced capsules led to a **general guideline** for the application of in situ encapsulation. If the **detailed decision tree** is applied to a new system, this process can be optimized and results in nicely shaped and stable products. It could be

shown, that the in situ encapsulation process is an effective and economic process for the encapsulation of liquids due to the only few process steps. It represents a good alternative to already established encapsulation techniques and allows the manufacturing of various products.

9. Zusammenfassung

Die Verkapselung von Flüssigkeiten ist ein gängiges Verfahren für die Verarbeitung empfindlicher Materialien, wie leicht-flüchtige Flüssigkeiten oder Pharmawirkstoffe, und verbessert die Qualität der diversen Produkte. Die bereits etablierten Verkapselungsverfahren schließen limitierte Partikelgrößen, hohe Materialverluste und dadurch hohe Prozesskosten ein. Das in situ Verkapselungsverfahren stellt aufgrund der wenigen Prozessschritte eine effektive, kostengünstige und ökonomische Alternative dar. Es kombiniert die bekannten Techniken Pastillierung und Kristallisation zu einem neuen Verkapselungsprozess, welcher in kristalliner Produkten mit flüssigem Kern resultiert.

Vor der Anwendung der in situ Verkapselung auf ein System, müssen die verwendeten Substanzen hinsichtlich ihrer kinetischen und thermodynamischen Eigenschaften untersucht werden. Der Proof of Concept und der Einfluss verschiedener Inhaltsstoffe auf Lösungen wurden anhand von drei Xylitol-Lösungen gezeigt.

Die gefärbte und aromatisierte Xylitol-Lösung kann zur Produktion von flüssig gefüllten Süßigkeiten verwendet werden. Es wurde gezeigt, dass der Zusatz von jeweils 1 wt% Farbe und Aroma die Löslichkeit und Keimbildung, im Vergleich zu einer reinen Xylitol-Lösung, nicht signifikant verändert. Folglich bleibt auch der metastabile Bereich unverändert. Die Viskosität ist gesunken wohingegen sich die Kristallwachstumsgeschwindigkeit nicht ändert. Das führt zu dem Schluss, dass das Kristallwachstum und die Keimbildung gehemmt sind. Jedoch führt die Überlagerung mit der verringerten Viskosität zu keinen sichtbaren Veränderungen der Wachstumsgeschwindigkeit. Diese kinetischen Effekte zeigen, dass die verwendeten Farb- und Aromastoffe als Additive betrachtet werden müssen.

Eine Xylitol-Ascorbinsäure-Lösung kann zur Produktion von kleinen Vitamin C-Kapseln als Nahrungsergänzungsmittel verwendet werden. Es wurde gezeigt, dass die Zugabe von 20 wt% Ascorbinsäure die Löslichkeit von Xylitol verringert und den metastabilen Bereich vergrößert. Die Kristallwachstumsgeschwindigkeit ist ebenfalls herabgesetzt, was durch die erhöhte Viskosität erklärt werden kann. Aufgrund dieser kinetischen und thermodynamischen Effekte, verhält sich Ascorbinsäure wie eine dritte Komponente in der Lösung.

Die Xylitol-Lösung mit Ethanol und Menthol kann zur Produktion von großen Kapseln verwendet werden, welche vordosiertes Mundwasser darstellen. Die Löslichkeit von Xylitol wird, im Vergleich zu einer reinen Xylitol-Lösung, durch die Zugabe von 1 vol% Ethanol und 1 wt% Menthol nicht verändert. Die Untersuchung verschiedener Ethanolgehalte hat gezeigt, dass dieser thermodynamische Effekt durch das Ethanol verursacht wird. Menthol selbst hat keinen Einfluss auf die Löslichkeit. Die Zugabe von Ethanol vergrößert den metastabilen Bereich, wobei ein Maximum für die Zugabe von 1 vol% Ethanol gefunden wurde. Die verringerte Viskosität überlagert sich mit der gehemmten Kristallwachstumsgeschwindigkeit, was zu insgesamt verringerten Wachstumsraten und verschieden breiten metastabilen Bereichen führt. Weiterhin wurde gezeigt, dass sowohl Menthol als auch Ethanol die Wachstumsgeschwindigkeit verringern. Daraus folgt, dass Menthol und bis zu 3 vol% Ethanol als Additiv fungieren. Höhere Ethanolgehalte wirken als Co-Solvent.

Basierend auf diesen Eigenschaften konnten die optimalen Produktionsbedingungen gefunden werden. Aufgrund der ähnlichen Eigenschaften der Lösungen sind auch die optimalen Prozessparameter sehr ähnlich. Allgemein sollte die Kühlfläche sehr rau gestaltet sein, damit optimale Kapselformen erreichen werden können. Weiterhin wurde gezeigt, dass die Verwendung von Saatkristallen für die Herstellung stabiler Produkte mit einer gleichmäßigen Hülle unerlässlich ist. Die Xylitol-Menthol-Kapseln wurden durch das Füllen der Lösung in Formen produziert, da die Viskosität zu gering und die Kapseln zu groß waren, um eine schöne Form durch das Tropfen auf eine ebene Oberfläche zu erreichen. Sie mussten auch in ein Stärkebett gewendet werden, um optimale Produkteigenschaften zu erzielen. Die Xylitol-Ascorbinsäure-Kapseln mussten einen zusätzlichen Kühlschritt durchlaufen, um die Kristallisation zu beschleunigen und somit die Prozesszeit zu verringern.

Alle produzierten Kapseln wurden hinsichtlich ihrer Stabilität, Reinheit und Schichtdicke der kristallinen Hülle bewertet. Es konnte gezeigt werden, dass das Verhältnis zwischen fester Hülle und flüssigem Kern wichtig für die Stabilität ist. Je größer dieses Verhältnis, desto stabiler die Kapseln. Es wurde herausgefunden, dass die Kristallhülle relativ rein ist, was stark von der Kristallisationsgeschwindigkeit abhängt. Die Hülle schnell kristallisierter Kapseln ist unreiner als langsam gewachsene Kristallschichten. Die Lagerstabilität der Produkte ist immer noch ein Problem. Aufgrund des thermodynamischen Gleichgewichts zwischen flüssigem Kern und kristalliner Hülle, sind die

Kapseln relativ empfindlich gegenüber Temperatur- und Luftfeuchtigkeitsänderungen. Entsprechende Verpackungen können helfen, dieses Problem zu überwinden. Das sollte Teil des industriellen Herstellungsprozesses sein, welcher in Zukunft entwickelt und optimiert werden sollte.

Abschließend lässt sich sagen, dass der **Proof of Concept** und die Anwendbarkeit des in situ Verkapselungsverfahrens anhand von drei verschiedenen Beispielen gezeigt werden konnte. Die Untersuchung der verwendeten Materialien und produzierten Kapseln führte zu einer **allgemeinen Handlungsvorschrift** für die Anwendung dieses Verfahrens. Wird der **detaillierte Entscheidungsbaum** auf ein neues System angewendet, kann damit dieser Prozess optimiert werden und führt zu wohlgeformten und stabilen Produkten. Es konnte gezeigt werden, dass das in situ Verkapselungsverfahren ein effektiver und wirtschaftlicher Prozess zur Verkapselung von Flüssigkeiten ist. Es repräsentiert eine gute Alternative zu bereits etablierten Verkapselungsprozessen und ermöglicht die Herstellung von vielfältigen Produkten.

10. Abbreviations and symbols

10.1 Abbreviations

FAO	Food and Agriculture Organization
Chap.	Chapter
DSC	Differential scanning calorimetry
Eq.	Equation
Fig.	Figure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MSZW	Metastable zone width
SD	Standard deviation
Tab.	Table
WHO	World Health Organization

10.2 Symbols

c	[g/L]	Concentration
d	[mm]	Diameter of the capsules
F_{cr}	[N]	Crushing force
G	[m/s]	Crystal growth rate
g	[m/s²]	Gravitational acceleration (9.81 m/s²]
h	[mm]	Height of the capsules
H_f	[J/mol]	Molar heat of fusion
h_{shell}	[mm]	Layer thickness of the capsule's shell
L_1	[m]	Crystal size (arithmetic mean)

m_1	[g]	Crystal mass before growth
m_2	[g]	Crystal mass after growth
$m_{capsule}$	[g]	Mass of the capsules
m_{max}	[g]	Maximum registered mass until capsules break
m_{shell}	[g]	Mass of the crystalline xylitol shell of the capsules
p_{st}	[N/cm²]	Stability of the capsules
R	[J/molK]	Universal gas constant (8.314 J/molK)
r	[mm]	Radius of the capsules
T	[°C]	Temperature
t	[s]	Time
T_o	[K]	Onset temperature
$V_{capsule}$	[cm³]	Volume of the capsules
V_{core}	[cm³]	Volume of the liquid core of the capsules
V_{shell}	[cm³]	Volume of the crystalline shell of the capsules
ΔT	[°C], [K]	Temperature difference
Δω	[wt%]	Solubility difference read from the phase diagram
η	[mPas]	Dynamic viscosity
π	[-]	Mathematical constant (3.14159)
ω	[wt%]	Mass fraction

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12. Appendix

Tab. 12-1: Solubility data for the three tested systems (Fig. 5.1-1).

ω [wt%]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	T [°C]	SD [°C]	T [°C]	SD [°C]	Xylitol	T [°C]	SD [°C]	T [°C]
60.00	20.31	0.51	22.20	0.38	25.50	0.46	21.41	0.47
66.67	31.48	0.63	33.09	0.47	34.10	0.71	32.22	0.63
71.43	38.30	0.33	40.13	0.59	40.70	0.38	39.39	0.39
75.00	43.52	0.57	45.20	0.39	46.91	0.53	44.71	0.50
77.78	48.77	0.31	50.37	0.71	52.37	0.33	49.72	0.47
80.00	52.40	0.45	54.05	0.46	58.20	0.62	52.90	0.67
81.81	55.24	0.29	56.95	0.55	67.03	0.49	55.85	0.42

Tab. 12-2: Nucleation data for the three tested systems (Fig. 5.1-1).

ω [wt%]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	T [°C]	SD [°C]	T [°C]	SD [°C]	T [°C]	SD [°C]	T [°C]	SD [°C]
60.00	13.43	0.46	15.03	0.39	15.98	0.63	10.86	0.47
66.67	23.82	0.59	25.38	0.62	25.30	0.53	21.30	0.39
71.43	32.08	0.31	33.61	0.37	33.10	0.47	29.87	0.62
75.00	37.14	0.47	38.78	0.48	38.76	0.39	35.20	0.54
77.78	43.39	0.46	45.04	0.54	44.47	0.45	40.10	0.31
80.00	48.64	0.54	49.99	0.39	50.35	0.56	45.19	0.49
81.81	52.14	0.41	52.68	0.41	58.66	0.49	49.93	0.53

Tab. 12-3: Solubility data for different ethanol contents (Fig. 5.1-2).

ω [wt%]	Pure xylitol		Xylitol + 1 vol% ethanol		Xylitol + 3 vol% ethanol		Xylitol + 5 vol% ethanol	
	T [°C]	SD [°C]	T [°C]	SD [°C]	T [°C]	SD [°C]	T [°C]	SD [°C]
60.00	20.31	0.47	21.41	0.31	22.39	0.59	24.19	0.48
66.67	31.48	0.39	32.22	0.49	32.78	0.31	34.53	0.54
71.43	38.30	0.45	39.39	0.53	40.15	0.47	41.37	0.39
75.00	43.52	0.56	44.71	0.47	44.95	0.46	47.28	0.41
77.78	48.77	0.49	49.72	0.39	50.24	0.54	52.64	0.39
80.00	52.40	0.63	52.90	0.62	53.33	0.41	55.78	0.62
81.81	55.24	0.53	55.85	0.54	56.71	0.46	58.40	0.37

Tab. 12-4: Nucleation data for different ethanol contents (Fig. 5.1-2).

ω [wt%]	Pure xylitol		Xylitol + 1 vol% ethanol		Xylitol + 3 vol% ethanol		Xylitol + 5 vol% ethanol	
	T [°C]	SD [°C]	T [°C]	SD [°C]	T [°C]	SD [°C]	T [°C]	SD [°C]
60.00	13.43	0.39	10.86	0.47	12.06	0.45	15.91	0.39
66.67	23.82	0.50	21.30	0.46	22.20	0.56	24.88	0.62
71.43	32.08	0.47	29.87	0.54	30.62	0.49	32.76	0.37
75.00	37.14	0.67	35.20	0.41	36.08	0.63	39.58	0.48
77.78	43.39	0.42	40.10	0.46	41.62	0.53	44.46	0.54
80.00	48.64	0.47	45.19	0.59	47.05	0.47	50.61	0.39
81.81	52.14	0.63	49.93	0.31	50.66	0.39	53.32	0.41

Tab. 12-5: Temporal decrease of crystal growth rate in a pure xylitol solution at 1 K supersaturation (Fig. 5.2-1).

t [min]	G [m/s]	SD [m/s]
5	$2.30 \cdot 10^{-7}$	$9.00 \cdot 10^{-9}$
10	$1.36 \cdot 10^{-7}$	$1.10 \cdot 10^{-8}$
15	$8.45 \cdot 10^{-8}$	$7.00 \cdot 10^{-9}$
20	$5.64 \cdot 10^{-8}$	$1.34 \cdot 10^{-8}$
30	$4.54 \cdot 10^{-8}$	$7.50 \cdot 10^{-9}$
50	$4.33 \cdot 10^{-8}$	$6.00 \cdot 10^{-9}$

Tab. 12-6: Crystal growth rates of the systems depending on the supersaturation (Fig. 5.2-2).

ΔT [°C]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	G [m/s]	SD [m/s]	G [m/s]	SD [m/s]	G [m/s]	SD [m/s]	G [m/s]	SD [m/s]
1	$1.95 \cdot 10^{-7}$	$7.72 \cdot 10^{-9}$	$1.92 \cdot 10^{-7}$	$3.85 \cdot 10^{-9}$	$1.15 \cdot 10^{-7}$	$4.30 \cdot 10^{-9}$	$1.73 \cdot 10^{-7}$	$4.85 \cdot 10^{-9}$
3	$2.57 \cdot 10^{-7}$	$3.85 \cdot 10^{-9}$	$2.50 \cdot 10^{-7}$	$7.72 \cdot 10^{-9}$	$1.63 \cdot 10^{-7}$	$7.72 \cdot 10^{-9}$	$2.34 \cdot 10^{-7}$	$5.72 \cdot 10^{-9}$
5	$2.91 \cdot 10^{-7}$	$4.30 \cdot 10^{-9}$	$2.89 \cdot 10^{-7}$	$4.30 \cdot 10^{-9}$	$1.75 \cdot 10^{-7}$	$4.85 \cdot 10^{-9}$	$2.69 \cdot 10^{-7}$	$4.30 \cdot 10^{-9}$

Tab. 12-7: Crystal growth rates of xylitol depending on the ethanol content (Fig. 5.2-3).

ΔT [°C]	Pure xylitol		Xylitol + 1 vol% ethanol		Xylitol + 3 vol% ethanol		Xylitol + 5 vol% ethanol	
	G [m/s]	SD [m/s]	G [m/s]	SD [m/s]	G [m/s]	SD [m/s]	G [m/s]	SD [m/s]
1	$1.95 \cdot 10^{-7}$	$7.72 \cdot 10^{-9}$	$1.88 \cdot 10^{-7}$	$4.85 \cdot 10^{-9}$	$1.78 \cdot 10^{-7}$	$5.30 \cdot 10^{-9}$	$1.69 \cdot 10^{-7}$	$3.05 \cdot 10^{-9}$
3	$2.57 \cdot 10^{-7}$	$3.85 \cdot 10^{-9}$	$2.49 \cdot 10^{-7}$	$5.72 \cdot 10^{-9}$	$2.42 \cdot 10^{-7}$	$3.95 \cdot 10^{-9}$	$2.32 \cdot 10^{-7}$	$5.10 \cdot 10^{-9}$
5	$2.91 \cdot 10^{-7}$	$4.30 \cdot 10^{-9}$	$2.84 \cdot 10^{-7}$	$4.30 \cdot 10^{-9}$	$2.65 \cdot 10^{-7}$	$5.15 \cdot 10^{-9}$	$2.49 \cdot 10^{-7}$	$8.00 \cdot 10^{-9}$

Tab. 12-8: Viscosities of the systems at 60 °C depending on the concentration (Fig. 5.3-1).

ω [wt%]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	η [mPas]	SD [mPas]	η [mPas]	SD [mPas]	η [mPas]	SD [mPas]	η [mPas]	SD [mPas]
71.43	15.10	0.85	14.72	0.56	15.25	0.92	14.64	0.34
75.00	21.86	0.40	21.32	0.66	23.36	0.36	21.94	0.48
77.78	31.11	0.99	29.10	0.66	32.67	0.37	30.14	0.50
80.00	43.82	0.47	39.87	0.33	47.25	0.30	42.83	0.23
81.81	58.14	0.38	54.00	0.32	63.05	0.29	54.84	0.31

Tab. 12-9 Viscosities of the systems with 78 wt% depending on the temperature (Fig. 5.3-2).

T [°C]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	η [mPas]	SD [mPas]	η [mPas]	SD [mPas]	η [mPas]	SD [mPas]	η [mPas]	SD [mPas]
40.00	100.18	0.23	90.31	0.27	102.82	0.57	95.43	0.27
45.00	74.08	0.29	68.92	0.24	75.61	0.35	70.34	0.24
50.00	56.12	0.30	51.65	0.21	56.95	0.20	53.19	0.21
55.00	42.03	0.33	40.32	0.21	44.03	0.20	41.01	0.21
60.00	33.33	0.32	30.88	0.26	34.96	0.21	32.54	0.26

Tab. 12-10: Progress of the stability (p_{st}) of the three different capsules (Fig. 5.4-1).

t [h]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	p_{st} [N/cm²]	SD [N/cm²]	p_{st} [N/cm²]	SD [N/cm²]	p_{st} [N/cm²]	SD [N/cm²]	p_{st} [N/cm²]	SD [N/cm²]
1.0	0.887	0.116	0.739	0.184	-	-	-	-
1.5	0.992	0.110	0.785	0.167	-	-	-	-
2.0	1.052	0.131	0.838	0.181	-	-	-	-
2.5	1.048	0.125	0.957	0.098	-	-	-	-
3.0	1.119	0.124	0.940	0.119	-	-	-	-
3.5	1.164	0.133	1.076	0.187	-	-	-	-
4.0	1.164	0.107	1.038	0.228	-	-	-	-
4.5	1.218	0.143	1.068	0.340	-	-	-	-
5.0	1.193	0.160	1.110	0.082	1.090	0.116	-	-
5.5	1.224	0.140	1.088	0.159	1.140	0.110	0.900	0.116
6.0	1.166	0.130	-	-	1.150	0.131	0.920	0.110
24.0	1.237	0.131	1.125	0.187	1.600	0.130	0.978	0.131
48.0	1.200	0.110	1.134	0.228	1.600	0.110	1.002	0.125

Tab. 12-11: Progress of the layer thickness (h_{shell}) of the three different capsules (Fig. 5.4-2).

t [h]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	h_{shell} [mm]	SD [mm]	h_{shell} [mm]	SD [mm]	h_{shell} [mm]	SD [mm]	h_{shell} [mm]	SD [mm]
1.0	0.484	0.055	0.445	0.060	-	-	-	-
1.5	0.501	0.065	0.475	0.068	-	-	-	-
2.0	0.510	0.063	0.485	0.072	-	-	-	-
2.5	0.510	0.065	0.480	0.070	-	-	-	-
3.0	0.516	0.063	0.495	0.065	-	-	-	-
3.5	0.536	0.060	0.515	0.068	-	-	0.805	0.116
4.0	0.532	0.068	0.510	0.068	0.200	0.122	0.890	0.052
4.5	0.545	0.072	0.525	0.072	0.230	0.066	0.920	0.145
5.0	0.549	0.070	0.520	0.063	0.220	0.110	0.891	0.122
5.5	0.526	0.065	0.525	0.065	0.262	0.136	0.933	0.066
6.0	0.548	0.068	0.505	0.063	0.263	0.116	1.021	0.110
24.0	0.530	0.068	0.525	0.060	0.412	0.052	1.133	0.136
48.0	0.556	0.068	0.515	0.065	0.402	0.110	1.103	0.066

Tab. 12-12: Stability (p_{st}) and layer thickness (h_{shell}) of pure xylitol capsules depending on different storage conditions (Fig. 5.4-6).

T [°C]	10 % humidity				40 % humidity			
	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]
10	0.621	0.145	0.561	0.057	0.682	0.112	0.502	0.053
25	1.163	0.082	0.528	0.051	1.157	0.081	0.514	0.041
40	0.190	0.044	0.505	0.060	0.189	0.043	0.462	0.052

Tab. 12-13: Stability (p_{st}) and layer thickness (h_{shell}) of flavored and colored xylitol capsules depending on different storage conditions (Fig. 5.4-7).

T [°C]	10 % humidity				40 % humidity			
	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]
10	0.580	0.090	0.558	0.061	0.563	0.080	0.561	0.052
25	1.145	0.080	0.547	0.051	1.125	0.087	0.525	0.060
40	0.231	0.037	0.503	0.055	0.216	0.041	0.497	0.046

Tab. 12-14: Stability (p_{st}) and layer thickness (h_{shell}) of xylitol-menthol capsules depending on different storage conditions (Fig. 5.4-8).

T [°C]	10 % humidity				40 % humidity			
	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]
10	0.516	0.093	1.166	0.110	0.509	0.081	1.154	0.136
25	0.989	0.127	1.163	0.111	0.978	0.131	1.133	0.134
40	0.350	0.037	1.053	0.055	0.289	0.041	1.021	0.046

Tab. 12-15: Stability (p_{st}) and layer thickness (h_{shell}) of xylitol-ascorbic acid capsules depending on different storage conditions (Fig. 5.4-9).

T [°C]	10 % humidity				40 % humidity			
	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]	p_{st} [N/cm²]	SD [N/cm²]	h_{shell} [mm]	SD [mm]
10	0.887	0.096	0.466	0.110	0.896	0.140	0.422	0.136
25	1.615	0.127	0.446	0.039	1.603	0.129	0.412	0.052
40	0.403	0.070	0.423	0.055	0.389	0.094	0.341	0.046

Tab. 12-16: Solubility data for gravimetric and ultrasound measurement of a pure xylitol solution (Fig. 6.1-1).

T [°C]	Gravimetric analysis		Ultrasound measurement	
	ω [wt%]	SD [wt%]	ω [wt%]	SD [wt%]
20.00	61.50	0.36	-	-
23.74	-	-	64.50	0.56
30.00	67.10	0.42	-	-
33.96	-	-	70.87	0.97
39.12	-	-	73.00	0.68
40.00	74.30	0.48	-	-
42.74	-	-	74.40	0.93
50.00	80.40	0.39	-	-
51.74	-	-	79.60	0.79

Tab. 12-17: Comparison of layer thickness (h_{shell}), crushing force (F_{cr}) and stability (p_{st}) of the capsules (Fig. 6.4-2).

T [°C]	Pure xylitol		Xylitol + 0.5 wt% flavor + 0.5 wt% color		Xylitol + ascorbic acid (4:1)		Xylitol + 1 vol% ethanol + 1 wt% menthol	
	Data	SD	Data	SD	Data	SD	Data	SD
h_{shell} [mm]	0.556	0.068	0.515	0.065	0.402	0.110	1.103	0.066
F_{cr} [N]	0.971	0.131	0.953	0.187	0.683	0.390	6.067	0.387
p_{st} [N/cm²]	1.237	0.125	1.125	0.189	1.601	0.130	1.002	0.131

13. Statement of authorship

I declare under oath that this is my own work entirely and has been written without any help from other people. I used only the sources mentioned and included all the citations correctly both in word and content.

This thesis has not been used previously at this or any other university in order to achieve an academic degree.

Halle (Saale), 09/11/2016

Anne Hartwig

14. Curriculum vitae

	Anne Hartwig
Date of birth	02.04.1989
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Halle (Saale), 09/11/2016

15. Publication list

Patents and journals (peer reviewed)

02/2017	Mameri, F., Koutchoukali, O., Bouhelassa, M., Hartwig, A., Nemdili, L., Ulrich, J., *Feasibility study of coating by cooling crystallization on ibuprofen naked tablets*, Frontiers of Chemical Science and Engineering (2017), 1-9.
08/2016	Hartwig, A., Ulrich, J.: *In situ encapsulation of liquids by means of crystallization*, Journal of Crystal Growth, published online, (http://dx.doi.org/10.1016/j.jcrysgro.2016.08.056), in press.
06/2016	Hartwig, A., Ulrich, J.: *Influences of ethanol on the thermodynamics and kinetics in the crystallization of xylitol*, Crystal Research & Technology, 51 (2016) 6, 405-408.
11/2015	Ulrich, J., Petersen, S., Wendt, K., Stelzer, T., Hartwig, A., Abouzeid, A.: *Verfahren und Vorrichtung zur Herstellung von beschichteten Granalien, Pastillen oder Tabletten mittels In-situ Beschichtung*, DE102014006502A1, Deutsches Patentamt, 12/11/2015.
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09/2016	Hartwig, A., Ulrich, J.: *Liquid-filled Xylitol Candies – An Application of In situ Encapsulation*, in Proceedings BIWIC 2016: 23rd International Workshop on Industrial Crystallization, 06-08/09/2016, eds. Lorenz, H., Buchholz, H., Max-Planck-Institute, Magdeburg, 226-231.

Mameri, F., Hartwig, A., Koutcoukali, O., Ulrich, J.: *The in-situ coating process applied on ibuprofen tablets*, in Proceedings BIWIC 2016: 23rd International Workshop on Industrial Crystallization, 06-08/09/2016, eds. Lorenz, H., Buchholz, H., Max-Planck-Institute, Magdeburg, 232-237.

05/2016 Hartwig, A., Ulrich, J.: *In situ encapsulation of liquids by means of crystallization*, in Proceedings Asian Crystallization Technology Symposium 2016, 25-27/05/2016, Tianjin University, Tianjin, 72-74.

Mameri, F., Hartwig, A., Koutcoukali, O., Ulrich, J.: *Coating of ibuprofen tablets by a cooling crystallization process*, in Proceedings Asian Crystallization Technology Symposium 2016, 25-27/05/2016, Tianjin University, Tianjin, 204-206.

09/2015 Hartwig, A., Ulrich, J.: *Crystallization behavior of xylitol in water and water-ethanol solutions*, in Proceedings BIWIC 2015: 22nd International Workshop on Industrial Crystallization, 09-11/09/2015, Hanbat National University, Daejeon, 122-129.

Oral presentations

05/2016 Hartwig, A., Ulrich, J.: *In situ encapsulation of liquids by means of crystallization*, Asian Crystallization Technology Symposium 2016, Tianjin University, Tianjin, China, 25-27/05/2016.

09/2015 Hartwig, A., Ulrich, J.: *The production of xylitol pastilles with a liquid core*, project meeting, work group Prof. Jie Lu, Shanghai University of Engineering Science, Shanghai, China, 14/09/2015.

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